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Development of Synthetic Methods for Functionalized Organoboron Compounds via Transition Metal Catalysis

Hokkaido University
Graduate School of Chemical Science and Engineering
Organoelement Laboratory

Jumpei Taguchi
2019
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General Introduction

Organoboron compound is a significant class of compounds in synthetic organic chemistry. They exhibit much higher stability against air and moisture compared with other organometallic reagents such as organolithium or Grignard reagents. This is because of low ionic-character of C–B bond (electronegativity of C: 2.55, B: 2.04 compared with Li: 0.98, Mg: 1.31). On the other hand, organoboronates become also sufficiently reactive for use in organic synthesis when an appropriate activation procedure is employed. They can be used for various transformation reactions such as Suzuki-Miyaura cross-coupling reaction, allylboration, oxidation, amination, and homologation reaction (Scheme 1a). For these reasons, these derivatives are utilized as intermediates for constructing pharmaceuticals, agrochemicals and materials chemistry. In addition, some organoboron compounds are important as organic emissive materials (Scheme 1b). BODIPY is the most enthusiastically studied organoboron-derived luminophore due to its high fluorescence quantum yields and its derivatives are applied for the biological labeling and imaging. Recently, air-stable triarylboranes are drawing intense interest as materials for EL devices due to their strong π-acceptor properties originating from the vacant p orbital of boron atom. Furthermore, bortezomib, which is the first drug containing boronic acid structure was approved for an anticancer agent by FDA in 2003 (Scheme 1c). Tavaborole was also approved as a drug for an antifungal agent very recently. Therefore, development of preparation methods of functionalized organoboron compounds is highly important in organic chemistry.

Scheme 1. Importance of organoboron compounds in organic chemistry. a) Derivatizations of organoboron compounds. b) Organic emissive materials containing boron atom. c) FDA-approved pharmaceuticals containing boron atom.
Conventional methods for the preparation of organoboron compounds had been achieved via halogen-metal exchange or metatation of aryl bromides or iodides and subsequent trapping with boron electrophiles such as BCl₃, BBr₃, B(OMe)₃ (Scheme 2a). However, the application of these methods to synthesize highly functionalized organoboron compounds is limited by the lack of functional group tolerance due to the high nucleophilicity of organolithium or Grignard reagents. In addition, hydroboration is one of the most straightforward methods to synthesize alkyl or alkenyl boronates. This method also has significant limitations such as regioselectivity issues in the case of hydroboration of internal alkenes or alkynes. Transition metal-catalyzed borylation reactions have been developed as alternatives to these conventional reactions, for example Miyaura-Ishiyama borylation reaction which is the reaction of organohalides and bis(pinacolato)diboron 1 using Pd catalyst and base, transition metal-catalyzed hydroboration or diboration reaction, and Hartwig-Miyaura C–H borylation reaction and so on (Scheme 2b). They generally exhibit high functional group tolerance compared with the conventional methods and their regio- or stereoselectivity can be controlled by the catalyst.

Scheme 2. Preparation methods of organoboron compounds. a) Conventional preparation methods of organoboron compounds. b) Transition metal-catalyzed borylation reactions.
In our laboratory, we have been working on the development of two kinds of transition metal-catalyzed borylation reactions. The first one is a Cu(I)-catalyzed nucleophilic borylation reaction and the other is an iridium-catalyzed C–H borylation reaction. In 2000, Hosomi and Ito, and Miyaura and Ishiyama independently reported copper(I)-catalyzed borylations of α,β-unsaturated ketones (Scheme 3a). These reactions are the first examples of activation of a B–B bond with a copper(I) salt to generate boryl–copper(I) species (Scheme 3b). Because this type of reaction does not always require a stoichiometric base for activation of diboron 1 and proceeds at room temperature, this reaction exhibits high functional group tolerance and this nucleophilic boron species has been applied for reactions with various electrophiles such as alkynes, alkenes, aldehydes, ketones, alkyl halides, allylic esters to afford the corresponding alkenyl, alkyl, α-hydroxy, and allyl boronates (Scheme 3c). In addition, these reactions can be used in asymmetric borylation reactions under mild conditions by using chiral ligands.

**Scheme 3.** Copper(I)-catalyzed nucleophilic borylation reactions. a) Cu(I)-catalyzed borylation reaction of α,β-unsaturated ketones. b) Generation of boryl–copper intermediates. c) Examples of reported borylation reaction using boryl–Cu species.

Direct C–H borylation reaction is an attractive approach in terms of step-economy compared with other metalation/borylation protocols or transition metal-catalyzed borylation reactions using organohalides as starting materials. (Scheme 4)
The initial example of C–H borylation was reported by Hartwig in 1999 (Scheme 5a).\textsuperscript{11} Excess amount of alkanes react with diboron 1 in the presence of Cp’Re(CO)\textsubscript{3} under irradiation of light to afford borylated alkane. Hartwig also reported alkyl C–H bond borylation reaction using Rh catalyst at 150ºC in 2000.\textsuperscript{12} After that, Smith III, Hartwig, Miyaura, Ishiyama reported that direct borylation reaction of aromatic C–H bond also proceed to afford arylboronates at almost same time.\textsuperscript{13} In particular, reaction using [Ir(OMe)(cod)\textsubscript{2}]dtbpy (cod = 1,5-cyclooctadiene, dtbpy = 4,4’-di-\textit{tert}-butyl-2,2’-bipyridine) catalyst has significant importance because it does not require light irradiation and high reaction temperature (Scheme 5b).\textsuperscript{13f} In addition, this C–H borylation reaction generally exhibits high functional group tolerance because of its mild reaction conditions; it proceeds at room temperature without addition of base. Because of these outstanding properties, C–H borylation has been studied enthusiastically, and this reaction has been applied for the total synthesis of natural products and the synthesis of pharmaceuticals, and organic functional materials.

C–H bonds, however, presents ubiquitously in organic compounds, the most important requirement for C–H borylation is to control the regioselectivities. There are mainly three factors to control regioselectivity of C–H borylation reaction. (a) Steric repulsion between substituents in substrate and transition metal catalyst, (b) Difference of acidities of C–H bonds, (c) Interaction between the coordinating functional groups and transition metal center. Initial studies of selective iridium-catalyzed C–H borylations at the \textit{meta}-positions of various substituents were reported by our group and the
groups of Smith III and Hartwig (Scheme 6a).\textsuperscript{13a-h} Their regioselectivities of borylation were controlled by the steric repulsion between the iridium catalysts and various functional groups, such as alkyl, aryl, halide, or carbonyl groups. Steric hindrance of the substrates can control the regioselectivities to some extent. For example, 1,3-disubstituted benzenes gave the 5-borylated product exclusively in the iridium-catalyzed borylation. However, other mono-substituted substrates gave a mixture of \textit{meta}- and \textit{para}-borylated products.

Iridium-catalyzed C–H borylation at the \textit{ortho}-position of the coordinating functionalities was reported by Ishiyama in 2010 (Scheme 6b).\textsuperscript{13b} Carbonyl-substituted benzenes react with diboron 1 in the presence of [Ir(OMe)(cod)]\textsubscript{2}/2 P(3,5-(CF\textsubscript{3})\textsubscript{2}-C\textsubscript{6}H\textsubscript{3})\textsubscript{3} catalyst to afford \textit{ortho}-borylated products. This selectivities arise from the interaction between the coordinating heteroatom in the carbonyl group and the iridium metal center to make iridium metal to close to the C–H bond at \textit{ortho}-position. As a result, subsequent oxidative addition proceeds at \textit{ortho}-position selectively.

![Scheme 6](image)

\textbf{Scheme 6.} Control of regioselectivity in aromatic C–H borylation reaction.

Chapter 1 describes the regiodivergent C–H borylation of 2,5-disubstituted heteroarenes with diboron 1 by using iridium catalysts formed \textit{in situ} from [Ir(OMe)(cod)]\textsubscript{2}/dtbpy or [Ir(OMe)(cod)]\textsubscript{2}/2 AsPh\textsubscript{3}.\textsuperscript{14} When [Ir(OMe)(cod)]\textsubscript{2}/dtbpy was used as the catalyst, borylation at the 4-position proceeded selectively to afford 4-borylated products in high yields. This regioselectivity is originated from the steric repulsion between carbonyl groups and iridium complex. The regioselectivity changed when the [Ir(OMe)(cod)]\textsubscript{2}/2 AsPh\textsubscript{3} catalyst was used; 3-borylated products were obtained in high yields with high regioselectivity, which is originating from the coordinating effect of the carbonyl group at 2-position. The regioselectivity of borylation was easily controlled by changing the ligands. This reaction was used in the syntheses of two different bioactive compound analogues from the same starting material.

Chapter 2 describes the iridium-catalyzed vinylic C–H borylation of $\alpha,\beta$-unsaturated esters using diboron 1.\textsuperscript{15} These reactions proceeded in octane solvent at temperatures ranging from 80 to 120°C to give the corresponding $\beta$-borylated $\alpha,\beta$-unsaturated esters in high yields with excellent regio- and
stereo-selectivities. The presence of the aryl esters resulted in a significant improvement in the yields of acyclic alkenylboronates. This reaction proceeds via the 1,4-addition/β-hydride removal mechanism.

In chapter 3 and 4, we focused on the synthesis of acylboron compounds by utilizing copper(I)-catalyzed borylation reaction and subsequent oxidation reactions. Research on the preparation and the reactivity of acylboron compounds is still immature compared with other organoboron compounds, such as alkyl, alkenyl and arylboronates. This is because of their inherent instability and high reactivity to oxidation or rearrangement. Although they have been proposed as transient intermediates since 1960s (Scheme 7a), their isolation and characterization had not reported until Yamashita and Nozaki achieved it in 2007. In 2010, Molander reported the first synthesis of potassium acyltrifluoroborate (KAT) and found that this compound has high stability against air and moisture. They also demonstrated that it reacts with azides to afford amides in the presence of Lewis acid. After that, Bode and Molander reported a more rapid and highly chemoselective amide-bond forming reaction between KATs and hydroxylamines that is called KAT ligation. (Scheme 7b) This reaction proceeds without any condensation reagents or catalysts under mild conditions at diluted concentrations in aqueous media at room temperature, and tolerates unprotected functional groups. Since these features are attractive for bio-conjugation, KAT ligation has been applied to site-specific functionalization of unprotected peptide side-chain. However conjugation between peptides consisting of natural amino acids with KAT ligation has not been achieved yet. To accomplish this goal, a synthetic route to α-amino acylborons, which are the terminal structures of acylboron-bearing peptides, is required, but currently, there has been no reported preparations of α-amino acylborons.

**Scheme 7.** Acylboron compounds. a) Acylborons proposed as reaction intermediates. b) KAT ligation

Reported methods for the preparation of acylborons can be categorized into mainly three approaches; 1) the reaction between acyl cation equivalents and boron nucleophiles, 2) the reaction between acyl anion equivalents and boron electrophiles, and 3) nucleophilic organometal reagents and electrophilic acylboron equivalent reagent. Yamashita and Nozaki’s first synthesis of acylboron
belongs to the first approach (Scheme 8a). In addition, Imamoto, Curran, Lacote, Grimmes, and Aldridge reported the acylboron synthesis using various boron nucleophiles such as phosphine borane–complexes, NHC–boron complex, boryl–zinc reagent and so on. In addition, Aldridge reported a Pd-catalyzed borylation reaction of acyl chlorides with a boryl–zinc reagent to afford acylboron compounds. Although this is the only one transition metal-catalyzed approach to synthesize acylboron compounds. However, access to the nucleophilic boron reagents is challenging in all these reactions in this first approaches.

Molander’s first synthesis of KAT is classified into the second approach (Scheme 8b). They synthesized the KAT by lithiation of acetal and subsequent trapping with boron electrophile, although this approach was applied for the synthesis of only one kind of KAT. After that, Bode reported a more general method using benzotriazole-based hemiaminal as starting materials. This method can be applied for the synthesis of various acylboron compounds bearing aryl and alkyl substituents.

As a third approach, Bode developed a reagent derived from thioformamide 2 that performs as electrophilic KAT equivalent in 2014 (Scheme 8c). This reagent 2 reacts with aryl lithium reagents or alkyl cuprate reagents to give various KATs in one-step. Most of these reactions in these three approaches require highly reactive and unstable nucleophiles, such as boryl–metal species or organolithium compounds, thus they exhibit low functional group tolerance.

Furthermore, Yudin and co-workers reported another mild synthetic route in 2012: Dess-Martin oxidation of α-hydroxy MIDA (N-methyliminodiacetic acid) boronates, which affords acyl MIDA boronates (Scheme 8d). This method proceeds under relatively mild conditions and is the only one reported procedure for α-heteroatom substituted acylboron, such as α-bromo-substituted acylboron or oxalyl boron, but this approach requires multi-step reactions from alkenylboronate and the tolerance toward functional groups was not explored (Scheme 8d).

These harsh reaction conditions and multi-step from easily available starting materials are the reason why there are no reported preparation of α-amino acylboron, which contains an amino-substituted stereocenter at the α-position. Therefore, development of a novel method for preparation of acylborons from easily available starting materials with high functional tolerance is highly desirable.
Chapter 3 describes the synthesis of acyl MIDA boronates by the ozonolysis of alkenyl MIDA boronates. This reaction exhibits excellent functional group tolerance and is applicable to synthesis of various acyl MIDA boronates and KATs that could not be synthesized by previous methods. In addition, α-amino acylborons were prepared for the first time. The acylboron of L-alanine analogue was obtained in high enantiopurity and found to be configurationally stable. Furthermore, oligopeptide synthesis between the α-amino KATs and amino acid in dilute aqueous media was also achieved.

Chapter 4 describes the preparation of KATs by copper(I)-catalyzed borylation of aldehydes and following oxidation. Accessibility of aldehydes, step- and redox-economical protocol, and mild reaction conditions enabled the preparation of wide range of KATs bearing functional groups such as halides, acetal, and ester, sulfide group. Moreover, this method was applied to the three-step synthesis of various α-amino acid analogues that bear a KAT moiety on the C-terminus by using naturally occurring amino acids as starting materials.

Scheme 8. Conventional synthesis method for acylborons. a) Reaction between acyl electrophiles and boron nucleophiles. b) Reaction between acyl electrophiles and boron nucleophiles. c) Reaction between organometal reagents and electrophilic KAT equivalent 2. d) Oxidation of α-hydroxy MIDA boronates.
References


Chapter 1.

Iridium-Catalyzed Regiodivergent C–H borylation of Multifunctionalized heteroarenes
Abstract
The regiodivergent C–H borylation of 2,5-disubstituted heteroarenes with bis(pinacolato)diboron (B$_2$(pin)$_2$, 1) was achieved by using iridium catalysts formed in situ from [Ir(OMe)(cod)]$_2$/dtbpy (cod=1,5-cyclooctadiene, dtbpy: 4,4′-di-tert-butyl-2,2′-bipyridine) or [Ir(OMe)(cod)]$_2$/2 AsPh$_3$. When [Ir(OMe)(cod)]$_2$/dtbpy was used as the catalyst, borylation at the 4-position proceeded selectively to afford 4-borylated products in high yields (dtbpy system A). The regioselectivity changed when the [Ir(OMe)(cod)]$_2$/2 AsPh$_3$ catalyst was used; 3-borylated products were obtained in high yields with high regioselectivity (AsPh$_3$ system B). The regioselectivity of borylation was easily controlled by changing the ligands. This reaction was used in the syntheses of two different bioactive compound analogues by using the same starting material.

Introduction
Multi-substituted heteroarenes bearing boryl substituent are important structural motifs because they can be utilized as intermediates in the synthesis of many naturally occurring compounds and biologically active agents.¹ Regioselective C–H borylation of mono- or di-substituted heteroarenes containing functional groups is a step-economical and reliable synthetic method for multi-substituted heteroarenes, in combination with various known derivatization reactions of C–B bonds. C–H bonds, however, presents ubiquitously in organic compounds, the most important requirement for C–H borylation is control of the site selectivity. In 2002, Ishiyama et al. reported regioselective C–H borylation whose regioselectivity is controlled based on the acidity of C–H bond.² In this reaction, reaction of thiophene and bis(pinacolato)diboron using [IrCl(cod)]$_2$/dtbpy catalyst afford 2-borylated thiophene, where the acidity of C–H bond is the highest. In 2005, Smith III reported that the borylation of 2-cyano-5-methylfurane selectively occurs at 3-position.³ This regioselectivity is driven by the steric repulsion between the iridium catalysts and methyl group. One example of borylation of heteroarenes at ortho-position of the coordinating functional group was published by Sawamura and co-workers; they used silica-SMAP (silica-supported silicon-constrained monodentate trialkylphosphine) as the ligand.⁴ The reaction took place in high yield with good regioselectivity. This selectivity arises from the interaction between the coordinating heteroatom in the carbonyl group and the iridium metal center.
Herein, we report the catalyst-controlled regiodivergent C–H borylation of multifunctionalized heteroarenes, such as furans, thiophenes, and pyrroles, by using two different iridium catalyst systems.\(^5\) The borylation of various heteroarenes I with bis(pinacolato)diboron (B\(_2\)pin\(_2\); \(2\)) proceeded regioselectively at the 3-position under catalysis with an [Ir(OMe)(cod)]\(_2\)/dtbpy complex (Scheme 1-2, dtbpy system A); the [Ir(OMe)(cod)]\(_2\)/AsPh\(_3\) complex afforded the 4-borylated product 4 (Scheme 1-2, AsPh\(_3\) system B).

**Scheme 1-1.** Regioselectivity in C–H borylation reactions of heteroaromatic compounds.

\[
\text{Scheme 1-2. This work: Regiodivergent C–H borylation reactions of heteroaromatic compounds.}
\]
Results and Discussion

We first examined the borylation of furan derivative 1a, which had a carbonyl group and a methyl group at the 2- and 5-positions, respectively, with [Ir(OMe)(cod)]2 and various ligands (Table 1-1, entries 1–7). The reaction of 1a with 2 (1.1 equiv) in the presence of [Ir(OMe)(cod)]2 (1.5 mol%) and dtbpy (3.0 mol%) in octane at room temperature afforded the 4-borylated product 3a in 92% yield after 16 h (Table 1, entry 1). The yield of 3a decreased to 82% when 3,4,7,8-tetramethyl-1,10-phenanthroline (TMPhen) was used as the ligand (entry 2). In contrast, the borylation of 1a with AsPh3 as the catalyst ligand gave the 3-borylated product 4a in 74% yield after 16 h (entry 3). Use of phosphorous-containing ligands resulted in significant decreases in the yields (4a: 0–31% after 16 h, entries 4–7). This borylation took place in the absence of a ligand to afford 4a in 28% yield (entry 8).

Although no reaction occurred in DMF as the solvent, other solvents such as diglyme and mesitylene could be successfully used (diglyme: 69%, mesitylene: 72%; entries 10 and 11). These results clearly show that the borylation regioselectivity was switched by changing the ligands in the iridium catalyst.

### Table 1-1. Optimization of reaction conditions.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (mol%)</th>
<th>T (°C)</th>
<th>Solvent</th>
<th>Yield (%)&lt;sup&gt;bc&lt;/sup&gt;</th>
<th>3a/4a&lt;sup&gt;[c]&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>dtbpy (3)</td>
<td>rt</td>
<td>octane</td>
<td>92 (76)&lt;sup&gt;[d]&lt;/sup&gt;</td>
<td>&gt;99:&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>TMphen (3)</td>
<td>rt</td>
<td>octane</td>
<td>82</td>
<td>&gt;99:&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>AsPh3 (6)</td>
<td>120</td>
<td>octane</td>
<td>74 (43)&lt;sup&gt;[d,e]&lt;/sup&gt;</td>
<td>&lt;1:&gt;99</td>
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<td>4</td>
<td>P[3,5-(CF3)2C6H3]3 (6)</td>
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<td>octane</td>
<td>0</td>
<td>-</td>
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<tr>
<td>5</td>
<td>P(C6F5)3 (6)</td>
<td>120</td>
<td>octane</td>
<td>31</td>
<td>&lt;1:&gt;99</td>
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<tr>
<td>6</td>
<td>PPh3 (6)</td>
<td>120</td>
<td>octane</td>
<td>22</td>
<td>&lt;1:&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>PCy3 (6)</td>
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<td>octane</td>
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<td>DMF</td>
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<td>10</td>
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<td>120</td>
<td>mesitylene</td>
<td>72</td>
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</table>

[a] Reaction conditions: 1a (0.5 mmol), 2 (0.55 mmol), [Ir(OMe)(cod)]2 (1.5 mol%), ligand (3.0–6.0 mol%) in solvent (3 mL). [b] Yields were determined by GC analysis (internal standard: dodecane). [c] Ratios of isomers in the crude reaction mixture were determined by 1H NMR spectroscopy analysis. [d] Yield of product isolated. [e] The yield of borylated product 4a significantly decreased during the isolation step.

With the optimal conditions in hand, we next examined the scope of heteroarenes with a methyl group at the 5-position and various functional groups at the 2-position, under systems A or B (Table 1-2). The yields of 3-borylated products significantly decreased during the isolation step; thus, we determined the regioselectivities and yields of the products by GC and 1H NMR spectroscopy analysis of the crude mixture. The reaction of 1b, which had an acetyl group at the 2-position, proceeded
regioselectively, whereas the 4-borylated product 3b was obtained in low yield under dtbpy system A (36 %, 3b/4b = >99:<1, Table 1-2, entry 1). In contrast, 3-borylated product 4b was produced in high yield with excellent regioselectivity (92 %, 3b/4b = <1:>99, entry 2). Furans substituted with methoxycarbonyl (1c) or aminocarbonyl (1d and 1e) groups reacted with 2 to afford the corresponding products in moderate to high yields under both systems (entries 3–8). Other heteroarenes, such as thiophenes or N-methoxycarbonyl-protected pyrroles, with functional groups at the 2-position could also be used as substrates for borylation with high selectivity (dtbpy system A: 77–99 %, >99:<1; AsPh3 system B: 43–99 %, 3/4 = <1:>99; entries 9–22), except for acetyl-substituted thiophene 1g (entry 11). These results suggested that different R groups on the carbonyl functionality at the 2-position did not affect the regioselectivity of borylation under either system.

Table 1-2. Scope of heteroarenes with a methyl group at 5-position.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>System</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>3/4 (c)</th>
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<tr>
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<td>Me (1b)</td>
<td>A</td>
<td>2</td>
<td>99</td>
<td>&gt;99:&lt;1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>9</td>
<td>56</td>
<td>1:99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>OMe (1c)</td>
<td>A</td>
<td>4</td>
<td>98</td>
<td>&gt;99:&lt;1</td>
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<td>B</td>
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<td>74</td>
<td>1:99</td>
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<td>94</td>
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<td>B</td>
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<td>14</td>
<td>B</td>
<td>6</td>
<td>93</td>
<td>1:99</td>
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<tr>
<td>15</td>
<td>N(i-Pr)2 (1i)</td>
<td>A</td>
<td>1</td>
<td>94</td>
<td>&gt;99:&lt;1</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>B</td>
<td>6</td>
<td>93</td>
<td>1:99</td>
<td></td>
<td></td>
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<tr>
<td>17</td>
<td>Et (1j)</td>
<td>A</td>
<td>2</td>
<td>99</td>
<td>&gt;99:&lt;1</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>B</td>
<td>9</td>
<td>56</td>
<td>1:99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>NMe2 (1k)</td>
<td>A</td>
<td>4</td>
<td>98</td>
<td>&gt;99:&lt;1</td>
<td></td>
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<tr>
<td>20</td>
<td>B</td>
<td>4</td>
<td>74</td>
<td>1:99</td>
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<td></td>
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<tr>
<td>21</td>
<td>OMe (1l)</td>
<td>A</td>
<td>1</td>
<td>94</td>
<td>&gt;99:&lt;1</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>B</td>
<td>6</td>
<td>93</td>
<td>1:99</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] System A: 1 (0.5 mmol), 2 (0.55 mmol), [Ir(OMe)(cod)]2 (1.5 mol%), and dtbpy (3.0 mol %) in octane (3 mL) at room temperature for 16 h. System B: 1 (0.5 mmol), 2 (0.55 mmol), [Ir(OMe)(cod)]2 (1.5 mol%), and AsPh3 (6.0 mol %) in octane (3 mL) at 120 ºC for 16 h. [b] Yields were determined by GC analysis (internal standard: dodecane). [c] Ratios of isomers in the crude reaction mixture were determined by 1H NMR spectroscopy analysis.
The regioselectivity of this borylation under dtbpy system A was affected by the steric properties of the 2- or 5-substituents because the selectivity originated from steric repulsion between the 2- or 5-substituents and the iridium catalyst. The use of heteroarenes with various substituents other than a methyl group at the 5-position would affect the isomer ratios. We therefore investigated the steric effect of the substituent at the 5-position on the borylation regioselectivity by using furan substrates with various alkyl or trimethylsilyl (TMS) groups at the 5-position and a propionyl group at the 2-position (Table 1-3). 5-Ethylfuran derivative 1m reacted smoothly with 2 to afford the 4-borylated product 3m in high yield, with high regioselectivity (dtbpy system A, 81%, 3m/4m = 97:3; entry 1).

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>System</th>
<th>time (h)</th>
<th>Yield (%)[^b]</th>
<th>3/4[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1m</td>
<td>A</td>
<td>24</td>
<td>81</td>
<td>97:3</td>
</tr>
<tr>
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<td></td>
<td>B</td>
<td>3</td>
<td>68</td>
<td>&lt;1:&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>1n</td>
<td>A</td>
<td>8</td>
<td>86</td>
<td>94:6</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>B</td>
<td>4</td>
<td>94</td>
<td>&lt;1:&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>1o</td>
<td>A</td>
<td>4</td>
<td>75</td>
<td>&lt;1:&gt;99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>3</td>
<td>67</td>
<td>&lt;1:&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>1p</td>
<td>A</td>
<td>3</td>
<td>58</td>
<td>&lt;1:&gt;99</td>
</tr>
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<td></td>
<td>B</td>
<td>30</td>
<td>48</td>
<td>&lt;1:&gt;99</td>
</tr>
</tbody>
</table>

[^a] System A: 1 (0.5 mmol), 2 (0.55 mmol), [Ir(OMe)(cod)]_2 (1.5 mol%), and dtbpy (3.0 mol%) in octane (3 mL) at room temperature. System B: 1 (0.5 mmol), 2 (0.55 mmol), [Ir(OMe)(cod)]_2 (1.5 mol %), and AsPh_3 (6.0 mol %) in octane (3 mL) at 120ºC. [^b] Combined yields and ratios of isomers in the crude reaction mixture were determined by ¹H NMR spectroscopy analysis (internal standard: dibromomethane). [^c] This reaction was carried out at 60ºC. [^d] This reaction was carried out at 80ºC.

Under AsPh_3 system B, the selectivity of borylation changed completely; only the 3-borylated product was obtained in good yield (68 %, 3m/4m = <1:>99; entry 2). Similar trends in terms of reactivity and selectivity were observed with substrate 1n, which contained a 5-Cy substituent (entries 3 and 4). The regioselectivity was completely reversed compared with those for entries 1 and 3, when tert-butyl derivative 1o was used as the substrate under dtbpy system A; only the 3-borylated product 4o was obtained in good yield (75 %, 3o/4o = <1:>99, entry 5). This result suggests that the tert-butyl moiety may act as a bulkier substituent than the propionyl group. AsPh_3 system B also led to 3-borylated furan 4o in 67 % yield (entry 6). The reactivity and selectivity of the TMS derivative 1p
were similar to those of 5-tert-butyl furan 1o, and the 3-borylated product 4p was produced in 58 and 48% yields under dtbpy system A and AsPh3 system B, respectively (entries 7 and 8).

Next, we examined the scope of thiophenes containing functional groups other than alkyl groups at the 5-position (Table 1-4). The CF3 group behaved as a larger substituent than that of a Cy group in this borylation.11 Borylation of the 5-CF3-substituted thiophene 1q produced a 1:1 mixture of isomers when the dtbpy ligand was used (dtbpy system A; Table 1-4, entry 1). In contrast, the 3-borylated product 4q was produced in 58 and 48% yield under dtbpy system A and AsPh3 system B, respectively (entries 7 and 8).

Table 1-4. Scope of thiophenes with a various functional groups at 5-position.

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>System</th>
<th>time (h)</th>
<th>Yield (%)</th>
<th>3/4</th>
<th>3/4 ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[c]</td>
<td>3q–t</td>
<td>A</td>
<td>20</td>
<td>80</td>
<td></td>
<td>56:44</td>
</tr>
<tr>
<td>2[d]</td>
<td>1q–t</td>
<td>B</td>
<td>20</td>
<td>75</td>
<td>&lt;1:99</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1r</td>
<td>A</td>
<td>16</td>
<td>82</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1s</td>
<td>B</td>
<td>30</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1t</td>
<td>A</td>
<td>16</td>
<td>82</td>
<td>&gt;99:1</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1s</td>
<td>B</td>
<td>16</td>
<td>46</td>
<td>26:74</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1t</td>
<td>A</td>
<td>48</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

[a] System A: 1 (0.5 mmol), 2 (0.55 mmol), [Ir(OMe)(cod)]2 (1.5 mol%), and dtbpy (3.0 mol%) in octane (3 mL) at room temperature. System B: 1 (0.5 mmol), 2 (0.55 mmol), [Ir(OMe)(cod)]2 (1.5 mol%), and AsPh3 (6.0 mol%) in octane (3 mL) at 120°C. [b] Combined yields and ratios of isomers in the crude reaction mixture were determined by 1H NMR spectroscopy analysis (internal standard: dibromomethane). [c] 2.5 mol% of [Ir(OMe)(cod)]2 and 5.0 mol% of dtbpy were used. [d] 2.5 mol% of [Ir(OMe)(cod)]2 and 10 mol% of AsPh3 were used.
In the borylation of 1r or 1t under AsPh₃ system B, the methoxy or bromo groups may inhibit coordination between the oxygen atom of the carbonyl group and the iridium center. Selective borylation was therefore achieved by changing the propionyl group to more strongly coordinating carbonyl groups. We have performed the borylations of 5-bromothiophenes with methoxycarbonyl 1u or dimethylaminocarbonyl 1v groups under both systems because heteroarenes containing both bromo and boryl substituents are important intermediates, which can be used in stepwise cross-coupling procedures (Scheme 4). The use of 2-methoxycarbonyl thiophene 1u significantly increased the reactivity and regioselectivity of borylation, compared with the reaction of 2-propionyl thiophene 1t, under both systems. Furthermore, the borylation of 2-dimethylaminocarbonyl-substituted thiophene 1v afforded the 3-borylated product 4v in 40% yield. These results indicate that substituting an amide group for an ester group at the 2-position improves the reactivity of this borylation.

Scheme 1-3. Borylation of 5-bromothiophene with ester 1u or amide groups 1v at the 2-position.

To confirm the utility of the dimethylamide group as a coordinating group, borylations of other heteroarenes were investigated (Table 1-5). The reaction of furan 1w with a bromo group at the 5-position proceeded regioselectively to give the 4-borylated product 3w in high yield under dtbpy system A (2 h, 99%, 3w/4w = 95:<5; Table 1-5, entry 1). AsPh₃ system B also led to 3-borylated 4w in good yield (9 h, 56%, 3w/4w = <1:>99; entry 2). The yields and regioselectivities increased when chloro-functionalized thiophene 1x was used instead of the 2-propionyl derivative 1s (dtbpy system A: 4 h, 98%, 3x/4x = >99:<1; AsPh₃ system B: 4 h, 74%, 3x/4x = 13:87; entries 3 and 4). The methoxy-substituted thiophene 1y reacted smoothly to afford both isomers in high yields and with excellent regioselectivities (dtbpy system A: 1 h, 94%, 3y/4y = >99:<1; AsPh₃ system B: 6 h, 93%, 3y/4y = <1:>99; entries 5 and 6). These results show that the regiodivergent borylation tolerated various functional groups at the 5-position when dimethylamide-substituted heteroarenes were used.
Table 1-5. Scope of heteroarenes with a dimethylamide group at 2-position.

To further demonstrate the synthetic utility of this regiodivergent borylation, we synthesized two different biologically active compound analogues by using borylated furans derived from 1w (Scheme 1-4). The one-pot synthesis of 6 was achieved by using a stepwise cross-coupling strategy without isolation of unstable boron intermediates. After borylation of 1w under dtbpy system A, the solvent was removed under reduced pressure; and then the cross-coupling reaction of crude 3w with 1-chloro-3-iodobenzene (1.1 equiv) took place at room temperature. After completion of the reaction, (4-fluorophenyl)boronic acid (2.0 equiv) was added to the reaction mixture. The mixture was stirred for 0.5 h, NRT inhibitor analogue 6 was obtained in 47% yield (one pot, three steps). NHE-1 inhibitor analogue 8 was obtained in 30% yield (one pot, three steps) by regioselective borylation of 1w under AsPh₃ system B, followed by a stepwise cross-coupling procedure by using iodobenzene (1.1 equiv) and (3-chlorophenyl)boronic acid (2.0 equiv).
Two proposed catalytic cycles are shown in Scheme 1-5. In Pathway 1 (dtbpy system A), tris(boryl)iridium complex A is first produced by reaction of an iridium/dtbpy complex with 2. Oxidative addition of the C–H bond at the 4-position to A produces complex B. This regioselectivity is probably caused by bulkiness around the iridium center, at which the coordinative carbonyl group only acts as a sterically congesting group. Reductive elimination of 3 produces the iridium–hydride complex C. Finally, oxidative addition of 2 to C, followed by reductive elimination of H–Bpin, regenerates A. In Pathway 2 (AsPh₃ system B), the mono- (n=1) or tris- (n=3) boryliridium complex D is first produced by reactions of iridium(I) complexes containing AsPh₃ with 2. Next, the oxygen atom in the carbonyl group coordinates with the iridium center (complex E), and then oxidative addition of the C–H bond neighboring the directing group to E produces the pseudo-metallacycle F. Reductive elimination produces the iridium–hydride complex G and the 3-borylated product 4. Finally, regeneration of D proceeds through the same mechanism as that in the reaction of complex G with 2.
We developed regiodivergent C–H borylation of multifunctionalized heteroarenes with 2 by using iridium catalysts generated from [Ir(OMe)(cod)]₂/dtbpy or [Ir(OMe)(cod)]₂/2 AsPh₃. The borylation proceeded regioselectively to afford the products in high yields. The use of the [Ir(OMe)(cod)]₂/dtbpy catalyst produced 4-borylated products in high yields (dtbpy system A). The regioselectivity changed when the [Ir(OMe)(cod)]₂/2 AsPh₃ catalyst (AsPh₃ system B) was used; 3-borylated products were obtained in high yields and with high regioselectivities. Additionally, the syntheses of two different bioactive compound analogues from one starting material were achieved by using this regiodivergent borylation.
Experimental

General and Materials.

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, dried over CaH$_2$, distilled and further degassed via three freeze-pump-thaw cycles. NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometer ($^1$H: 400 MHz and $^{13}$C: 100 MHz). Tetramethylsilane ($^1$H) and CDCl$_3$ ($^{13}$C) were employed as external standards, respectively. NMR yields and regioselectivities were determined by $^1$H NMR analysis using dibromomethane as internal standard. GLC analysis was performed on a Hitachi G-3500 instrument equipped with a glass column (OV-101 on Uniport B, 2 m) and a FID detector. n-Dodecane was used as an internal standard to determine GC yield. [Ir(OMe)(cod)]$_2$ was synthesized according to the reported procedure.$^{[1]}$ High-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University.

General Experimental Procedures.

A General Procedure for the [Ir(OMe)(cod)]$_2$/dtbpy-Catalyzed C–H Borylation of Heteroarenes 1a–1y (Catalytic System A).

[Ir(OMe)(cod)]$_2$ (5.0 mg, 7.5 µmol), bis(pinacolato)diboron (2) (139 mg, 0.55 mmol) and dtbpy (4,4’-di-tert-butyl-2,2’-bipyridine) (4.0 mg, 15 µmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Octane (3.0 mL) was then added in the flask through the rubber septum using a syringe, and stirred at room temperature for 15 min. Heteroarene (0.50 mmol) was then added to the reaction mixture using a syringe, and stirred at room temperature. After the reaction was complete, the reaction mixture was concentrated and purified by Kugelrohr distillation to give the corresponding heteroarylboronate.

A General Procedure for the [Ir(OMe)(cod)]$_2$/AsPh$_3$-Catalyzed C–H Borylation of Heteroarenes 1a–1y (Catalytic System B).

[Ir(OMe)(cod)]$_2$ (5.0 mg, 7.5 µmol), 2 (139 mg, 0.55 mmol) and AsPh$_3$ (9.2 mg, 30 µmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Octane (3.0 mL) was then added in the flask through the rubber septum using a syringe, and stirred at room temperature for 15 min. Heteroarene (0.50 mmol) was then added to the reaction mixture using a syringe, and stirred at 120 °C. After the reaction was complete, the reaction mixture was concentrated and purified by Kugelrohr distillation to give the corresponding heteroarylboronate. 3-Borylated heteroarenes were easily decomposed in the isolation step, full isolation thus resulted in a lower yield. In addition, separation of AsPh$_3$ from the crude product was difficult, causing the low full isolation yield.
1. Preparation of Substrates.

The starting materials (1a, 1b, and 1g) were purchased from commercial suppliers. The starting materials (1u and 1w) were synthesized according to the reported procedure.

**Preparation of methyl 5-methylfuran-2-carboxylate (1c).**

5-Methylfuran-2-carboxylic acid (1.00 g, 7.93 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. SOCl₂ (2.88 mL, 39.7 mmol) and DMF (6.2 µL, 0.08 mmol) were then added in the flask through the rubber septum using syringes, and the resultant solution was then refluxed for 3 h. The reaction mixture was cooled to room temperature, and excess SOCl₂ was removed under reduced pressure. Et₂O (10 mL) was then added in the flask through the rubber septum using a syringe, and the solution was cooled to 0 °C. MeOH (642 µL, 15.9 mmol), and Et₃N (1.66 mL, 11.9 mmol) were then added dropwise to the reaction mixture using syringes, and stirred at 0 °C for 1 h. After the reaction was complete, the reaction mixture was extracted with Et₂O three times. The combined organic layer was washed with H₂O, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 1c as a colorless oil. The spectral data was consistent with those reported in the literature.

**Preparation of N,N-dimethyl-5-methylfuran-2-carboxamide (1d).**

5-Methylfuran-2-carboxylic acid (504 mg, 4.00 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. SOCl₂ (1.0 mL, 1.64 g, 13.8 mmol) and DMF (16.0 µL, 15.1 mg, 0.21 mmol) were then added in the flask through the rubber septum using syringes, and the solution was refluxed for 3 h. The reaction mixture was cooled to room temperature, excess SOCl₂ was removed under reduced pressure. Et₂O (3.2 mL) was then added in the flask through the rubber septum using a syringe, and the solution was cooled to 0 °C. An aqueous solution of Me₂NH (50%, 2.0 mL) was then added dropwise to the reaction mixture using a syringe, and stirred at 0 °C for 1 h. After the reaction was complete, the reaction mixture was extracted with Et₂O three times. The combined organic layer was washed with H₂O, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by Kugelrohr distillation to obtain 1d (483 mg, 3.15 mmol, 79%) as a colorless oil. ¹H NMR (396 MHz, CDCl₃, δ): 2.36 (s, 3H), 3.19 (br s, 6H), 6.07–6.08 (m, 1H), 6.87 (d, J = 3.2 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.0 (CH₃), 35.7 (br, CH₃), 37.5 (br, CH₃), 106.8 (CH), 116.5 (CH), 145.5 (C), 153.5 (C), 159.6 (C). HRMS-EI (m/z): [M⁺] calcd for C₉H₁₁NO₂, 153.07898; found, 153.07863.
Preparation of \(N,N\)-diisopropyl-5-methylfuran-2-carboxamide (1e).

1e was prepared from 5-methylfuran-2-carboxylic acid and \((i-\text{Pr})_2\text{NH}\) according to the procedure for the synthesis of 1d. \(^1\)H NMR (392 MHz, CDCl\(_3\), δ): 1.37 (br s, 6H), 1.38 (br s, 6H), 2.33 (s, 3H), 4.01 (br s, 2H), 6.03–6.04 (m, 1H), 6.70 (d, \(J = 3.2\) Hz, 1H). \(^13\)C NMR (99 MHz, CDCl\(_3\), δ): 13.3 (C\(\text{H}_3\)), 20.6 (C\(\text{H}_3\)), 47.7 (br, C\(\text{H}\)), 106.8 (C\(\text{H}\)), 114.7 (CH), 147.2 (C), 152.9 (C), 160.1 (C). HRMS–EI (m/z): [M]\(^+\) calcd for C\(_{12}\)H\(_{19}\)NO\(_2\), 209.1 4158; found, 209.14103.

Preparation of 1-(5-chlorothiophen-2-yl)propan-1-one (1f).

\(N\)-Methoxy-\(N\)-methylpropionamide (2.02 g, 17.3 mmol, yellow oil) was prepared in 72% yield from propionyl chloride (2.23 g, 24.1 mmol) according to the reported procedure. To an oven-dried flask, 2-methylthiophene (1.92 mL, 1.96 g, 20.0 mmol) was dissolved in THF (100 mL) under nitrogen atmosphere at room temperature. A hexane solution of \(n\)-BuLi (1.6 M, 13.8 mL, 22.0 mmol) was then added using a syringe at 0°C and the reaction mixture was stirred for 3 h at room temperature. The mixture was cooled to 0°C and \(N\)-methoxy-\(N\)-methylpropionamide (2.60 g, 22.2 mmol) was then added using a syringe. The reaction mixture was then stirred at room temperature for 4 h before being quenched with H\(_2\)O. The reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with brine, and dried over MgSO\(_4\). After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to afford 1f (1.37 g, 8.87 mmol, 45%) as a colorless oil. \(^1\)H NMR (392 MHz, CDCl\(_3\), δ): 1.22 (t, \(J = 7.4\) Hz, 3H), 2.53 (d, \(J = 0.7\) Hz, 3H), 2.88 (q, \(J = 7.3\) Hz, 2H), 6.78–6.79 (m, 1H), 7.52 (d, \(J = 4.0\) Hz, 1H). \(^13\)C NMR (99 MHz, CDCl\(_3\), δ): 8.4 (CH\(_3\)), 15.7 (CH\(_3\)), 31.8 (CH\(_2\)), 126.4 (CH), 132.0 (CH), 141.7 (C), 148.9 (C), 193.2 (C). HRMS–EI (m/z): [M]\(^+\) calcd for C\(_8\)H\(_{10}\)OS, 154.04524; found, 154.04485.

Preparation of methyl 5-methylthiophene-2-carboxylate (1h).

1h (2.89 g, 18.5 mmol, white solid) was prepared in 92% yield from 5-methylthiophene-2-carboxylic acid (2.85 g, 20.0 mmol) and MeOH according to the procedure for the synthesis of 1c. The spectral data was consistent with those reported in the literature.
Preparation of \(N,N\)-dimethyl-5-methyl-thiophene-2-carboxamide (1i).

![Chemical Structure](image)

\(1i\) (2.54 g, 15.0 mmol, white solid) was prepared in 75% yield from 5-methylthiophene-2-carboxylic acid (2.85 g, 20.0 mmol) and an aqueous solution of Me\(_2\)NH (50%) according to the procedure for the synthesis of \(1d\). \(^1\)H NMR (392 MHz, CDCl\(_3\), \(\delta\)): 2.50 (d, \(J = 1.1\) Hz, 3H), 3.18 (br s, 6H), 6.70–6.71 (m, 1H), 7.17 (d, \(J = 3.6\) Hz, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 14.7 (CH\(_3\)), 36.7 (br, CH\(_3\)), 39.0 (br, CH\(_3\)), 124.7 (CH), 129.2 (CH), 135.1 (C), 143.4 (C), 163.7 (C). HRMS–EI (m/z): [M–H]\(^+\) calcd for C\(_8\)H\(_{10}\)NOS, 168.04831; found, 168.04762.

Preparation of \(N,N\)-diisopropyl-5-methylthiophene-2-carboxamide (1j).

![Chemical Structure](image)

\(1j\) (2.98 g, 13.2 mmol, white solid) was prepared in 66% yield from 5-methylthiophene-2-carboxylic acid (2.85 g, 20.0 mmol) and (i-Pr)_2NH according to the procedure for the synthesis of \(1d\). \(^1\)H NMR (392 MHz, CDCl\(_3\), \(\delta\)): 1.35 (br s, 6H), 1.37 (br s, 6H), 2.48 (d, \(J = 1.1\) Hz, 3H), 3.98 (br s, 2H), 6.65–6.66 (m, 1H), 7.00 (d, \(J = 3.6\) Hz, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 14.9 (CH\(_3\)), 20.6 (CH\(_3\)), 48.2 (br, CH), 124.4 (CH), 126.8 (CH), 137.2 (C), 141.9 (C), 163.5 (C). HRMS–EI (m/z): [M\(^+\)] calcd for C\(_{12}\)H\(_{16}\)NOS, 225.11873; found, 225.11874.

Preparation of methyl 2-methyl-5-propionyl-1H-pyrrole-1-carboxylate (1k).

![Chemical Structure](image)

To an oven-dried flask, 1,2-dichloroethane (50 ml) and \(N,N\)-dimethylpropionamide (5.50 mL, 5.09 g, 50.3 mmol) were added using syringes under nitrogen atmosphere. The reaction mixture was cooled to \(\sim 78\) °C. POCl\(_3\) (7.67 g, 50.0 mmol) and 2-methyl-1H-pyrrole (4.00 g, 49.3 mmol) were then added dropwise in the flask through the rubber septum using syringes, and the reaction mixture was refluxed for 2 h. A solution of CH\(_3\)CO\(_2\)Na (23 g) in H\(_2\)O (108 mL) was then added using a syringe, and refluxed for 1 h. The reaction mixture was cooled to room temperature. The reaction mixture was extracted with EtOAc three times. The combined organic layer was dried over MgSO\(_4\). After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 1-(5-methyl-1H-pyrrol-2-yl)propan-1-one (2.71 g, 19.8 mmol, 40%).

NaH (792 mg, 19.8 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (30 mL) was then added in the flask through the rubber septum using a syringe at 0 °C. A solution of 1-(5-methyl-1H-pyrrol-2-yl)propan-1-one (2.71 g, 19.8 mmol) in THF (30 mL), methyl chloroformate (1.83 mL, 2.24 g, 23.7 mmol) were then added dropwise using syringes, and the reaction mixture was refluxed for
16 h. The reaction mixture was quenched with H₂O, and extracted with EtOAc three times. The combined organic layer was dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 1k (1.50 g, 7.68 mmol, 39%). ¹H NMR (392 MHz, CDCl₃, δ): 1.18 (t, J = 7.5 Hz, 3H), 2.34 (s, 3H), 2.76 (q, J = 7.4 Hz, 2H), 3.97 (s, 3H), 5.95 (d, J = 3.6 Hz, 1H), 6.82 (d, J = 3.6 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.5 (CH₃), 12.5 (CH₃), 31.2 (CH₂), 54.9 (CH), 109.6 (CH), 119.2 (CH), 132.5 (C), 137.6 (C), 152.6 (C), 189.9 (C). HRMS–EI (m/z): [M]+ calcd for C₁₀H₁₃NO₃, 195.08954; found, 195.08958.

**Preparation of dimethyl 5-methyl-1H-pyrrole-1,2-dicarboxylate (1l).**

2,2,2-Trichloro-1-(5-methyl-1H-pyrrol-2-yl)ethan-1-one (8.33 g, 36.8 mmol) was prepared in 75% yield from 2-methylpyrrole (4.00 g, 49.3 mmol) according to the reported procedure.[⁷] To an oven-dried flask, 2,2,2-trichloro-1-(5-methyl-1H-pyrrol-2-yl)ethanone (8.33 g, 36.8 mmol) and NaOMe (750 mg, 13.9 mmol) were dissolved in MeOH (60 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 1 h. The resulting mixture was extracted with EtOAc three times. The combined organic layer was dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 5-methyl-1H-pyrrole-1,2-dicarboxylate (4.91 g, 35.3 mmol, 96%).

NaH (1.40 g, 35.3 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (30 mL) was then added in the flask using a syringe through the rubber septum at 0 °C. A solution of methyl 5-methyl-1H-pyrrole-2-carboxylate (4.91 g, 35.3 mmol) in THF (30 mL), methyl chloroformate (3.24 mL, 4.00 g, 42.4 mmol) were then added dropwise using a syringe, and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was quenched with H₂O, and extracted with EtOAc three times. The combined organic layer was dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 1l (3.50 g, 17.8 mmol, 50%). ¹H NMR (392 MHz, CDCl₃, δ): 2.37 (d, J = 0.7 Hz, 3H), 3.82 (s, 3H), 3.97 (s, 3H), 5.93–5.94 (m, 1H), 6.82 (d, J = 3.6 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 13.4 (CH₃), 51.4 (CH₃), 54.6 (CH₃), 110.0 (CH), 119.8 (CH), 124.1 (C), 137.1 (C), 151.8 (C), 160.6 (C). HRMS–EI (m/z): [M]+ calcd for C₇H₁₁O₄N, 197.06881: found, 197.06882.

**Preparation of 1-(5-ethylfuran-2-yl)propan-1-one (1m).**

1m (695 mg, 4.57 mmol, colorless oil) was prepared in 9% yield from 2-ethylfuran (5.00 g, 52.0 mmol) according to the reported procedure.[⁸] ¹H NMR (392 MHz, CDCl₃, δ): 1.20 (t, J = 7.5 Hz, 3H), 1.28 (t, J = 7.5 Hz, 3H), 2.73 (q, J = 7.7 Hz, 2H), 2.80 (q, J = 7.4 Hz, 2H), 6.15 (d, J = 3.6 Hz, 1H), 7.11 (d, J = 3.6 Hz, 1H). ¹³C NMR (99 MHz,
CDCl₃, δ): 8.1 (CH₃), 11.5 (CH₃), 21.4 (CH₃), 31.0 (CH₂), 106.9 (CH), 118.3 (CH), 150.8 (C), 162.6 (C), 189.3 (C).

HRMS-ESI (m/z): [M+Na]⁺ calcd for C₃H₅O₂Na, 175.07295; found, 175.07310.

**Preparation of 1-(5-cyclohexylfuran-2-yl)propan-1-one (1n).**

2-Cyclohexylfuran (938 mg, 6.24 mmol) was prepared in 48 % yield from 3,3-diethoxy-1-propyne (2.14 g, 16.7 mmol) and cyclohexanecarboxaldehyde (1.51 g, 13.5 mmol) according to the reported procedure. To an oven dried flask, under nitrogen atmosphere, 2-cyclohexylfuran (751 mg, 5.00 mmol) and propionyl anhydride (794 mg, 6.10 mmol) were then added using syringes. BF₃·Et₂O (76.2 mg, 0.54 mmol) was added once in the reaction mixture using a syringe and the reaction mixture was stirred for 1 h at 100 °C. The resulting mixture was quenched with H₂O (2.5 mL), and extracted with Et₂O three times. The combined organic layer was washed with saturated aqueous solution of Na₂CO₃, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by Kugelrohr distillation to obtain 1n (308 mg, 1.49 mmol, 30%). ¹H NMR (392 MHz, CDCl₃, δ): 1.20 (t, J = 7.4 Hz, 3H), 1.24–1.47 (m, 5H), 1.63–1.83 (m, 3H), 2.04–2.07 (m, 2H), 2.66–2.73 (m, 1H), 2.80 (q, J = 7.4 Hz, 2H), 6.11–6.12 (m, 1H), 7.10 (d, J = 3.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 8.2 (CH₃), 25.5 (CH₂), 25.7 (CH₂), 31.0 (CH₂), 31.2 (CH₂), 37.3 (CH), 105.8 (CH), 118.1 (CH), 150.7 (C), 165.6 (C), 189.4 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₃H₁₈O₂Na, 229.11990; found, 229.11993.

**Preparation of 1-[5-(tert-butyl)furan-2-yl]propan-1-one (1o).**

1o (1.18 g, 6.54 mmol, colorless oil) was prepared in 85% yield from 2-(tert-butyl)furan (957 mg, 7.71 mmol) according to the procedure for the synthesis of 1f. ¹H NMR (392 MHz, CDCl₃, δ): 2.81 (q, J = 7.4 Hz, 2H), 6.13 (d, J = 3.6 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.1 (CH₃), 28.6 (CH₃), 31.2 (CH₂), 32.9 (C), 105.0 (CH), 117.7 (CH), 150.9 (C), 168.6 (C), 189.5 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₁H₁₆O₂Na, 203.10425; found, 203.10446.

**Preparation of 1-[5-(trimethylsilyl)furan-2-yl]propan-1-one (1p).**

2-Trimethylsilylfuran (2.54 g, 18.1 mmol, colorless oil) was prepared in 28% yield from furan (4.33 g, 63.6 mmol) according to the reported procedure. 1p (1.88 g, 9.58 mmol, colorless oil) was prepared in 64% yield from 2-trimethylsilylfuran (2.19 g, 15.6 mmol) according to the procedure for the synthesis of 1f. ¹H NMR (392 MHz, CDCl₃, δ): 0.31 (s, 9H), 1.21 (t, J = 7.3 Hz, 3H), 2.88 (q, J = 7.3 Hz, 2H), 6.69 (d, J = 3.6 Hz, 1H), 7.15 (d, J = 3.6 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃): -2.1 (CH₃), 7.9 (CH₃), 31.6 (CH₂), 116.2 (CH), 121.0 (CH), 156.2 (C), 165.7 (C), 190.1 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₀H₁₆O₂NaSi, 219.08118; found, 219.08137.
Preparation of 1-(5-(trifluoromethyl)thiophen-2-yl)propan-1-one (1q).

(a) (EtCO)₂O (1.2 equiv) BF₃·Et₂O (10 mol%)

(b) HO-\(\text{Et-OH}\) (7.0 equiv)

(c) K[CF₃B(OH)₃] (3.0 equiv)

1,10-phen (20 mol%) DMSO, 60 °C, 16 h

(d) \(p\)-TsOH (23 mol%)

acetone/H₂O (1:1), reflux, 5 h

Step a: Preparation of 1-(5-iodothiophen-2-yl)propan-1-one.

1-(5-Iodothiophen-2-yl)propan-1-one (3.94 g, 14.8 mmol, colorless oil) was prepared in 33% yield from 2-iodothiophene (4.60 mL, 9.45 g, 45.0 mmol) according to the procedure for the synthesis of 1n.

Step b: Preparation of 2-ethyl-2-(5-iodothiophen-2-yl)-1,3-dioxolane.

To a dried flask, under nitrogen atmosphere, 1-(5-iodothiophen-2-yl)propan-1-one (3.51 g, 13.2 mmol), ethylene glycol (5.15 mL, 57.2 g, 92.1 mmol), and \(p\)-toluenesulfonic acid (8.0 mg, 0.05 mmol) were dissolved in toluene (20 mL). The reaction mixture was refluxed under a Dean-Stark trap for 18 h. The mixture was diluted with EtOAc and washed with an aqueous solution of Na₂CO₃ (5%, w/w), H₂O, and brine, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 2-ethyl-2-(5-iodothiophen-2-yl)-1,3-dioxolane (2.62 g, 8.46 mmol, 64%) as a colorless oil.

Step c: Preparation of 2-ethyl-2-[5-(trifluoromethyl)thiophen-2-yl]-1,3-dioxolane.

CuI (307 mg, 1.61 mmol), 1,10-phenanthroline (291 mg, 1.62 mmol), and potassium trimethoxy(trifluoromethyl)borate (4.12 g, 24.3 mmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DMSO (16 mL) and 2-ethyl-2-(5-iodothiophen-2-yl)-1,3-dioxolane (2.27 g, 7.31 mmol) were then added in the flask through the rubber septum using syringes, and the solution was stirred at 60 °C for 28 h. After cooling to room temperature, the solution was diluted with Et₂O (40 mL) and washed with 1 M HCl (100 mL). The aqueous layer was extracted with Et₂O (20 mL) twice and the combined organic layer was washed with conc. NH₃ (25% in H₂O, 100 mL). The aqueous layer was extracted with Et₂O (20 mL) twice and the combined organic layer was washed with brine (60 mL), dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by Kugelrohr distillation to yield 2-ethyl-2-[5-(trifluoromethyl)thiophen-2-yl]-1,3-dioxolane (1.31 g, 5.18 mmol, 71%) as a white solid.

Step d: Preparation of 1q.

To an oven-dried flask, 2-ethyl-2-[5-(trifluoromethyl)thiophen-2-yl]-1,3-dioxolane (1.11 g, 4.41 mmol) and \(p\)-toluenesulfonic acid (100.5 mg, 0.528 mmol) were dissolved in H₂O (15 ml) and acetone (15 mL) under nitrogen atmosphere at room temperature. The reaction mixture was refluxed for 1 h. The resulting solution was treated with a saturated aqueous solution of NaHCO₃ and extracted with EtOAc three times. The combined organic layer was washed with H₂O, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude
product was purified by Kugelrohr distillation to yield 1q (785 mg, 3.77 mmol, 87%) as a white solid. ¹H NMR (392 MHz, CDCl₃, δ): 1.25 (t, J = 7.4 Hz, 3H), 2.96 (q, J = 7.4 Hz, 2H), 7.44–7.45 (m, 1H), 7.62–7.63 (m, 1H). ¹³C NMR (99 MHz, CDCl₃): 8.0 (CH₃), 32.5 (CH₂), 121.8 (q, ¹JC-δ = 269.7 Hz, CF₃), 128.9 (q, ¹JC-δ = 3.4 Hz, CH), 130.2 (CH), 137.5 (q, ²JC-δ = 3.85 Hz, C), 146.9 (C), 193.5 (C). HRMS-ESI (m/z): [M–H]⁺ calcd for C₇H₆OF₂S, 207.00969; found, 207.00962.

Preparation of 1-(5-methoxythiophen-2-yl)propan-1-one (1r).

![1r](image)

1r (1.78 g, 11.5 mmol, colorless oil) was prepared in 49% yield from 2-methoxythiophene (2.35 mL, 2.49 g, 25.4 mmol) according to the procedure for the synthesis of 1f. ¹H NMR (392 MHz, CDCl₃, δ): 1.21 (t, J = 7.3 Hz, 3H), 2.82 (q, J = 7.4 Hz, 2H), 3.95 (s, 3H), 6.24 (d, J = 4.3 Hz, 1H), 7.45 (d, J = 4.3 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.8 (CH₃), 30.7 (CH₂), 60.1 (CH₃), 105.5 (CH), 130.1 (C), 131.9 (CH), 173.9 (C), 193.1 (C). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₈H₁₁O₂NaS, 193.02937; found, 193.02962.

Preparation of 1-(5-chlorothiophen-2-yl)propan-1-one (1s).

![1s](image)

1s (4.20 g, 24.1 mmol, white solid) was prepared in 76% yield from 2-chlorothiophene (3.76 g, 31.7 mmol) according to the procedure for the synthesis of 1n. ¹H NMR (396 MHz, CDCl₃, δ): 1.22 (t, J = 7.2 Hz, 3H), 2.87 (q, J = 7.4 Hz, 2H), 6.95 (d, J = 3.6 Hz, 1H), 7.48 (d, J = 4.1 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 8.2 (CH₃), 31.6 (CH₂), 127.4 (CH), 130.9 (CH), 138.8 (C), 142.6 (C), 192.7 (C). HRMS-ESI (m/z): [M+H]⁺ calcd for C₇H₆OCIS, 174.99789; found, 174.99822.

Preparation of 1-(5-bromothiophen-2-yl)propan-1-one (1t).

![1t](image)

1t (3.96 g, 18.1 mmol, 1t:enol-1t = 94:6, white solid) was prepared in 60% yield from 2-bromothiophene (4.90 g, 30.1 mmol) according to the procedure described for the synthesis of 1n. 1t: ¹H NMR (392 MHz, CDCl₃, δ): 1.22 (t, J = 7.4 Hz, 3H), 2.87 (q, J = 7.4 Hz, 2H), 7.10 (d, J = 4.0 Hz, 1H), 7.44 (d, J = 4.3 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.3 (CH₃), 31.8 (CH₂), 122.0 (C), 131.1 (CH), 131.6 (CH), 145.5 (C), 192.7 (C). enol-1t: ¹H NMR (392 MHz, CDCl₃, δ): 1.88 (d, J = 6.8 Hz, 3H), 5.05 (q, J = 6.8 Hz, 1H), 7.14 (d, J = 4.4 Hz, 1H), 7.59 (d, J = 4.0 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 20.1 (CH₃), 41.5 (CH), 123.8 (C), 131.3 (CH), 133.2 (CH), 142.1 (C), 185.6 (C). HRMS–ESI (m/z): [M+H]⁺ calcd for C₇H₆O⁷⁹BrS, 218.94737; found, 218.94764.
Preparation of 5-bromo-\(\text{N},\text{N}\)-dimethylthiophene-2-carboxamide (1v).

\[
\text{Br-S=O} \quad \text{NMe}_2
\]

1v (1.41 g, 6.02 mmol, white solid) was prepared in 83% yield from 5-bromothiophene-2-carboxylic acid (1.50 g, 7.25 mmol) and an aqueous solution of Me\(_2\)NH (50%) according to the procedure for the synthesis of 1d. \(^1\)H NMR (392 MHz, CDCl\(_3\), \(\delta\)): 3.18 (br s, 6H), 7.00–7.02 (m, 1H), 7.12 (d, \(J = 3.9\) Hz, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 36.6 (br, C\(\text{H}_3\)), 39.1 (br, C\(\text{H}_3\)), 116.6 (C), 129.4 (CH), 129.5 (CH), 139.5 (C), 162.6 (C). HRMS-ESI (m/z): [M+Na\(^+\)]\(^+\) calcd for C\(_7\)H\(_8\)ON\(_\text{BrNaS}\), 255.94022; found, 255.94021.

Preparation of 5-chloro-\(\text{N},\text{N}\)-dimethylthiophene-2-carboxamide (1x).

\[
\text{Cl-S=O} \quad \text{NMe}_2
\]

1x (2.07 g, 10.9 mmol, white solid) was prepared in 91% yield from 5-chlorothiophene-2-carboxylic acid (1.95 g, 12.0 mmol) and aqueous solution of Me\(_2\)NH (50%) according to the procedure described above. \(^1\)H NMR (392 MHz, CDCl\(_3\), \(\delta\)): 3.18 (br s, 6H), 6.87 (d, \(J = 3.9\) Hz, 1H), 7.15 (d, \(J = 3.9\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 37.1 (br, C\(\text{H}_3\)), 38.9 (br, C\(\text{H}_3\)), 125.9 (C), 128.6 (C), 134.1 (C), 136.8 (C), 162.8 (C). HRMS-ESI (m/z): [M+Na\(^+\)]\(^+\) calcd for C\(_7\)H\(_8\)ONClNaS, 211.99073; found, 211.99089.

Preparation of 5-methoxy-\(\text{N},\text{N}\)-dimethylthiophene-2-carboxamide (1y).

To an oven-dried flask, under nitrogen atmosphere at room temperature, \((i-\text{Pr})_2\)NH (2.0 mL, 14.4 mmol) in THF (66 ml). A hexane solution of n-BuLi (1.6 M, 9.0 mL, 14.4 mmol) was slowly added dropwise at −78 °C, and the mixture was warmed to room temperature and stirred for 15 min. The mixture was then cooled to −78 °C, 2-methoxythiophene (1.50 mL, 1.47 g, 12.9 mmol) was then added to the reaction mixture using a syringe, and stirred at the same temperature for 1 h. Powdered dry ice (ca. 10 g) was then added to the reaction mixture, and it was warmed to room temperature with stirring. The solvents were removed by evaporation, and the slurry was taken up in 1 M NaOH and extracted with Et\(_2\)O. The aqueous mixture was acidified with 12 M HCl. The resulting solution was extracted with EtOAc three times. The combined organic layer was washed with brine, and dried over MgSO\(_4\). After filtration, the solvents were removed by evaporation. The product was used in the next reaction without further purification. 1y (1.87 g, 10.1 mmol, white solid) was prepared in 80% yield from 5-methoxythiophene-2-carboxylic acid (2.00 g, 12.6 mmol) and an aqueous solution of Me\(_2\)NH (50%) according to the procedure for the synthesis of 1d. \(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 3.19 (br s, 6H), 3.92 (s, 3H), 6.16 (d, \(J = 4.5\) Hz, 1H), 7.10 (d, \(J = 4.5\) Hz, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 37.8 (br, C\(\text{H}_3\)), 59.8 (C\(\text{H}_3\)), 103.7 (CH), 124.0 (C), 128.5 (CH), 163.6 (C), 169.5 (C).
Characterization of Borylation Products.

1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (3a).

The NMR yield of 3a in the crude mixture was 92%. The crude mixture was purified by Kugelrohr distillation (51 Pa, 150 °C) to obtain 3a (99.6 mg, 0.377 mmol, 76%) as a colorless oil from 1a (68.6 mg, 0.497 mmol). $^1$H NMR (401 MHz, CDCl$_3$, $\delta$): 1.20 (t, $J = 7.2$ Hz, 3H), 1.32 (s, 12H), 2.54 (s, 3H), 2.76 (q, $J = 7.5$ Hz, 2H), 7.30 (s, 1H).

$^{13}$C NMR (99 MHz, CDCl$_3$, $\delta$): 8.7 (C$_{H_3}$), 14.5 (C$_{H_3}$), 24.8 (C$_{H_3}$), 31.3 (C$_{H_2}$), 83.6 (C), 123.6 (CH), 150.9 (C), 166.9 (C), 189.4 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M$^+$]$^+$ calcd for C$_{14}$H$_{21}$BO$_4$, 264.15329; found, 264.15296.

1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4a).

The NMR yield of 4a in the crude mixture was 74%. The crude mixture was purified by Kugelrohr distillation (30 Pa, 130 °C) to obtain 4a (283.6 mg, 1.07 mmol, 43%) as a colorless oil from 1a (345 mg, 2.50 mmol). $^1$H NMR (401 MHz, CDCl$_3$, $\delta$): 1.18 (t, $J = 7.4$ Hz, 3H), 1.38 (s, 12H), 2.36 (d, $J = 0.8$ Hz, 3H), 2.92 (q, $J = 7.3$ Hz, 2H), 6.25–6.26 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 7.8 (CH$_3$), 13.3 (CH$_3$), 24.5 (CH$_3$), 31.6 (CH$_2$), 83.6 (C), 112.9 (CH), 119.4 (br, B–C), 154.7 (C), 155.6 (C), 190.5 (C). HRMS–EI (m/z): [M$^+$]$^+$ calcd for C$_{14}$H$_{21}$BO$_4$, 264.15329; found, 264.15247.

1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]ethan-1-one (3b).

The NMR yield of 3b in the crude mixture was 36%. The crude mixture was purified by Kugelrohr distillation (83 Pa, 130 °C) to obtain 3b (26.4 mg, 0.106 mmol, 21%) as a white solid from 1b (61.3 mg, 0.494 mmol). $^1$H NMR (392 MHz, CDCl$_3$, $\delta$): 1.32 (s, 12H), 2.41 (s, 3H), 2.54 (s, 3H), 7.31 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, $\delta$): 14.5 (CH$_3$), 24.8 (CH$_3$), 25.7 (CH$_3$), 83.6 (C), 124.5 (CH), 151.2 (C), 167.3 (C), 185.7 (C). The carbon directly attached
to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI(m/z): [M+Na]+ calcd for C_{13}H_{19}O_{11}BNa, 273.12686; found: 273.12686.

1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]ethan-1-one (4b).

The NMR yield of 4b in the crude mixture was 92%. The crude mixture was purified by Kugelrohr distillation (78 Pa, 150 °C) to obtain 4b (68.9 mg, 0.276 mmol, 55%) as a white solid from 1b (62.5 mg, 0.503 mmol). ^1H NMR (401 MHz, CDCl₃, δ): 1.37 (s, 12H), 2.36 (d, J = 0.8 Hz, 3H), 2.52 (s, 3H), 6.27 (m, 1H). ^13C NMR (99 MHz, CDCl₃, δ): 13.6 (CH₃), 24.7 (CH₃), 26.6 (CH₃), 84.3 (C), 113.4 (CH), 155.1 (C), 156.3 (C), 187.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI(m/z): [M+Na]+ calcd for C_{13}H_{19}O_{11}BNa, 273.12686; found: 273.12667.

Methyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylate (3c).

The NMR yield of 3c in the crude mixture was 99%. The crude mixture was purified by Kugelrohr distillation (61 Pa, 160 °C) to obtain 3c (112.4 mg, 0.422 mmol, 86%) as a white solid from 1c (68.8 mg, 0.491 mmol). ^1H NMR (392 MHz, CDCl₃, δ): 1.31 (s, 12H), 2.53 (s, 3H), 3.86 (s, 3H), 7.30 (s, 1H). ^13C NMR (99 MHz, CDCl₃, δ): 14.3 (CH₃), 24.7 (CH₃), 51.6 (CH₃), 83.4 (C), 108.9 (br, B–C), 123.6 (CH), 142.8 (C), 159.1 (C), 166.2 (C). HRMS–ESI(m/z): [M+Na]+ calcd for C_{13}H_{19}O_{10}BNa, 288.12541; found: 288.12543.

Methyl 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylate (4c).

The NMR yield of 4c in the crude mixture was 51%. The crude mixture was purified by Kugelrohr distillation (61 Pa, 160 °C) to obtain 4c (38.2 mg, 0.144 mmol, 29%) as a white solid from 1c (69.7 mg, 0.497 mmol). ^1H NMR (401 MHz, CDCl₃, δ): 1.37 (s, 12H), 2.36 (s, 3H), 3.88 (s, 3H), 6.22 (s, 1H). ^13C NMR (99 MHz, CDCl₃, δ): 13.5 (CH₃), 24.7 (CH₃), 51.7 (CH₃), 84.2 (C), 112.4 (CH), 146.1 (C), 156.5 (C), 159.3 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI(m/z): [M+Na]+ calcd for C_{13}H_{19}O_{10}BNa, 288.12541; found: 288.12543.

N,N-Dimethyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (3d).
The NMR yield of 3d in the crude mixture was 93%. The crude mixture was purified by Kugelrohr distillation (50 Pa, 150 °C) to obtain 3d (108.7 mg, 0.389 mmol, 78%) as a white solid from 1d (77.0 mg, 0.503 mmol). $^1$H NMR (392 MHz, CDCl$_3$, δ): 1.31 (s, 12H), 2.51 (s, 3H), 3.16 (br s, 6H), 6.97 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): 14.0 (CH$_3$), 24.6 (CH$_3$), 36.3 (br, CH$_3$), 38.5 (br, CH$_3$), 83.2 (C), 107.7 (br, B–C), 120.4 (CH), 145.5 (C), 160.2 (C), 163.8 (C). HRMS–EI (m/z): [M]$^+$ calecd for C$_{14}$H$_{22}$BNO$_4$, 279.16419; found, 279.16506.

N,N-Dimethyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (4d).

The NMR yield of 4d in the crude mixture was 99%. The crude mixture was purified by Kugelrohr distillation (43 Pa, 160 °C) to obtain 4d (59.7 mg, 0.214 mmol, 43%) as a white solid from 1d (77.1 mg, 0.503 mmol). $^1$H NMR (392 MHz, CDCl$_3$, δ): 1.31 (s, 12H), 2.31 (s, 3H), 3.09 (s, 6H), 6.17 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): 13.1 (CH$_3$), 24.7 (CH$_3$), 35.8 (br, CH$_3$), 38.4 (br, CH$_3$), 83.5 (C), 110.5 (CH), 151.6 (C), 152.9 (C), 161.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]$^+$ calecd for C$_{14}$H$_{32}$O$_3$Na, 301.15704; found, 301.15782.

N,N-Diisopropyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (3e).

The NMR yield of 3e in the crude mixture was 97%. The crude mixture was purified by Kugelrohr distillation (46 Pa, 180 °C) to obtain 3e (156.4 mg, 0.457 mmol, 93%) as a white solid from 1e (104.9 mg, 0.501 mmol). $^1$H NMR (401 MHz, CDCl$_3$, δ): 1.30 (s, 12H), 1.35 (br s, 6H), 1.37 (br s, 6H), 2.49 (s, 3H), 4.00 (br s, 2H), 6.76 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): 14.0 (CH$_3$), 20.8 (CH$_3$), 24.7 (CH$_3$), 47.9 (br, CH), 83.2 (C), 107.4 (br, B–C), 117.5 (CH), 146.8 (C), 160.3 (C), 163.1 (C). HRMS–EI (m/z): [M]$^+$ calecd for C$_{18}$H$_{36}$BNO$_4$, 335.22679; found, 335.22612.
**N,N-Diisopropyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (4e).**

The NMR yield of 4e in the crude mixture was 99%. The crude mixture was purified by Kugelrohr distillation (50 Pa, 180 °C) to obtain 4e (162.9 mg, 0.486 mmol, 90%) as a white solid from 1e (113.0 mg, 0.539 mmol). 

$^1$H NMR (401 MHz, CDCl$_3$, δ): 1.20 (br s, 6H), 1.27 (s, 12H), 1.50 (br s, 6H), 2.28 (d, $J = 0.8$ Hz, 3H), 3.58 (br s, 1H), 3.68 (br s, 1H), 6.12 (m, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): 12.8 (CH$_3$), 20.1 (br, CH$_3$), 24.6 (CH$_3$), 45.5 (br, CH), 50.6 (br, CH), 83.1 (C), 109.3 (CH), 151.0 (C), 155.4 (C), 162.2 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]$^+$ calcd for C$_{18}$H$_{30}$O$_{10}$BNa, 357.21964; found, 357.22066.

1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]propan-1-one (3f).

The NMR yield of 3f in the crude mixture was 84%. The crude mixture was purified by Kugelrohr distillation (80 Pa, 140 °C) to obtain 3f (110.8 mg, 0.395 mmol, 79%) as a white solid from 1f (77.2 mg, 0.501 mmol). 

$^1$H NMR (401 MHz, CDCl$_3$, δ): 1.20 (t, $J = 7.2$ Hz, 3H), 1.33 (s, 12H), 2.70 (s, 3H), 2.90 (q, $J = 7.3$ Hz, 2H), 7.82 (s, 1H). 

$^{13}$C NMR (99 MHz, CDCl$_3$, δ): 8.7 (CH$_3$), 16.6 (CH$_3$), 24.8 (CH$_3$), 31.9 (CH$_2$), 83.6 (C), 138.5 (CH), 141.3 (C), 161.3 (C), 194.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]$^+$ calcd for C$_{14}$H$_{21}$BO$_2$S, 280.13045; found, 280.13022.

1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]propan-1-one (4f).

The NMR yield of 4f in the crude mixture was 86%. The crude mixture was purified by Kugelrohr distillation (80 Pa, 160 °C) to obtain 4f (89.0 mg, 0.318 mmol, 63%) as a colorless oil from 1f (77.4 mg, 0.502 mmol). 

$^1$H NMR (401 MHz, CDCl$_3$, δ): 1.20 (t, $J = 7.4$ Hz, 3H), 1.40 (s, 12H), 2.50 (d, $J = 0.8$ Hz, 3H), 2.90 (q, $J = 7.3$ Hz, 2H), 6.90 (m, 1H). 

$^{13}$C NMR (99 MHz, CDCl$_3$, δ): 8.6 (CH$_3$), 15.3 (CH$_2$), 24.7 (CH$_3$), 33.5 (CH$_2$), 84.2 (C), 131.5 (CH), 145.6 (C), 147.1 (C), 194.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]$^+$ calcd for C$_{14}$H$_{21}$BO$_2$S, 280.1304; found, 280.1304.

35
1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]ethan-1-one (3g).

\[
\text{Me} \quad \text{S} \quad \text{Me} \\
\text{O} \quad \text{B} \quad \text{O}
\]

3g

The NMR yield of 3g in the crude mixture was 24%. The crude mixture was purified by Kugelrohr distillation (80 Pa, 160 °C) to obtain 3g (102.1 mg, 0.384 mmol, 19%) as a colorless oil from 1g (280.0 mg, 2.00 mmol). \(^1\)H NMR (401 MHz, CDCl\(_3\), δ): 1.34 (s, 12H), 2.52 (s, 3H), 2.71 (s, 3H), 7.81 (s, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), δ): 16.6 (CH\(_3\)), 24.8 (CH\(_3\)), 26.4 (CH\(_3\)), 83.6 (C), 139.6 (CH), 141.8 (C), 161.9 (C), 190.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{13}\)H\(_{19}\)O\(_3\)BNaS, 289.10402; found: 289.10380.

1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]ethan-1-one (4g).

\[
\text{Me} \quad \text{S} \quad \text{Me} \\
\text{O} \quad \text{B} \quad \text{O}
\]

4g

The NMR yield of 4g in the crude mixture was 96%. The crude mixture was purified by Kugelrohr distillation (64 Pa, 150 °C) to obtain 4g (54.0 mg, 0.203 mmol, 41%) as a white solid from 1g (69.9 mg, 0.499 mmol). \(^1\)H NMR (401 MHz, CDCl\(_3\), δ): 1.40 (s, 12H), 2.51 (s, 3H), 2.54 (s, 3H), 6.92 (s, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), δ): 15.3 (CH\(_3\)), 24.7 (CH\(_3\)), 28.0 (CH\(_3\)), 84.2 (C), 131.9 (CH), 146.1 (C), 147.8 (C), 191.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{13}\)H\(_{19}\)O\(_3\)BNaS, 289.10402; found: 289.10386.

Methyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (3h).

\[
\text{Me} \quad \text{S} \quad \text{Me} \\
\text{O} \quad \text{B} \quad \text{O}
\]

3h

The NMR yield of 3h in the crude mixture was 99%. The crude mixture was purified by Kugelrohr distillation (51 Pa, 150 °C) to obtain 3h (113.5 mg, 0.402 mmol, 78%) as a white solid from 1h (80.3 mg, 0.514 mmol). \(^1\)H NMR (401 MHz, CDCl\(_3\), δ): 1.32 (s, 12H), 2.70 (s, 3H), 3.84 (s, 3H), 7.93 (s, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), δ): 16.2 (CH\(_3\)), 24.8 (CH\(_3\)), 51.8 (CH\(_3\)), 83.4 (C), 129.9 (C), 140.3 (CH), 159.6 (C) 162.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{13}\)H\(_{19}\)O\(_4\)BNaS, 305.09893; found: 305.09874.
Methyl 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (4h).

The NMR yield of 4h in the crude mixture was 81%. The crude mixture was purified by Kugelrohr distillation (53 Pa, 150 °C) to obtain 4h (97.1 mg, 0.344 mmol, 68%) as a white solid from 1h (78.9 mg, 0.505 mmol). 1H NMR (392 MHz, CDCl3, δ): 1.39 (s, 12H), 2.49 (d, J = 0.7 Hz, 3H), 3.85 (s, 3H), 6.85 (m, 1H). 13C NMR (99 MHz, CDCl3, δ): 15.1 (CH3), 24.6 (CH3), 51.8 (CH3), 84.1 (C), 130.6 (CH), 135.2 (C), 147.1 (C), 162.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]⁺ calcd for C13H19O411BNaS, 305.09893; found: 305.09875.

N,N-Dimethyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3i).

The NMR yield of 3i in the crude mixture was 81%. The crude mixture was purified by Kugelrohr distillation (80 Pa, 180 °C) to obtain 3i (117.4 mg, 0.398 mmol, 80%) as a white solid from 1i (84.7 mg, 0.501 mmol). 1H NMR (401 MHz, CDCl3, δ): 1.31 (s, 12H), 2.67 (s, 3H), 3.18 (br s, 6H), 7.43 (s, 1H). 13C NMR (99 MHz, CDCl3, δ): 15.6 (CH3), 24.6 (CH3), 36.5 (br, CH3), 39.1 (br, CH3), 83.1 (C), 127.7 (br, B–C), 134.7 (C), 135.1 (CH), 156.0 (C), 164.0 (C). HRMS–ESI (m/z): [M+Na]⁺ calcd for C14H22O3N11BNaS, 318.13057; found, 318.13120.

N,N-Dimethyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4i).

The NMR yield of 4i in the crude mixture was 99%. The crude mixture was purified by Kugelrohr distillation (80 Pa, 180 °C) to obtain 4i (99.1 mg, 0.336 mmol, 67%) as a colorless oil from 1i (84.5 mg, 0.499 mmol). 1H NMR (396 MHz, CDCl3, δ): 1.29 (s, 12H), 2.46 (d, J = 1.3 Hz, 3H), 3.02 (br s, 6H), 6.91–6.92 (m, 1H). 13C NMR (99 MHz, CDCl3, δ): 14.6 (CH3), 24.8 (CH3), 35.2 (br, CH3), 38.7 (br, CH3), 83.3 (C), 129.9 (CH), 140.7 (C), 143.6 (C), 166.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]⁺ calcd for C14H22O3N10BNaS, 317.13420; found, 317.13431.
N,N-Diisopropyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)thiophene-2-carboxamide (3j).

![Chemical Structure](image)

The NMR yield of 3j in the crude mixture was 77%. The crude mixture was purified by Kugelrohr distillation (56 Pa, 190 °C) to obtain 3j (106.9 mg, 0.304 mmol, 61%) as a white solid from 1j (113.2 mg, 0.502 mmol). 1H NMR (401 MHz, CDCl3, δ): 1.31 (s, 12H), 1.35 (br s, 6H), 1.36 (br s, 6H), 2.66 (s, 3H), 3.99 (br s, 2H), 7.25 (s, 1H). 13C NMR (99 MHz, CDCl3, δ): 15.6 (CH3), 20.8 (CH3), 24.8 (CH3), 48.8 (br, CH), 83.2 (C), 127.5 (br, B–C), 132.6 (CH), 136.6 (C), 154.4 (C), 163.8 (C). HRMS–EI (m/z): [M]+ calcd for C18H1610BNO3S, 350.20758; found, 350.20720.

N,N-Diisopropyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)thiophene-2-carboxamide (4j).

![Chemical Structure](image)

The NMR yield of 4j in the crude mixture was 81%. The crude mixture was purified by Kugelrohr distillation (53 Pa, 190 °C) to obtain 4j (115.4 mg, 0.329 mmol, 66%) as a colorless oil from 1j (113.0 mg, 0.501 mmol). 1H NMR (401 MHz, CDCl3, δ): 1.15 (br s, 6H), 1.28 (s, 12H), 1.52 (br s, 6H), 2.45 (s, 3H), 3.50 (br s, 1H), 3.88 (br s, 1H), 6.89 (s, 1H). 13C NMR (99 MHz, CDCl3, δ): 14.4 (CH3), 20.0 (CH3), 24.6 (CH3), 45.8 (br, CH), 51.0 (br, CH), 83.1 (C), 129.7 (CH), 139.0 (C), 146.1 (C), 164.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]+ calcd for C18H1610BNO3S, 351.20394; found, 351.20396.

Methyl 2-methyl-5-propionyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborol-2-yl)-1H-pyrrrole-1- carboxylate (3k).

![Chemical Structure](image)

The NMR yield of 3k in the crude mixture was 90%. The crude mixture was purified by Kugelrohr distillation (80 Pa, 190 °C) to obtain 3k (146.5 mg, 0.456 mmol, 91%) as a pale-yellow oil from 1k (97.6 mg, 0.500 mmol). 1H NMR (396 MHz, CDCl3, δ): 1.17 (t, J = 7.5 Hz, 3H), 1.31 (s, 12H), 2.50 (s, 3H), 2.76 (q, J = 7.4 Hz, 2H), 3.98 (s, 3H), 7.15 (s, 1H). 13C NMR (99 MHz, CDCl3, δ): 8.7 (CH3), 12.4 (CH3), 24.7 (CH3), 31.2 (CH2), 55.2 (CH2), 83.1 (C), 109.7 (br, B–C), 125.0 (CH), 132.9 (C), 146.2 (C), 152.8 (C), 190.1 (C). HRMS–EI (m/z): [M]+ calcd for C16H2410BNO3S, 320.17838; found, 320.17721.
Methyl 5-methyl-2-propionyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1-carboxylate (4k).

The NMR yield of 4k in the crude mixture was 92%. The crude mixture was purified by Kugelrohr distillation (78 Pa, 200 °C) to obtain 4k (100.9 mg, 0.314 mmol, 63%) as a colorless oil from 1k (97.8 mg, 0.501 mmol). $^1$H NMR (396 MHz, CDCl$_3$, $\delta$): 1.17 (t, J = 7.2 Hz, 3H), 1.31 (s, 12H), 2.32 (s, 3H), 2.98 (q, J = 7.4 Hz, 2H), 3.92 (s, 3H), 6.18 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, $\delta$): 8.4 (CH$_3$), 13.2 (CH$_3$), 24.6 (CH$_3$), 34.8 (CH$_2$), 54.6 (CH$_3$), 83.6 (C), 115.4 (br, B–C), 116.1 (CH), 134.5 (C), 139.3 (C), 152.2 (C), 196.8 (C). HRMS–EI (m/z): [M]$^+$ calcd for C$_{16}$H$_{24}$BNO$_5$, 320.17838; found, 320.17705.

Dimethyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2-dicarboxylate (3l).

The NMR yield of 3l in the crude mixture was 81%. The crude mixture was purified by Kugelrohr distillation (54 Pa, 200 °C) to obtain 3l (123 mg, 0.379 mmol, 75%) as a white solid from 1l (99.2 mg, 0.503 mmol). $^1$H NMR (396 MHz, CDCl$_3$, $\delta$): 1.30 (s, 12H), 2.54 (s, 3H), 3.80 (s, 3H), 3.97 (s, 3H), 7.15 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, $\delta$): 13.2 (CH$_3$), 24.8 (CH$_3$), 51.6 (CH$_3$), 55.0 (CH$_3$), 83.2 (C), 124.4 (C), 125.6 (CH), 145.9 (C), 152.1 (C), 160.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]$^+$ calcd for C$_{15}$H$_{22}$BNO$_6$, 322.15765; found, 322.15768.

Dimethyl 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2-dicarboxylate (4l).

The NMR yield of 4l in the crude mixture was 43%. Colorless oil; $^1$H NMR (396 MHz, CDCl$_3$, $\delta$): 1.31 (s, 12H), 2.35 (s, 3H), 3.84 (s, 3H), 3.93(s, 3H), 6.12 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, $\delta$): 13.9 (CH$_3$), 24.7 (CH$_3$), 51.9 (CH$_3$), 54.6 (CH$_3$), 83.6 (C), 115.1 (CH), 130.3 (C), 135.1 (C), 151.5 (C), 162.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]$^+$ calcd for C$_{15}$H$_{22}$BNO$_6$, 322.15765; found, 322.15669.
1-[5-Ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (3m).

The total NMR yield in the crude mixture was 81% (3m:4m = 97:3). The crude mixture was purified by Kugelrohr distillation (44 Pa, 130 °C) to obtain 3m (86.1 mg, 0.310 mmol, 62%) as a colorless oil from 1m (76.6 mg, 0.503 mmol). ¹H NMR (392 MHz, CDCl₃, δ): 1.20 (t, J = 7.4 Hz, 3H), 1.27 (t, J = 7.4 Hz, 3H), 1.32 (s, 12H), 2.77 (q, J = 7.3 Hz, 2H), 2.93 (q, J = 7.6 Hz, 2H), 7.31 (s, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.6 (CH₃), 13.0 (CH₃), 22.0 (CH₂), 24.7 (CH₃), 31.3 (CH₂), 85.5 (C), 123.5 (CH), 150.8 (C), 171.9 (C), 189.3 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₅H₂₃O₄⁺BNa, 300.16179; found, 300.16162.

1-[5-Ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4m).

The NMR yield of 4m in the crude mixture was 68%. The crude mixture was purified by Kugelrohr distillation (33 Pa, 140 °C) to obtain 4m (60.6 mg, 0.218 mmol, 44%) as a colorless oil from 1m (76.0 mg, 0.499 mmol). ¹H NMR (392 MHz, CDCl₃, δ): 1.18 (t, J = 7.3 Hz, 3H), 1.26 (t, J = 7.5 Hz, 3H), 1.38 (s, 12H), 2.70 (q, J = 7.5 Hz, 2H), 2.92 (q, J = 7.4 Hz, 2H), 6.27 (s, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.1 (CH₃), 11.8 (CH₃), 21.3 (CH₂), 24.7 (CH₃), 31.9 (CH₂), 84.2 (C), 111.5 (CH), 154.8 (C), 161.4 (C), 191.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₅H₂₃O₄⁺BNa, 300.16179; found, 300.16190.

1-[5-Cyclohexyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (3n).

The total NMR yield in the crude mixture was 86% (3n:4n = 94:6). The crude mixture was purified by Kugelrohr distillation (79 Pa, 200 °C) to obtain 3n (29.8 mg, 0.090 mmol, 18%) as a colorless oil from 1n (102.7 mg, 0.498 mmol). ¹H NMR (396 MHz, CDCl₃, δ): 1.19 (t, J = 7.5 Hz, 3H), 1.31 (s, 12H), 1.24–1.41 (m, 2H), 1.63–1.84 (m, 8H), 2.76 (q, J = 7.4 Hz, 2H), 3.15 (tt, J = 3.2, 11.9 Hz, 1H), 7.30 (s, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.6 (CH₃), 24.8 (CH₃), 25.7 (CH₂), 26.1 (CH₂), 31.3 (CH₂), 31.5 (CH₂), 38.2 (CH), 83.5 (C), 123.5 (CH), 150.6 (C), 174.5 (C), 189.4 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.
HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{19}$H$_{29}$O$_4^{10}$BNa, 354.20874; found, 354.20860.

1-[5-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4n).

The NMR yield of 4n in the crude mixture was 94%. The crude mixture was purified by Kugelrohr distillation (51 Pa, 200 °C) to obtain 4n (26.1 mg, 0.079 mmol, 16%) as a white solid from 1n (102.6 mg, 0.497 mmol). This product contains small amount of impurities. $^1$H NMR (392 MHz, CDCl$_3$, δ): 1.18 (t, $J = 7.4$ Hz, 3H), 1.22–1.45 (m, 5H), 1.38 (s, 12H), 2.01–2.04 (m, 2H), 2.63–2.70 (m, 1H), 2.91 (q, $J = 7.3$ Hz, 2H), 6.24 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 7.8 (CH$_3$), 24.6 (CH$_3$), 25.6 (CH$_2$), 25.8 (CH$_2$), 31.1 (CH$_2$), 31.8 (CH$_2$), 37.0 (CH), 84.1 (C), 110.2 (CH), 118.9 (br, B–C), 154.4 (C), 164.2 (C), 190.8 (C). HRMS-ESI (m/z): [M]$^+$ calcd for C$_{19}$H$_{29}$BO$_4$, 332.21589; found, 332.21729.

1-[5-(tert-Butyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4o).

The NMR yields of 4o in the crude mixture were 75% (catalytic system A) and 67% (catalytic system B). The crude mixture, which was produced under catalytic system A, was purified by Kugelrohr distillation (54 Pa, 180 °C) to obtain 4o (100.9 mg, 0.330 mmol, 66%) as a colorless oil from 1o (90.1 mg, 0.500 mmol). $^1$H NMR (392 MHz, CDCl$_3$, δ): 1.18 (t, $J = 7.3$ Hz, 3H), 1.30 (s, 9H), 1.39 (s, 12H), 2.91 (q, $J = 7.3$ Hz, 2H), 6.25 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): 7.8 (CH$_3$), 24.6 (CH$_3$), 28.7 (CH$_3$), 31.8 (CH$_2$), 32.8 (C), 84.1 (C), 109.3 (CH), 154.6 (C), 167.4 (C), 190.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+H]$^+$ calcd for C$_{17}$H$_{28}$O$_4^{11}$B, 332.21115; found, 332.21131.

1-[3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trimethylsilyl)furan-2-yl]propan-1-one (4p).

The NMR yields of 4p in the crude mixture were 58% (catalytic system A) and 48% (catalytic system B). The crude mixture, which was produced under catalytic system B, was purified by Kugelrohr distillation (83 Pa, 200 °C) to obtain 4p (55.7 mg, 0.168 mmol, 34%) as a colorless oil from 1p (97.5 mg, 0.497 mmol). This product contains small amount of impurities. $^1$H NMR (401 MHz, CDCl$_3$, δ): 0.29 (s, 9H), 1.19 (t, $J = 7.4$ Hz, 3H), 1.38 (s, 12H), 2.97 (q, $J = 7.3$ Hz, 2H), 6.81 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): −1.9 (CH$_3$), 7.7 (CH$_3$), 24.7 (CH$_3$), 32.2 (CH$_2$), 84.1
(C), 125.5 (CH), 160.0 (C), 164.3 (C), 191.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]^+ calcd for C_{16}H_{27}O_{10}BNaSi, 344.17002; found, 344.17025.

1-[4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)thiophen-2-yl]propan-1-one (3q).

The total NMR yield in the crude mixture was 80% (3q:4q = 56:44). The crude mixture was purified by Kugelrohr distillation (50 Pa, 100 °C) to obtain 3q (15.6 mg, 0.047 mmol, 9%) as a white solid from 1q (104.5 mg, 0.502 mmol). This product contains small amount of impurities. ^1H NMR (396 MHz, CDCl_3, δ): 1.23 (t, J = 7.5 Hz, 3H), 1.35 (s, 12H), 2.97 (q, J = 7.2 Hz, 2H), 7.88 (s, 1H). ^13C NMR (99 MHz, CDCl_3, δ): 8.2 (C_H_3), 24.6 (C_H_3), 32.5 (C_H_2), 84.6 (C), 121.8 (q, ^1J_{C-F} = 271.2 Hz, C_F_3), 137.4 (CH), 144.8 (q, ^2J_{C-F} = 36.6 Hz, C), 145.3 (C), 193.9 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): [M]^+ calcd for C_{14}H_{18}O_{11}BF_3O_3S, 334.10218; found, 334.10118.

1-[3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)thiophen-2-yl]propan-1-one (4q).

The NMR yield of 4q in the crude mixture was 75%. The crude mixture was purified by Kugelrohr distillation (28 Pa, 100 °C) to obtain 4q (54.0 mg, 0.162 mmol, 32%) as a white solid from 1q (105.1 mg, 0.505 mmol). This product contains small amount of impurities. ^1H NMR (396 MHz, CDCl_3, δ): 1.22 (t, J = 7.2 Hz, 3H), 1.41 (s, 12H), 3.01 (q, J = 7.2 Hz, 2H), 7.56 (s, 1H). ^13C NMR (100 MHz, CDCl_3, δ): 8.2 (CH_3), 24.7 (CH_3), 34.0 (CH_2), 84.8 (C), 121.8 (q, ^1J_{C-F} = 269.9 Hz, C_F_3), 134.0 (m, CH), 135.6 (q, ^2J_{C-F} = 38.5 Hz, C), 151.0 (C), 194.4 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]^+ calcd for C_{14}H_{18}O_{10}BF_3NaS, 356.09503; found, 356.09538.

1-[5-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]propan-1-one (3r).

The NMR yield of 3r in the crude mixture was 82%. The crude mixture was purified by Kugelrohr distillation (58 Pa, 180 °C) to obtain 3r (96.4 mg, 0.344 mmol, 77%) as a white solid from 1r (76.3 mg, 0.448 mmol). ^1H NMR (392
MHz, CDCl₃, δ): 1.20 (t, J = 7.3 Hz, 3H), 1.34 (s, 12H), 2.85 (q, J = 7.4 Hz, 2H), 4.05 (s, 3H), 7.74 (s, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.8 (CH₃), 24.6 (CH₃), 30.6 (CH₂), 61.8 (CH₂), 83.4 (C), 110.5 (br, B–C), 130.3 (C), 138.4 (CH), 182.2 (C), 193.3 (C). HRMS –ESI (m/z): [M+H]⁺ calcd for C₁₁H₂₂O₄, 296.13627; found, 296.13645.

1-[5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-yl]propan-1-one (3s).

The NMR yield of 3s in the crude mixture was 82%. The crude mixture was purified by Kugelrohr distillation (32 Pa, 160 °C) to obtain 3s (94.3 mg, 0.314 mmol, 63%) as a white solid from 1s (87.6 mg, 0.501 mmol). ¹H NMR (396 MHz, CDCl₃, δ): 1.21 (t, J = 7.5 Hz, 3H), 1.35 (s, 12H), 2.88 (q, J = 7.4 Hz, 2H), 7.74 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 8.3 (CH₃), 24.7 (CH₃), 31.5 (CH₂), 84.1 (C), 130.3 (br, B–C), 137.0 (CH), 142.3 (C), 148.4 (C), 193.2 (C). HRMS –ESI (m/z): [M+H]⁺ calcd for C₁₁H₁₈BCl₂S, 300.07582; found, 300.07679.

1-[5-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-yl]propan-1-one (4s).

The total NMR yield in the crude mixture was 46% (4s:3s = 74:26). The reaction mixture was first purified by flash column chromatography (SiO₂ containing 5 wt% B(OH)₃ as the eluent). Then, the resulting mixture was recrystallized from hexane. Finally, the resultant liquid phase was further purified by Kugelrohr distillation (38 Pa, 160 °C) to obtain 4s (217.8 mg, 0.725 mmol, 15%) as a colorless oil from 1s (873.0 mg, 5.00 mmol). This product contains small amount of impurities. ¹H NMR (396 MHz, CDCl₃, δ): 1.20 (t, J = 7.3 Hz, 3H), 1.40 (s, 12H), 2.90 (q, J = 7.3 Hz, 2H), 7.06 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 8.2 (CH₃), 24.6 (CH₃), 33.4 (CH₂), 84.4 (C), 132.2 (CH), 136.5 (C), 146.1 (C), 193.2 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+H]⁺ calcd for C₁₃H₂₀O₃BClS, 300.08673; found, 300.08763.

1-[5-Bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-yl]propan-1-one (3t).

The NMR yield of 3t in the crude mixture was 53%. The crude mixture was purified by Kugelrohr distillation (40 Pa, 190 °C) to obtain 3t (62.3 mg, 0.181 mmol, 36%) as a white solid from 1t (108.5 mg, 0.498 mmol). ¹H NMR (396 MHz, CDCl₃, δ): 1.21 (t, J = 7.3 Hz, 3H), 1.36 (s, 12H), 2.88 (q, J = 7.3 Hz, 2H), 7.71 (s, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 8.3 (CH₃), 24.8 (CH₃), 31.7 (CH₂), 84.2 (C), 131.9 (C), 137.6 (CH), 145.2 (C), 193.1 (C). The
carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₃H₁₆O₁₁B⁷⁹BrNaS, 366.01816; found, 366.01825.

Methyl 5-bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (3u).

The NMR yield of 3u in the crude mixture was 91%. The crude mixture was purified by Kugelrohr distillation (40 Pa, 180 °C) to obtain 3u (66.4 mg, 0.191 mmol, 39%) as a white solid from 3u (109.8 mg, 0.497 mmol). ¹H NMR (396 MHz, CDCl₃, δ): 1.34 (s, 12H), 3.86 (s, 3 H), 7.84 (s, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 24.8 (CH₃), 52.2 (CH₃), 84.2 (C), 129.7 (C), 134.0 (C), 139.7 (CH), 161.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-APCI (m/z): [M+H]⁺ calcd for C₁₂H₁₇O₁₁B⁷⁹BrO₄S, 348.00253; found, 348.00172.

Methyl 5-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (4u).

The NMR yield of 4u in the crude mixture was 20%. The reaction mixture was first purified by flash column chromatography (SiO₂ containing 5 wt% B(OH)₃, [¹¹³]EtOAc/hexane, 5:95 as the eluent). Then, the resulting mixture was purified by Kugelrohr distillation (50 Pa, 200 °C) to obtain 4u (63.3 mg, 0.182 mmol, 4%) as a colorless oil from 1u (1.11 g, 5.02 mmol). This product contains small amount of impurities. ¹H NMR (396 MHz, CDCl₃, δ): 1.39 (s, 12H), 3.86 (s, 3 H), 7.14 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 24.7 (CH₃), 52.3 (CH₃), 84.6 (C), 119.6 (C), 134.9 (CH), 138.7 (C), 161.9 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M⁺]⁺ calcd for C₁₂H₁₆¹¹³B⁸¹BrO₄S, 348.00253; found, 348.00172.

5-Bromo-N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3v).

The NMR yield of 3v in the crude mixture was 94%. The crude mixture was purified by Kugelrohr distillation (42 Pa, 190 °C) to obtain 3v (50.7 mg, 0.141 mmol, 31%) as a white solid from 1v (107.1 mg, 0.457 mmol). ¹H NMR (396 MHz, CDCl₃, δ): 1.34 (s, 12H), 3.18 (br s, 6H), 7.35 (s, 1H). ¹³C NMR (100 MHz, CDCl₃, δ): 24.7 (CH₃), 36.6 (br, CH₃), 39.4 (br, CH₃), 84.0 (C), 126.9 (C), 134.9 (CH), 139.4 (C), 162.9 (C). The carbon directly attached to the
boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]$^+$ calcd for $\text{C}_{13}\text{H}_{19}\text{O}_3\text{N}^{10}\text{B}^{79}\text{BrNaS}$, 381.02906; found, 381.02931.

5-Bromo-N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4v).

![5-Bromo-N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4v).](image)

The NMR yield of 4v in the crude mixture was 40%. The reaction mixture was first purified by flash column chromatography (SiO$_2$ containing 5 wt% B(OH)$_3$,[13] EtOAc/hexane, 5:95 as the eluent). Then, the resulting mixture was purified by Kugelrohr distillation (47 Pa, 200 °C) to obtain 4v (85.4 mg, 0.237 mmol, 5%) as a colorless oil from 1v (1.171 g, 5.00 mmol). This product contains small amount of impurities. $^1$H NMR (392 MHz, CDCl$_3$, $\delta$): 1.29 (s, 12H), 3.02 (br s, 6H), 7.22 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, $\delta$): 24.3 (CH$_3$), 34.7 (br, CH$_3$), 38.6 (br, CH$_3$), 83.2 (C), 112.5 (C), 132.2 (br, B–C), 133.8 (CH), 146.5 (C), 163.8 (C). HRMS-APCI (m/z): [M+H]$^+$ calcd for C$_{13}$H$_{20}$O$_3$N$^{10}$B$^{79}$BrS, 359.04712; found, 359.04742.

5-Bromo-N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (3w).

![5-Bromo-N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (3w).](image)

The NMR yield of 3w in the crude mixture was 99%. The crude mixture was purified by Kugelrohr distillation (26 Pa, 200 °C) to obtain 3w (55.1 mg, 0.160 mmol, 32%) as a white solid from 1w (110.2 mg, 0.505 mmol). $^1$H NMR (396 MHz, CDCl$_3$, $\delta$): 1.33 (s, 12H), 3.09 (br s, 3H), 3.24 (br s, 3H), 7.09 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, $\delta$): 24.5 (CH$_3$), 36.1 (br, CH$_3$), 38.1 (br, CH$_3$), 83.8 (C), 113.4 (br, B–C), 121.8 (CH), 132.6 (C), 149.2 (C), 158.8 (C). HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{13}$H$_{19}$O$_3$N$^{10}$B$^{79}$BrNa, 365.05190; found, 365.05200.

5-Bromo-N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (4w).

![5-Bromo-N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (4w).](image)

The NMR yield of 4w in the crude mixture was 56%. The crude mixture was first purified by Kugelrohr distillation (42 Pa, 190 °C). Then, the resulting mixture was recrystallized from hexane to obtain 4w (127.0 mg, 0.369 mmol, 12%) as a white solid from 1w (654.7 mg, 3.00 mmol). $^1$H NMR (392 MHz, CDCl$_3$, $\delta$): 1.32 (s, 12H), 3.10 (br s, 6H), 6.50 (s, 1H). $^{13}$C NMR (99 MHz, CDCl$_3$, $\delta$): 24.7 (CH$_3$), 35.8 (br, CH$_3$), 38.4 (br, CH$_3$), 84.0 (C), 116.1 (CH), 123.1 (C), 154.6 (C), 160.3 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{13}$H$_{19}$O$_3$N$^{10}$B$^{79}$BrNa, 365.05190; found, 365.05197.
5-Chloro-N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3x).

\[
\begin{align*}
\text{Cl} & \quad \text{S} & \quad \text{O} & \quad \text{NMe}_2 \\
\text{O} & \quad \text{B} & \quad \text{Cl} \\
\end{align*}
\]

The NMR yield of 3x in the crude mixture was 98%. The crude mixture was purified by Kugelrohr distillation (63 Pa, 180 °C) to obtain 3x (101.4 mg, 0.321 mmol, 64%) as a white solid from 1x (94.5 mg, 0.498 mmol). \(^1\)H NMR (396 MHz, CDCl\textsubscript{3}, δ): 1.34 (s, 12H), 3.18 (br s, 6H), 7.37 (s, 1H). \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}, δ): 24.7 (CH\textsubscript{3}), 36.6 (br, CH\textsubscript{3}), 39.3 (br, CH\textsubscript{3}), 83.9 (C), 129.0 (br, B–C), 134.1 (CH), 136.5 (C) 143.7 (C), 162.8 (C). HRMS-ESI (m/z): [M+Na]\textsuperscript{+} calcd for C\textsubscript{13}H\textsubscript{19}O\textsubscript{3}N\textsubscript{10}BClNaS, 337.07958; found, 337.07972.

5-Chloro-N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4x).

\[
\begin{align*}
\text{Cl} & \quad \text{S} & \quad \text{O} & \quad \text{NMe}_2 \\
\text{O} & \quad \text{B} & \quad \text{Cl} \\
\end{align*}
\]

The total NMR yield in the crude mixture was 74% (4x:3x = 87:13). The reaction mixture was first purified by flash column chromatography (SiO\textsubscript{2} containing 5 wt% B(OH)\textsubscript{3},\textsuperscript{[13]} EtOAc/hexane, 5:95 as the eluent). Then, the resulting mixture was purified by Kugelrohr distillation (57 Pa, 170 °C) to obtain 4x+3x (63:37) as a white solid. For 4x: \(^1\)H NMR (401 MHz, CDCl\textsubscript{3}, δ): 1.29 (s, 12H), 3.03 (br s, 6H), 7.07 (s, 1H). \(^{13}\)C NMR (99 MHz, CDCl\textsubscript{3}, δ): 24.8 (CH\textsubscript{3}), 35.8 (br, CH\textsubscript{3}), 39.3 (br, CH\textsubscript{3}), 83.8 (C), 130.6 (CH), 136.5 (C), 143.9 (C), 164.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. The regioisomer ratio (4x:3x = 63:37) that was observed after the isolation was found to be changed as compared to that was observed (4x:3x = 87:13) by \(^1\)H NMR measurement of the crude mixture, because of decomposition.

5-Methoxy-N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3y).

\[
\begin{align*}
\text{MeO} & \quad \text{S} & \quad \text{O} & \quad \text{NMe}_2 \\
\text{O} & \quad \text{B} & \quad \text{Cl} \\
\end{align*}
\]

The NMR yield of 3y in the crude mixture was 94%. The crude mixture was purified by Kugelrohr distillation (70 Pa, 200 °C) to obtain 3y (121.0 mg, 0.389 mmol, 78%) as a white solid from 1y (92.9 mg, 0.502 mmol). \(^1\)H NMR (392 MHz, CDCl\textsubscript{3}, δ): 1.32 (s, 12H), 3.20 (br s, 6H), 4.02 (s, 3H), 7.33 (s, 1H). \(^{13}\)C NMR (100 MHz, CDCl\textsubscript{3}, δ): 24.7 (CH\textsubscript{3}), 38.1 (br, CH\textsubscript{3}), 61.8 (CH\textsubscript{3}), 83.2 (C), 124.5 (C), 134.5 (CH), 163.7 (C), 178.5 (C). The carbon directly attached
to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]^+ calcd for C_{14}H_{23}O_{4}N_{10}^+BNaS, 333.12911; found, 333.12949.

5-Methoxy-N,N-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4y).

The NMR yield of 4y in the crude mixture was 93%. The crude mixture was purified by Kugelrohr distillation (40 Pa, 190 °C) to obtain 4y (75.3 mg, 0.242 mmol, 48%) as a white solid from 1y (93.0 mg, 0.502 mmol).^1^H NMR (392 MHz, CDCl_3, δ): 1.30 (s, 12H), 3.09 (s, 6H), 3.90 (s, 3H), 6.36 (s, 1H).^13^C NMR (99 MHz, CDCl_3, δ): 24.9 (CH_3), 37.5 (br, CH_2), 60.2 (CH_3), 82.7 (C), 106.9 (CH), 128.0 (C), 166.3 (C), 169.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]^+ calcd for C_{14}H_{23}O_{4}N_{10}^+BNaS, 333.12911; found, 333.12930.

Regiodivergent Synthesis of Biologically Active Furan Derivatives from 1w.


[Ir(OMe)(cod)]_2 (10.0 mg, 15 μmol), 2 (279 mg, 1.10 mmol) and dtbpy (8.0 mg, 30 μmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Octane (6.0 mL) was then added in the flask through the rubber septum using a syringe, and stirred at room temperature for 15 min. 1w (218.4 mg, 1.00 mmol) was then added to the reaction mixture, and stirred at 80 °C for 2 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure.

Without purification, PdCl_2(dppf)-CH_2Cl_2 (81.0 mg, 0.10 mmol), K_2PO_4 (1.27 g, 6.00 mmol) were added to the reaction mixture. The flask was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DME (3.0 mL), 1-chloro-3-iodobenzene (262.0 mg, 1.10 mmol) and H_2O (1.5 mL) were then added in the flask through the rubber septum using syringes, and stirred at room temperature for 30 min. 4-Fluorophenylboronic acid (279.8 mg, 2.00 mmol) was then added, and stirred at room temperature for 30 min. After the reaction was complete, the reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with H_2O and brine, and dried over MgSO_4. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 6 (160.5 mg, 0.467 mmol, 47%) as a syrup. ^1^H NMR (401 MHz, CDCl_3, δ): 3.15 (br s, 3H), 3.40 (br s, 3H), 7.00–7.06 (m, 2H), 7.13 (s, 1H), 7.24–7.34 (m, 3H), 7.38 (m, 1H), 7.48–7.53 (m, 2H).^13^C NMR (99 MHz, CDCl_3, δ): 36.4 (br, CH_3), 38.2 (br, CH_3), 115.6 (d, ^2^J_{C-F} = 21.6 Hz, CH), 119.4 (CH), 121.8 (C), 125.9 (d, ^3^J_{C-F} = 3.8 Hz, C), 126.6 (CH), 127.7 (CH), 128.4 (d, ^3^J_{C-F} = 4.7 Hz, CH), 128.5 (CH), 130.0 (CH), 134.5 (C), 134.7 (C), 146.7 (C), 149.0 (C), 159.7 (C), 162.6 (d, ^1^J_{C-F} = 249.0 Hz, C). HRMS-ESI (m/z): [M]^+ calcd for C_{10}H_{15}ClFNO_2, 343.07753; found, 343.07680.
The Procedure for One-pot Synthesis of 8.

[Ir(OMe)(cod)]₂ (33.1 mg, 50 μmol), 2 (277 mg, 1.09 mmol) and AsPh₃ (61.4 mg, 0.20 mmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Octane (6.0 mL) was then added in the flask through the rubber septum using a syringe, and stirred at room temperature for 15 min. 1w (208.0 mg, 1.0 mmol) was then added to the reaction mixture, and stirred at 120 °C for 9 h. After the reaction was complete, the reaction mixture was concentrated under reduced pressure.

Without purification, PdCl₂(dppf)·CH₂Cl₂ (88.0 mg, 0.11 mmol), K₃PO₄ (688 mg, 3.24 mmol) were added to the reaction mixture. The flask was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DME (1.5 mL), iodobenzene (125 mg, 0.61 mmol) and H₂O (0.75 mL) were then added in the flask through the rubber septum using syringes, and stirred at room temperature for 1 h. 3-Chlorophenylboronic acid (171 mg, 1.09 mmol) was then added, and stirred at room temperature for 24 h. After the reaction was complete, the reaction mixture was extracted with EtOAc three times. The combined organic layer was washed with H₂O and brine, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 8 (102.5 mg, 0.300 mmol, 30%) as a syrup. ¹H NMR (392 MHz, CDCl₃, δ): 2.86 (s, 3H), 3.09 (s, 3H), 6.91 (s, 1H), 7.30 (dq, J = 1.1, 8.0 Hz, 1H), 7.33–7.37 (m, 2H), 7.39–7.44 (m, 2H), 7.52–7.55 (m, 2H), 7.62 (dt, J = 1.4, 7.7 Hz, 1H), 7.73 (t, J = 1.8 Hz, 1H). ¹³C NMR (99 MHz, CDCl₃, δ): 34.8 (CH₃), 37.6 (CH₃), 107.1 (CH), 121.8 (CH), 123.6 (CH), 127.2 (CH), 127.5 (CH), 127.6 (CH), 128.3 (CH), 128.8 (C), 129.7 (CH), 130.9 (C), 131.2 (C), 134.2 (C), 141.2 (C), 151.9 (C), 161.5 (C). HRMS-El (m/z): [M]+ calcd for C_{19}H_{16}ClNO₂, 325.08696; found, 325.08639.
References


8) Smith and co-workers reported that the borylation of 5-bromo-2-cyano-thiophene was unsuccessful in the presence of Ir/dtbpy/HBpin/THF catalysis (ref. 2e), which is similar to our system A (Ir/dtbpy/2/octane).

Chapter 2.

Iridium(I)-catalyzed Vinlyic C–H Borylation of Acyclic $\alpha\beta$-Unsaturated Esters
Abstract
We developed a method for the iridium catalyzed vinyl C–H borylation of α,β-unsaturated esters using bis(pinacolato)diboron (B$_2$pin$_2$, 1). These reactions proceeded in octane at temperatures ranging from 80 to 120°C to give the corresponding alkenylboron compounds in high yields with excellent regio- and stereo-selectivities. The presence of the aryl ester resulted in a significant improvement in the yield of acyclic alkenyl boronates. This reaction proceeds via the 1,4-addition/β-hydride removal mechanism.

Introduction
β-borylated α,β-unsaturated carbonyl compounds are versatile intermediates in synthetic organic chemistry and their utility is demonstrated in the cross-coupling reaction, synthesis of optically active secondary alkylboron compounds, cycloaddition reactions as dienophiles, and radical acceptors.$^{1-4}$ The reported methods for the preparation of them include the hydroboration reaction of alkyne or cross-coupling reaction of vinyl triflates (Scheme 2-1).$^{5,6}$ But these methods are unable or difficult to apply the synthesis of tetra-substituted alkenylboron compounds. Hydroboration only afford di- or tetra-substituted product and there are a limited number of examples of carboboration.$^7$ In the case of cross-coupling reaction, tetra-substituted alkenyl halides and triflates are not readily available.


As a solution of this problem, direct vinylic C–H borylation of tri-substituted α,β-unsaturated carbonyl compounds would be one of the most efficient method. However, conventional borylation reactions using transition metal catalyst only proceed through 1,4-addition, and afford alkylboron compounds (Scheme 2-2).$^8$ To the best of our knowledge, there are no report on the vinylic C–H borylation of α,β-unsaturated carbonyl compounds.
Scheme 2-2. Transition metal-catalyzed borylation reaction of α,β-unsaturated carbonyl compounds.

Some representative examples of transition metal-catalyzed vinylic C–H borylation is shown in scheme 2-3. Szabo et al. reported C–H borylation of alkenyl compounds with a palladium pincer complex in 2010. This reaction proceeded at room temperature to afford the desired alkenylboronates in good yields, but it also afforded the corresponding allylboronates as byproducts. Iwasawa et al. reported the dehydrogenation reaction of alkenyl substrate using (PSiP)PdOTf as a catalyst in 2011. This borylation reaction proceeded smoothly to obtain the corresponding alkenyl boronic esters in high yields, although this reaction sometimes affords products as a mixture of E- and Z-isomers. Recently, we have reported the C–H borylation of alkenes using iridium catalyst. Although this particular reaction provided facile access to a wide range of alkenylboronates in high yield with good regioselectivity, it was only amenable to cyclic vinyl ether substrates.

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{Cu, Rh, Pt catalyst} & \quad \text{Cu, Rh, Pt catalyst} \\
\text{alkyl boronates} & \quad \text{alkenyl boronates} \\
& \quad \text{via 1,4-addition} \\
\text{via C–H borylation}
\end{align*}
\]

Scheme 2-3. Previously Reported Vinylic C–H borylation reactions

In addition, we recently reported the vinylic C–H borylation of α,β-unsaturated esters with an iridium catalyst. Borylation of 1-cyclohexene-1-carboxylic acid esters with 1 and Ir/2 AsPh₃ catalyst affords alkenyl boronic acid. Although, this particular reaction is easily accessible to a wide range of tetra-
substituted alkenylboronates in high yields with good regioselectivities, it was only amenable to cyclic vinyl ether substrates.

\[ \text{Scheme 2-4. Previously Reported Vinylic C–H borylation reactions} \]

Herein, we describe the development of a new process for vinylic C–H borylation of acyclic α,β-unsaturated esters 2 with 1, using an *in situ* generated iridium complex generated from the readily available \([\text{IrCl(cod)}]_2\) and \(\text{AsPh}_3\) as a catalyst, and in octane solvent at 80 or 120°C. Borylation of acyclic substrates would be more difficult than that of cyclic substrate because \(E/Z\) selectivity is problematic in the case of linear substrate. This reaction proceeded chemoselectively to give the corresponding alkenyl boron compounds 3 in high yield (Scheme 2-5). We also investigated the effect of carbonyl directing groups to the selectivity. The stereoselective borylation of acyclic compound 2 gave \((E)\)-alkenyl boronate 3. The mechanism of this reaction is consisted from the reaction of a sequential 1,4-addition /β-hydride elimination. Even the reaction of \(E/Z\) isomer mixture afford only \(E\) product selectively. This result also confirmed that iridium C-enolate is involved as an important intermediate determining the selectivity of the borylation reaction.

\[ \text{Scheme 2-5. This work} \]
Results and Discussion

The reaction of unsaturated methyl ester 2a with B2(pin)2 1 (1.1 equiv) in the presence of 1.5 mol% [Ir(Cl)(cod)]2 and 6.0 mol% AsPh3 in octane at 120°C afford the desired β-borylated product 3a in 43% yield. As a iridium precursor, [Ir(OMe)(cod)]2 gave 3a in slightly lower yields. We next investigated ligands for iridium catalyst. A variety of different monodentate phosphine ligands, including P[3,5-(CF)2C6H3]3, P(C6F5)3, PPh3, and P(4-MeO-C6H4)3 were also evaluated in this reaction, but found to be in effective (3a: 0–7% after 16 h; Table 2-1, entries 2–5). The yield of 3a decreased when bidentate ligands. Ligands often used in iridium-catalyzed C–H borylation, such as dtbpy or TMphen, proceed even in low yield. Other ligands did not afford the desired product. As a result, it is confirmed that AsPh3 is the best ligand for this catalytic system as well as the borylation of cyclic substrate.

Table 2-1. Investigation of ligands.[a]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>yield (%)</th>
<th>entry</th>
<th>ligand</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AsPh3</td>
<td>43</td>
<td>6</td>
<td>dtbpy</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>PPh3</td>
<td>7</td>
<td>7</td>
<td>phen</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>PCy3</td>
<td>6</td>
<td>8</td>
<td>Me4phen</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>P(OPh)3</td>
<td>0</td>
<td>9</td>
<td>dppe</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>P(C6F5)3</td>
<td>6</td>
<td>10</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>P[3,5-(CF)2-C6H3]3</td>
<td>trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>P(2-furyl)3</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Yields were determined by GC analysis.

Next, we investigated the directing groups. We investigated α,β-unsaturated ester, ketone, amide bearing two methyl groups at α and β position. (Table 2-2) The reaction of methyl and phenyl ester 2a, 2b afforded 3a and 3b in good yields in 3 hours (entries 1 and 2). On the other hand, phenyl ketone was fully consumed in 24 h, but desired product was not detected. (entry 3) And borylation of amide resulted in no reaction. (entries 4 and 5) Furthermore, borylation of Weinreb amide resulted in decomposition of substrate and the product was not detected (entry 6).
Table 2-2. Investigation of the directing groups.\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>time (h)</th>
<th>conv. of 2 (%)</th>
<th>conv. of 1 (%)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OMe (2a)</td>
<td>16</td>
<td>100</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>OPh (2b)</td>
<td>16</td>
<td>100</td>
<td>54</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>24</td>
<td>98</td>
<td>72</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>NMe\textsubscript{2}</td>
<td>24</td>
<td>0</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>N(iPr)\textsubscript{2}</td>
<td>48</td>
<td>28</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>NMe(OMe)</td>
<td>2</td>
<td>100</td>
<td>81</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Yields were determined by GC analysis.

With the optimized conditions in hand, we proceeded to examine the scope of this C–H borylation reaction using a variety of acyclic α,β-unsaturated esters (Table 2-3). The reaction of methyl (\textit{E})-2-methylbut-2-enoate 2a with 2.0 equivalents of 1 proceeded at 120 °C in the presence of [IrCl(cod)]\textsubscript{2} (1.5 mol %) as the catalyst precursor and AsPh\textsubscript{3} (6.0 mol %) as the ligand to afford the (\textit{E})-alkenylboronate 3a in moderate yield with excellent stereoselectivity. Several other alkyl (\textit{E})-2-methylbut-2-enotes, including the methoxy 3c and ethyl thioether 3d substrates showed moderate-to-low reactivity, with both reactions providing the \textit{E}-isomer exclusively (3c: 48 %, 3d: 21 %). Based on the higher yield of aryl ester 3b compared with 3a, we proceeded to examine the borylation of various aryl esters. The reactions of the para- and ortho-methoxyphenyl esters 2e and 2f proceeded smoothly to give the desired alkenylboronates 3e and 3f in 76 and 74 % yields, respectively. Notably, 2,4-dimethoxyphenyl ester 2g showed better reactivity than 3e or 2f to afford the corresponding (\textit{E})-alkenylboronate 3g in 82 % yield. However, the reaction of 2,4,6-trimethoxyphenyl ester 2h afforded only a moderate yield of the corresponding (E)-alkenylboronate 3g (64 %). The benzodioxole ester 2i, bearing an ortho-dialkoxyphenyl moiety, reacted with 1 to afford the boronate 3i in moderate yield (65 %). The borylation of para-dimethylaminophenyl ester 2j produced alkenylboronate 3j in 77 % yield. Several sterically congested substrates, including 4-methoxyphenyl-(\textit{E})-2-methylpent-2-enotes 2k and 4-methoxyphenyl-(\textit{E})-2-methyl-3-phenylacrylate 2l, were also evaluated but showed low reactivity, with the borylated products being isolated in low yields (3k: 41 %, 3l: 19 %). In all cases, the stereoselectivity of the product was completely retained, whilst the yield of the borylated compounds varied considerably.
The two catalytic cycles proposed for the current transformation are shown in Scheme 2-6. Both of these cycles would involve the initial formation of the mono- \((n=1)\) or tris- \((n=3)\) boryliridium complex \(A\) by the reaction of the corresponding Ir(I) complex with 1. According to pathway 1, the electron-donating oxygen atom of the ester group would coordinate to the Ir metal center of complex \(A\) to give complex \(B\), which would undergo an oxidative addition to the vinylic C–H bond to produce the pseudo metallacycle \(C\). The subsequent reductive elimination of the Ir–hydride complex \(D\) would lead to the formation of the desired products \(3a\). Finally, the oxidative addition of \(\text{B}_2\text{pin}_2\) to \(D\), followed by the reductive elimination of \(\text{H–Bpin}\), would regenerate \(A\). According to the pathway 2, complex \(B\) would undergo a 1,4-insertion reaction as opposed to an oxidative insertion reaction to the iridium enolate \(E\) (Scheme 2-6).\(^{14}\) The subsequent isomerization of \(E\) would afford the Ir complex \(F\), which would have an Ir–C bond with a \textit{syn}-configuration between the Ir center and the \(\beta\)-H atom. Finally, the \(\beta\)-hydride elimination of complex \(F\) would result in the formation of desired products \(3\) and \(D\). Although the above two mechanistic experiments could not give a decisive result, we currently suppose pathway 2 is more plausible.
This mechanism can explain the following stereo-convergent results by considering the enolate intermediate in pathway 2. When a 1:1 mixture of the (E)- and (Z)-isomers of 2e was used as the substrate, both of the isomers were consumed at the same rate. However, this reaction only afforded the (E)-isomer 3e as the major product (98:2) in 44 % yield (Scheme 2-7a). To develop a better understanding of this reaction, we investigated the borylation of a mixture of (Z)-2e and (E)-para-ethoxyphenyl ester 2m (Scheme 2-7b). The mixture of (Z)-2e and (E)-2m reacted with 2 to afford (E)-3e and (E)-3m in 15 and 71 % yields, respectively. Notably, the reaction of (Z)-2e alone under the optimized conditions also gave (E)-3e in 13 % yield. These results therefore suggested that the (E)- and (Z)-isomers were both reacting under these conditions to give a single isomer. The selectivity observed in this case therefore most likely occurred because of steric repulsion between the β-methyl group and the carbonyl group of the ester moiety.
It is noteworthy that the borylation of acyclic compounds under these conditions afforded the (E)-products selectively. This selectivity can be explained by the difference between the stability of configuration. There is an equilibrium between Ir C-enolate $E$ and Ir C-enolate $F$ and $F'$, which are diastereomers (Scheme 2-8). By proceeding β-elimination from Ir C-enolate $F$ to give (E)-alkenyl boronates, and β-elimination from $F'$ give Z-isomer. The configuration to β-elimination require syn-confirmation between Ir–C bond and C–H bond. In this configuration of $F$, carbonyl group coordinate to the boron atom. On the other hand, the configuration of $F$ is destabilized by the steric repulsion between carbonyl group and methyl group. As a result, $F'$ is relatively unstable than $E$ at the configuration to β-elimination. That is why β-elimination proceed selectively from $F$ to afford $E$ isomer.

**Scheme 2-7.** C–H Borylation reaction using E/Z mixture of substrate.

**Summary**

In summary, the iridium complexes prepared by the reaction of [Ir(Cl)(cod)]$_2$ with AsPh$_3$ have been shown to be efficient catalysts for the vinylic C–H borylation of acyclic α,β-unsaturated esters with 1. These borylation reactions proceeded at the vinylic position with good chemo- and stereoselectivity, even for substrates bearing an aryl group, which would normally react though their own C–H bonds under conventional Ir-catalyzed borylation conditions. This transformation proceeds through a sequential 1,4-addition/β-hydride elimination reactions.
**General and Materials.**

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, degassed via N\textsubscript{2} bubbling, and further dried over molecular sieves (MS 4 Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (\textsuperscript{1}H: 400 MHz and \textsuperscript{13}C: 100 MHz). Tetramethylsilane (\textsuperscript{1}H) and CDCl\textsubscript{3} (\textsuperscript{13}C) were employed as external standards, respectively. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with an ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. 1,4-Diisopropylbenzene was used as an internal standard to determine GC yield. [Ir(Cl)(cod)]\textsubscript{2} and [Ir(OMe)(cod)]\textsubscript{2} were synthesized according to the reported procedure. High-resolution mass spectra were recorded at the Center for Instrumental Analysis, Hokkaido University.

**General Experimental Procedures.**

A Representative Procedure for the Iridium(I)-catalyzed Vinylic C–H Borylation of 2a.

[Ir(Cl)(cod)]\textsubscript{2} (5.0 mg, 7.3 µmol), bis(pinacolato)diboron (1) (254 mg, 1.0 mmol) and AsPh\textsubscript{3} (9.2 mg, 30 µmol) were placed in an oven-dried two-necked flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Octane (3.0 mL) was then added in the flask through the rubber septum using a syringe, and stirred at room temperature for 10 min. Then, 2a (57.1 mg, 0.50 mmol) and 1,4-diisopropylbenzene (62.5 mg, internal standard) were then added to the reaction mixture using syringes, and stirred at 120 ºC. After the reaction was complete, the reaction mixture was concentrated and purified by flash column chromatography to give the corresponding alkenylboronate 3a.

The Procedure for the Iridium(I)-catalyzed Vinylic C–H Borylation of the E/Z mixture of 2e.

[Ir(Cl)(cod)]\textsubscript{2} (5.2 mg, 7.7 µmol), 1 (254 mg, 1.0 mmol) and AsPh\textsubscript{3} (9.3 mg, 30 µmol) were placed in an oven-dried two-necked flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Octane (3.0 mL) was then added in the flask through the rubber septum using a syringe, and stirred at room temperature for 10 min. Then, the solution of (E)-2e (56.3 mg, 0.27 mmol) and (Z)-2e (52.7 mg, 0.26 mmol) in octane (300 µL) and 1,4-diisopropylbenzene (67.6 mg, internal standard) were then added to the reaction mixture using syringes, and stirred at 120 ºC. After the reaction was complete, the reaction mixture was concentrated and purified by flash column chromatography (SiO\textsubscript{2}, EtOAc/hexane, 1:99–5:95) to give the corresponding alkenylboronate 3e (E/Z = 98:2).

A Representative Procedure for the Competition Experiment with 2e and 2m.

[Ir(Cl)(cod)]\textsubscript{2} (5.1 mg, 7.6 µmol), 1 (253.3 mg, 1.00 mmol) and AsPh\textsubscript{3} (9.1 mg, 30 µmol) were placed in an oven-dried two-necked flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Octane (3.0 mL) was then added in the flask through the rubber septum using a syringe, and stirred at room temperature for 10 min. Then, the solution of 2e (51.9 mg, 0.25 mmol) and 2m (55.9 mg, 0.25 mmol) in octane (300 µL) and 1,4-diisopropylbenzene (76.1 mg, internal standard) were then added to the reaction mixture using syringes, and stirred at 120 ºC. The yields of the products were decided based on 3 by GC.
Preparation of Substrates.

The starting material 2a was purchased from commercial supplier.

Preparation of phenyl (E)-2-methylbut-2-enoate (2b).

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{C} & \quad \text{C}
\end{align*}
\]

To an oven-dried flask, tiglic acid (5.00 g, 50.0 mmol), phenol (4.70 g, 50.0 mmol) and sulfuric acid (0.15 mL) were dissolved in toluene (75 mL) under nitrogen atmosphere at room temperature. The reaction mixture was refluxed under a Dean-Stark trap for 20 h. After cooling to room temperature, the solution was washed with 2 N NaOH (100 mL) and iced-water (100 mL). The aqueous layer was extracted with toluene, and dried over MgSO\(_4\). After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 3d (6.09 g, 34.6 mmol, 69%) as a white solid. \(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 1.88 (dq, \(J = 1.1\), 7.0 Hz, 3H), 1.96 (q, \(J = 1.1\) Hz, 3H), 7.09–7.14 (m, 3H), 7.20–7.24 (m, 1H), 7.36–7.41 (m, 2H). \(^13\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 12.2 (CH\(_2\)), 14.6 (CH\(_3\)), 121.7 (CH), 125.5 (CH), 128.2 (C), 128.3 (CH), 139.3 (CH), 151.1 (C), 166.6 (C). HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{11}\)H\(_{12}\)O\(_2\)Na, 199.07295; found, 199.07301.

Preparation of 2-methoxyethyl (E)-2-methylbut-2-enoate (2c).

\[
\begin{align*}
\text{O} & \quad \text{OMe} \\
\text{C} & \quad \text{C}
\end{align*}
\]

To an oven-dried flask, tiglic acid (2.00 g, 20.0 mmol) and 2-methoxyethanol (1.52 g, 20.0 mmol) were dissolved in CH\(_2\)Cl\(_2\) (100 mL) under nitrogen atmosphere at room temperature. DCC (6.19 g, 30.0 mmol) and DMAP (1.20 g, 10.0 mmol) were then added at 0 °C, and the reaction mixture was stirred for 21 h at room temperature. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 2b (1.80 g, 11.4 mmol, 57%) as a colorless oil. \(^1\)H NMR (392 MHz, CDCl\(_3\), \(\delta\)): 1.78–1.80 (m, 3H), 1.85 (t, \(J = 1.3\) Hz, 3H), 3.40 (s, 3H), 3.63–3.65 (m, 2H), 4.27–4.30 (m, 2H), 6.90 (qq, \(J = 1.4\), 7.1 Hz, 1H). \(^13\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 11.7 (CH\(_3\)), 14.0 (CH\(_2\)), 58.6 (CH\(_3\)), 63.2 (CH\(_2\)), 70.3 (CH\(_2\)), 128.1 (C), 137.2 (CH), 167.6 (C). HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{9}\)H\(_{14}\)O\(_3\)Na, 181.08352; found, 181.08400.

Preparation of 2-(ethylthio)ethyl (E)-2-methylbut-2-enoate (2d).

\[
\begin{align*}
\text{O} & \quad \text{SEt} \\
\text{C} & \quad \text{C}
\end{align*}
\]

2d (1.20 g, 6.39 mmol, colorless oil) was prepared in 64% from tiglic acid (1.00 g, 10.0 mmol) and 2-(ethylthio)ethanol (1.06 g, 10.0 mmol) according to the procedure for the synthesis of 2c. \(^1\)H NMR (392 MHz, CDCl\(_3\), \(\delta\)): 1.28 (t, \(J = 7.3\) Hz, 3H), 1.79–1.81 (m, 3H), 1.836–1.843 (m, 3H), 2.61 (q, \(J = 7.3\) Hz, 2H), 2.79 (t, \(J = 7.0\) Hz, 2H), 4.29 (t, \(J = 7.0\) Hz, 2H), 6.88 (qq, \(J = 1.4\), 7.1 Hz, 1H). \(^13\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 11.7 (CH\(_3\)), 14.1 (CH\(_3\)), 14.6 (CH\(_3\)), 25.9 (CH\(_2\)), 29.8 (CH\(_2\)), 63.4 (CH\(_2\)), 128.2 (C), 137.3 (CH), 167.5 (C). HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{9}\)H\(_{14}\)O\(_3\)S, 211.07632; found, 211.07670.
Preparation of 4-methoxyphenyl (E)-2-methylbut-2-enoate (3e).

2e (2.44 g, 11.9 mmol, white solid) was prepared in 59% from tiglic acid (2.00 g, 20.0 mmol) and 4-methoxyphenol (2.48 g, 20.0 mmol) according to the procedure for the synthesis of 2b. \(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 1.87 (dq, \(J = 0.9, 7.2\) Hz, 3H), 1.94–1.95 (m, 3H), 3.80 (s, 3H), 6.89 (dt, \(J = 2.9, 10.0\) Hz, 2H), 6.99–7.02 (m, 2H), 7.06–7.13 (m, 1H). \(^13\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 12.0 (CH\(_3\)), 14.4 (CH\(_3\)), 55.4 (CH\(_3\)), 114.2 (CH), 122.3 (CH), 128.0 (C), 139.0 (CH), 144.4 (C), 156.9 (C), 166.7 (C). HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{12}\)H\(_4\)O\(_3\)Na, 229.08352; found, 229.08405.

Preparation of 2-methoxyphenyl (E)-2-methylbut-2-enoate (2f).

2f (1.02 g, 49.5 mmol, white solid) was prepared in 50% from tiglic acid (1.00 g, 10.0 mmol) and 2-methoxyphenol (1.24 g, 10.0 mmol) according to the procedure for the synthesis of 2b. \(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 1.88 (d, \(J = 6.8\) Hz, 3H), 1.96 (s, 3H), 3.82 (s, 3H), 6.92–6.98 (m, 2H), 7.04 (dt, \(J = 1.8, 7.7\) Hz, 1H), 7.10–7.22 (m, 2H). \(^13\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 11.9 (CH\(_3\)), 14.2 (CH\(_3\)), 55.5 (CH\(_3\)), 112.1 (CH), 120.4 (CH), 122.7 (CH), 126.3 (CH), 127.6 (C), 138.9 (CH), 139.9 (C), 151.1 (C), 165.7 (C). HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{12}\)H\(_4\)O\(_3\)Na, 229.08352; found, 229.08391.

Preparation of 2,4-dimethoxyphenyl (E)-2-methylbut-2-enoate (2g).

2,4-Dimethoxyphenol (3.62 g, 23.5 mmol) was prepared in 78% yield from 2,4-dimethoxybenzaldehyde (5.01 g, 30.1 mmol) according to the reported procedure. 2g (1.44 g, 6.08 mmol, white solid) was prepared in 61% from tiglic acid (1.01 g, 10.1 mmol) and 2,4-dimethoxyphenol (1.56 g, 10.1 mmol) according to the procedure for the synthesis of 2b. \(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 1.87 (dq, \(J = 1.1, 7.0\) Hz, 3H), 1.949–1.955 (m, 3H), 3.79 (s, 3H), 3.80 (s, 3H), 6.45 (dd, \(J = 2.7, 8.6\) Hz, 1H), 6.54 (d, \(J = 2.7\) Hz, 1H), 6.95 (d, \(J = 8.6\) Hz, 1H), 7.11 (qq, \(J = 1.4, 7.7\) Hz, 1H). \(^13\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 12.2 (CH\(_3\)), 14.5 (CH\(_3\)), 55.5 (CH\(_3\)), 55.8 (CH\(_3\)), 100.1 (CH), 103.7 (CH), 122.8 (CH), 127.9 (C), 133.8 (C), 139.1 (CH), 151.9 (C), 158.1 (C), 166.5 (C). HRMS–EI (m/z): [M]\(^+\) calcd for C\(_{13}\)H\(_{16}\)O\(_4\), 236.10486; found, 236.10442.
Preparation of 2,4,6-trimethoxyphenyl (E)-2-methylbut-2-enoate (2h).

2,4,6-Trimethoxyphenol (4.50 g, 24.5 mmol, white solid) was prepared in 82% from 2,4,6-
trimethoxybenzaldehyde (5.89 g, 30.0 mmol) according to the procedure for the synthesis of 2,4-dimethoxyphenol. 
2h (1.07 g, 4.03 mmol, white solid) was prepared in 40% from tiglic acid (1.01 g, 10.1 mmol) and 2,4,6-
trimethoxyphenol (1.85 g, 10.0 mmol) according to the procedure for the synthesis of 2b. 

H NMR (396 MHz, CDCl₃, δ): 1.87 (dq, J = 1.1, 7.0 Hz, 3H), 1.956–1.963 (m, 3H), 3.79 (s, 6H), 3.80 (s, 3H), 6.18 (s, 2H), 7.15 (qq, J = 1.4, 7.1 Hz, 1H). 

C NMR (100 MHz, CDCl₃, δ): 12.1 (CH₃), 14.4 (CH₃), 55.3 (CH₃), 55.9 (CH₃), 91.2 (CH), 122.7 (C), 127.6 (C), 138.9 (CH), 152.6 (C), 157.9 (C), 166.0 (C). HRMS – EI (m/z): [M]+ calcd for C₁₄H₁₀O₅, 266.11542; found, 266.11521.

Preparation of benzo[d][1,3]dioxol-5-yl (E)-2-methylbut-2-enoate (2i).

2i (1.73 g, 7.87 mmol, white solid) was prepared in 78% from tiglic acid (1.01 g, 10.1 mmol) and sesamol (1.38 g, 10.0 mmol) according to the procedure for the synthesis of 2b. 

H NMR (392 MHz, CDCl₃, δ): 1.87 (dq, J = 1.4, 7.2 Hz, 3H), 1.93–1.94 (m, 3H), 5.98 (s, 2H), 6.53 (dd, J = 2.2, 8.5 Hz, 1H), 6.62 (d, J = 2.2 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 7.05–7.12 (m, 1H). 

C NMR (100 MHz, CDCl₃, δ): 12.0 (CH₃), 14.5 (CH₃), 101.5 (CH₂), 103.8 (CH), 107.8 (CH), 113.9 (CH), 127.9 (C), 139.3 (CH), 145.0 (C), 145.3 (C), 147.8 (C), 166.7 (C). HRMS – EI (m/z): [M]+ calcd for C₁₂H₂₂O₄, 220.07356; found, 220.07339.

Preparation of 4-(dimethylamino)phenyl (E)-2-methylbut-2-enoate (2j).

4-(Dimethylamino)phenol (2.16 g, 15.8 mmol, white solid) was prepared in 40% yield from 4-aminophenol (4.36 g, 40.0 mmol) according to the reported procedure. 
2j (1.61 g, 7.34 mmol, white solid) was prepared in 73% from tiglic acid (1.01 g, 10.1 mmol) and 4-(dimethylamino)phenol (1.37 g, 10.0 mmol) according to the procedure for the synthesis of 2b. 

H NMR (396 MHz, CDCl₃, δ): 1.87 (dq, J = 0.9, 7.2 Hz, 3H), 1.938–1.944 (m, 3H), 2.93 (s, 6H), 6.72 (dt, J = 3.1, 10.3 Hz, 2H), 6.96 (dt, J = 2.9, 10.0 Hz, 2H), 7.08 (qq, J = 1.7, 7.7 Hz, 1H). 

C NMR (100 MHz, CDCl₃, δ): 12.1 (CH₃), 14.5 (CH₃), 40.9 (CH₃), 113.1 (CH), 121.8 (CH), 128.3 (C), 138.6 (CH), 141.9 (C), 148.4 (C), 167.1 (C). HRMS – EI (m/z): [M]+ calcd for C₁₃H₁₇NO₂, 219.12593; found, 219.12525.

Preparation of 4-methoxyphenyl (E)-2-methylpent-2-enoate (2k).

4-Methoxyphenol (2.16 g, 15.8 mmol, white solid) was prepared in 40% yield from 4-aminophenol (4.36 g, 40.0 mmol) according to the reported procedure. 
2k (1.61 g, 7.34 mmol, white solid) was prepared in 73% from tiglic acid (1.01 g, 10.1 mmol) and 4-(dimethylamino)phenol (1.37 g, 10.0 mmol) according to the procedure for the synthesis of 2b. 

H NMR (396 MHz, CDCl₃, δ): 1.87 (dq, J = 0.9, 7.2 Hz, 3H), 1.938–1.944 (m, 3H), 2.93 (s, 6H), 6.72 (dt, J = 3.1, 10.3 Hz, 2H), 6.96 (dt, J = 2.9, 10.0 Hz, 2H), 7.08 (qq, J = 1.7, 7.7 Hz, 1H). 

C NMR (100 MHz, CDCl₃, δ): 12.1 (CH₃), 14.5 (CH₃), 40.9 (CH₃), 113.1 (CH), 121.8 (CH), 128.3 (C), 138.6 (CH), 141.9 (C), 148.4 (C), 167.1 (C). HRMS – EI (m/z): [M]+ calcd for C₁₃H₁₇NO₂, 219.12593; found, 219.12525.
4-Methoxyphenyl propionate (9.16 g, 50.8 mmol, colorless oil) was prepared in 91% yield from propionyl chloride (15.5 g, 168 mmol) and 4-methoxyphenol (6.95 g, 56.0 mmol) according to the reported procedure.\(^5\) To an oven-dried flask, (i-Pr)\(_2\)NH (1.21 g, 12.0 mmol) were dissolved in THF (70 ml) under nitrogen atmosphere at room temperature. A hexane solution of n-BuLi (2.6 M, 4.6 mL, 12.0 mmol) was slowly added dropwise at −78 °C, and the mixture was warmed to 0 °C and stirred for 1 h. The mixture was then cooled to −78 °C, a solution of 4-methoxyphenyl propionate (1.98 g, 11.0 mmol) in THF (20 mL) was then added to the reaction mixture using a syringe, and stirred at the same temperature for 45 min. Propanal (639 mg, 11.0 mmol) was then added to the reaction mixture, and stirred the same temperature for 25 min. The reaction mixture was quenched with saturated aqueous solution of NH\(_4\)Cl, and extracted with Et\(_2\)O three times. The combined organic layer was washed with brine, and dried over MgSO\(_4\). After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 4-methoxyphenyl 3-hydroxy-2-methylpentanoate (828 mg, 3.48 mmol, 32%) as a colorless oil.

To an oven-dried flask, under nitrogen atmosphere, 4-methoxyphenyl 3-hydroxy-2-methylpentanoate (630.0 mg, 2.64 mmol) and methanesulfonyl chloride (700.0 mg, 6.11 mmol) were dissolved in CH\(_2\)Cl\(_2\) (6.0 ml) at −30 °C. The reaction mixture was extracted with CH\(_2\)Cl\(_2\) three times. The combined organic layer was washed with 1 M HCl aqueous solution and brine, and dried over MgSO\(_4\). After filtration, the solvents were removed by evaporation. The product was used in the next reaction without further purification.

To an oven-dried flask, under nitrogen atmosphere, obtained crude product and DBU (1.30 g, 8.54 mmol) was dissolved in CH\(_2\)Cl\(_2\) (6.0 ml) at 0 °C, and stirred at the same temperature for 1 h. The reaction mixture was extracted with CH\(_2\)Cl\(_2\) three times. The combined organic layer was washed with 1 M HCl aqueous solution and brine, and dried over MgSO\(_4\). After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 2k (368 mg, 1.67 mmol, 63%) as a white solid. \(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 1.10 (t, \(J = 7.5\) Hz, 3H), 1.94 (s, 3H), 2.23–2.30 (m, 2H), 3.80 (s, 3H), 6.89 (dt, \(J = 2.8, 9.8\) Hz, 2H), 6.96–7.04 (m, 3H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 12.3 (CH\(_3\)), 12.9 (CH\(_3\)), 22.1 (CH\(_2\)), 55.4 (CH\(_3\)), 114.3 (CH), 122.4 (CH), 126.6 (C), 144.5 (C), 145.8 (CH), 156.9 (C), 167.0 (C). HRMS–EI (m/z): [M]+ calcd for C\(_{13}\)H\(_{16}\)O\(_5\); 268.10994; found, 220.10937.

### Preparation of 4-methoxyphenyl (E)-2-methyl-3-phenylacrylate (2l).

![Chemical Structure](image)

2l (2.14 g, 7.97 mmol, white solid) was prepared in 80% from \(\alpha\)-methylcinnamic acid (1.62 g, 10.0 mmol) and 4-methoxyphenol (1.24 g, 10.0 mmol) according to the procedure for the synthesis of 2b. \(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 2.24 (d, \(J = 1.4\) Hz, 3H), 3.82 (s, 3H), 6.93 (dt, \(J = 2.9, 10.0\) Hz, 2H), 7.09 (dt, \(J = 2.9, 10.0\) Hz, 2H), 7.36 (tt, \(J = 1.9, 7.0\) Hz, 1H), 7.41–7.48 (m, 4H), 7.91 (s, 1H). \(^{13}\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 14.4 (CH\(_3\)), 55.7 (CH\(_3\)), 114.6 (CH), 122.5 (CH), 127.9 (C), 128.6 (CH), 128.7 (CH), 129.9 (CH), 135.8 (C), 140.5 (CH), 144.7 (C), 157.3 (C), 167.7 (C). HRMS–EI (m/z): [M]+ calcd for C\(_{17}\)H\(_{16}\)O\(_3\), 268.10994; found, 268.10915.

63
Preparation of 4-methoxyphenyl (Z)-2-methylbut-2-enoate ((Z)-2e).

To an oven-dried flask, angelic acid (904 mg, 9.03 mmol) and 4-methoxyphenol (1.12 g, 9.03 mmol) were dissolved in CH$_2$Cl$_2$ (45 mL) under nitrogen atmosphere at room temperature. EDC·HCl (2.60 g, 13.5 mmol) and DMAP (551.6 mg, 4.5 mmol) were then added at 0 °C and the reaction mixture was stirred for 4 h at room temperature. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain (Z)-2e (809.1 mg, 3.92 mmol, 43%) as a white solid. 

$^{1}$H NMR (396 MHz, CDCl$_3$, δ): 2.03–2.04 (m, 3H), 2.06–2.09 (m, 3H), 3.80 (s, 3H), 6.21–6.27 (m, 1H), 6.90 (dt, $J = 2.9$, 10.0 Hz, 2H), 7.03 (dt, $J = 2.9$, 10.0 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 15.9 (CH$_3$), 20.6 (CH$_3$), 55.6 (CH$_3$), 114.4 (CH), 122.4 (CH), 127.2 (CH), 140.3 (CH), 144.1 (C), 157.1 (C), 166.6 (C). HRMS–ESI (m/z): [M+Na]$^+$ calcd for C$_{12}$H$_{14}$O$_3$Na, 229.08352; found, 229.08385.

Preparation of 4-ethoxyphenyl (E)-2-methylbut-2-enoate (2m).

2m (1.83 g, 8.33 mmol, white solid) was prepared in 83% from tiglic acid (1.00 g, 10.0 mmol) and 4-ethoxyphenol (1.38 g, 10.0 mmol) according to the procedure for the synthesis of 2b. $^{1}$H NMR (396 MHz, CDCl$_3$, δ): 1.41 (t, $J = 7.0$ Hz, 3H), 1.87 (dq, $J = 1.1$, 7.0 Hz, 3H), 1.939–1.944 (m, 3H), 4.02 (q, $J = 7.1$ Hz, 2H), 6.88 (dt, $J = 2.8$, 9.8 Hz, 2H), 7.00 (dt, $J = 2.9$, 10.0 Hz, 2H), 7.06–7.12 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 11.8 (CH$_3$), 14.1 (CH$_3$), 14.4 (CH$_3$), 63.3 (CH$_2$), 114.5 (CH), 122.0 (CH), 127.8 (C), 138.6 (CH), 144.1 (C), 156.1 (C), 166.3 (C). HRMS–EI (m/z): [M]$^+$ calcd for C$_{13}$H$_{16}$O$_3$, 220.10994; found, 220.10959.
2. Characterization of Borylation Products.

Methyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3a).

![Structure of 3a](image)

$^1$H NMR (396 MHz, CDCl$_3$, δ): 1.34 (s, 12H), 1.82 (q, $J = 0.9$ Hz, 3H), 1.84 (q, $J = 1.3$ Hz, 3H), 3.77 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 11.8 (CH$_3$), 16.5 (CH$_3$), 24.6 (CH$_3$), 52.1 (CH$_3$), 82.9 (C), 131.6 (C), 149.1 (br, B–C), 170.7 (C). HRMS–ESI (m/z): [M+Na]$^+$ calecd for C$_{12}$H$_{21}$O$_4$Na, 262.14614; found: 262.14619.

2-Methoxyethyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3c).

![Structure of 3c](image)

$^1$H NMR (401 MHz, CDCl$_3$, δ): 1.33 (s, 12H), 1.84 (s, 6H), 3.38 (s, 3H), 3.62 (t, $J = 4.8$ Hz, 2H), 4.32 (t, $J = 4.8$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 11.9 (CH$_3$), 16.7 (CH$_3$), 24.7 (CH$_3$), 58.9 (CH$_3$), 64.4 (CH$_2$), 70.3 (CH$_2$), 83.1 (C), 131.9 (C), 170.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]$^+$ calecd for C$_{14}$H$_{25}$O$_4$Na, 306.17236; found, 306.17305.

2-(Ethylthio)ethyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3d).

![Structure of 3d](image)

$^1$H NMR (396 MHz, CDCl$_3$, δ): 1.27 (t, $J = 7.2$ Hz, 3H), 1.33 (s, 12H), 1.82 (q, $J = 0.9$ Hz, 3H), 1.84 (q, $J = 0.9$ Hz, 3H), 2.59 (q, $J = 7.4$ Hz, 2H), 2.78 (t, $J = 7.2$ Hz, 2H), 4.31 (t, $J = 7.2$ Hz, 2H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): 11.9 (CH$_3$), 14.7 (CH$_3$), 16.7 (CH$_3$), 24.7 (CH$_3$), 26.1 (CH$_2$), 29.6 (CH$_2$), 64.6 (CH$_2$), 83.1 (C), 131.8 (C), 170.3 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]$^+$ calecd for C$_{15}$H$_{27}$O$_4$NaS, 336.16516; found, 336.16608.

Phenyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3b).

![Structure of 3b](image)

$^1$H NMR (396 MHz, CDCl$_3$, δ): 1.25 (s, 12H), 1.92 (q, $J = 0.9$ Hz, 3H), 1.98 (q, $J = 0.9$ Hz, 3H), 7.07–7.13 (m, 2H), 7.20–7.24 (m, 1H), 7.35–7.39 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 12.8 (CH$_3$), 17.3 (CH$_3$), 24.7 (CH$_3$), 83.5 (C), 121.8 (CH), 125.6 (CH), 129.2 (CH), 132.2 (C), 150.8 (C), 167.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]$^+$ calecd for C$_{17}$H$_{23}$O$_4$Na, 324.16179; found, 324.16187.

4-Methoxyphenyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3e).
Benzo\[d\][1,3]dioxol-5-yl (E)-2-methyl-3(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3f).

\[
\text{3f}
\]

\[\text{1H NMR (396 MHz, CDCl}_3, \delta): 1.23 (s, 12H), 1.92 (q, J = 0.9 Hz, 3H), 2.00 (q, J = 1.3 Hz, 3H), 3.79 (s, 3H), 6.90–6.97 (m, 2H), 7.07 (dd, J = 1.6, 7.9 Hz, 1H), 7.16–7.20 (m, 1H). 13C NMR (100 MHz, CDCl3, δ): 12.9 (CH3), 17.3 (CH3), 24.7 (CH3), 55.8 (CH3), 83.4 (C), 112.5 (CH), 120.5 (CH), 123.0 (CH), 126.6 (CH), 132.2 (C), 139.9 (C), 151.4 (C), 166.9 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–ESI (m/z): [M+Na]\(^+\) calcd for C\(_{18}\)H\(_{23}\)O\(_3\)B\(_3\)Na, 354.17334; found: 354.17334.\]

2,4-Dimethoxyphenyl (E)-2-methyl-3(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3g).

\[
\text{3g}
\]

\[\text{1H NMR (392 MHz, CDCl}_3, \delta): 1.23 (s, 12H), 1.91 (q, J = 0.9 Hz, 3H), 1.98 (q, J = 0.9 Hz, 3H), 3.77 (s, 3H), 3.80 (s, 3H), 6.43 (dd, J = 2.7, 9.0 Hz, 1H), 6.52 (d, J = 2.7 Hz, 1H), 6.97 (d, J = 8.5 Hz, 1H). 13C NMR (99 MHz, CDCl3, δ): 12.8 (CH3), 17.2 (CH3), 24.6 (CH3), 55.3 (CH3), 55.6 (CH3), 83.2 (C), 100.0 (CH), 103.5 (CH), 122.8 (CH), 132.0 (C), 133.5 (C), 147.5 (br, B–C), 151.8 (C), 158.0 (C), 167.0 (C). HRMS–ESI (m/z): [M]\(^+\) calcd for C\(_{19}\)H\(_{25}\)B\(_3\)O\(_6\), 361.19370; found: 361.19285.\]

2,4,6-trimethoxyphenyl (E)-2-methyl-3(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3h).

\[
\text{3h}
\]

\[\text{1H NMR (396 MHz, CDCl}_3, \delta): 1.23 (s, 12H), 1.90 (q, J = 0.9 Hz, 3H), 2.00 (q, J = 1.3 Hz, 3H), 3.76 (s, 6H), 3.79 (s, 3H), 6.15 (s, 2H). 13C NMR (100 MHz, CDCl3, δ): 13.0 (CH3), 17.2 (CH3), 24.7 (CH3), 55.4 (CH3), 56.0 (CH3), 83.2 (C), 91.5 (CH), 123.0 (C), 132.1 (C), 147.3 (br, B–C), 152.7 (C), 158.0 (C), 166.7 (C). HRMS–EI (m/z): [M]\(^+\) calcd for C\(_{20}\)H\(_{25}\)B\(_3\)O\(_5\), 391.20426; found: 391.20307.\]

Benzo[d][1,3]dioxol-5-yl (E)-2-methyl-3(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3i).
4-(Dimethylamino)phenyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3j).

\[
\text{(pin)BO} \quad \text{O} \quad \text{O} \quad \text{NMe}_2
\]

\[3j\]

\(^1\)H NMR (392 MHz, CDCl\(_3\), \(\delta\)): 1.25 (s, 12H), 1.91 (q, \(J = 0.7\) Hz, 3H), 1.96 (q, \(J = 1.1\) Hz, 3H), 2.93 (s, 6H). 6.69 (dt, \(J = 2.9, 9.9\) Hz, 2H), 6.98 (dt, \(J = 2.9, 9.9\) Hz, 2H). \(^1\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 12.7 (CH\(_3\)), 17.1 (CH\(_3\)), 24.7 (CH\(_3\)), 40.8 (CH\(_3\)), 83.3 (C), 112.7 (CH), 121.9 (CH), 132.3 (C), 141.6 (C), 147.7 (br, B–C), 148.4 (C), 168.0 (C). HRMS–EI (m/z): [M]+ calcd for C\(_{19}\)H\(_{25}\)BO\(_{2}\), 344.21477; found, 344.21401.

4-Methoxyphenyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate (3k).

\[
\text{(pin)BO} \quad \text{O} \quad \text{O} \quad \text{OMe}
\]

\[3k\]

\(^1\)H NMR (401 MHz, CDCl\(_3\), \(\delta\)): 1.10 (t, \(J = 7.6\) Hz, 3H), 1.26 (s, 12H), 1.97 (s, 3H), 2.34 (q, \(J = 7.6\) Hz, 2H), 3.80 (s, 3H), 6.87 (dt, \(J = 3.0, 10.0\) Hz, 2H), 7.03 (dt, \(J = 2.8, 9.7\) Hz, 2H). \(^1\)C NMR (99 MHz, CDCl\(_3\), \(\delta\)): 12.2 (CH\(_3\)), 12.5 (CH\(_3\)), 24.9 (CH\(_3\)), 25.0 (CH\(_3\)), 55.4 (CH\(_3\)), 83.5 (C), 114.1 (CH), 122.5 (CH), 131.5 (C), 144.3 (C), 157.0 (C), 168.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS–EI (m/z): [M]+ calcd for C\(_{19}\)H\(_{27}\)BO\(_{5}\), 345.19775; found, 345.19775.

4-Methoxyphenyl (E)-2-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (3l).

\[
\text{(pin)BO} \quad \text{O} \quad \text{O} \quad \text{OMe}
\]

\[3l\]

\(^1\)H NMR (396 MHz, CDCl\(_3\), \(\delta\)): 1.21 (s, 12H), 2.01 (s, 3H), 3.81 (s, 3H), 6.90 (dt, \(J = 2.9, 10.0\) Hz, 2H), 7.10 (dt, \(J = 2.9, 10.0\) Hz, 2H), 7.27–7.31 (m, 3H), 7.37–7.41 (m, 2H). \(^1\)C NMR (100 MHz, CDCl\(_3\), \(\delta\)): 14.3 (CH\(_3\)), 24.6 (CH\(_3\)), 55.1 (CH\(_3\)), 83.5 (C), 114.0 (CH), 122.2 (CH), 127.2 (CH), 127.5 (CH), 128.0 (CH), 132.9 (C), 138.6 (C), 144.1 (C), 151.6 (br, B–C), 157.0 (C), 168.3 (C). HRMS–EI (m/z): [M]+ calcd for C\(_{23}\)H\(_{37}\)BO\(_{5}\), 393.19879; found, 393.19805.

4-Ethoxyphenyl (E)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3m).
1H NMR (392 MHz, CDCl₃, δ): 1.25 (s, 12H), 1.41 (t, J = 7.0 Hz, 3H), 1.91 (q, J = 1.1 Hz, 3H), 1.97 (q, J = 1.1 Hz, 3H), 4.01 (q, J = 7.1 Hz, 2H), 6.86 (dt, J = 2.9, 9.9 Hz, 2H), 7.02 (dt, J = 2.9, 9.9 Hz, 2H). 13C NMR (100 MHz, CDCl₃, δ): 12.8 (CH₃), 14.8 (CH₃), 17.3 (CH₃), 24.8 (CH₃), 63.6 (CH₂), 83.4 (C), 114.7 (CH), 122.5 (CH), 132.2 (C), 144.2 (C), 156.4 (C), 167.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]+ calcd for C₁₉H₂₇₁₀BO₅, 345.19879; found, 345.19777.
References


Chapter 3.

Synthesis of Acyl MIDA boronates by Ozonolysis of Alkenyl MIDA boronates
Abstract

A concise synthesis of acylborons was achieved by the ozonolysis of alkenyl MIDA (N-methyliminodiacetic acid) boronates. This reaction exhibits excellent functional group tolerance and is applicable to synthesis of various acyl MIDA boronates and potassium acyltrifluoroborates (KATs) that could not be synthesized by previous methods. In addition, α-amino acylborons, which would be essential for peptide–peptide conjugations, were prepared for the first time. The acylboron of L-alanine analogue was obtained in high enantiopurity and found to be configurationally stable. Oligopeptide synthesis between the α-amino KATs and amino acid in diluted aqueous media was also achieved.

Introduction

The chemical synthesis of proteins provides control over the protein sequence, including any desired modifications or tags. Solid-phase peptide synthesis (SPPS) has been automated and is currently considered as the best method to synthesize peptides that contain less than 50 amino acid residues (AAs). Chemical ligation, such as native chemical ligation (NCL) has been developed to synthesize longer peptide chains by connecting two peptide fragments. Although NCL is the most widely used ligation method in biochemistry, there is still room for improvement, especially regarding the reaction rate and conjugation site. The molecular weight of peptides synthesized by NCL does usually not exceed 200 residues. Moreover, NCL requires a cysteine residue, which is relative rarely in protein sequences, at its conjugation site.

| Table 3-1. Breakthroughs in chemical protein synthesis |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Reaction Rate   |                 | △               | ○               | ○                | ○                |
| Accessible Peptide (Residues of AAs) | | 50              | 200             | 200              | >200?            |
| Conjugation Site |                 | –               | only Cys        | Applicable to any AAs |

Bode reported protein synthesis using chemical ligation reactions developed by themselves (e.g. KAHA ligation and KAT ligation). KAHA ligation is a peptide-bond-forming reaction between α-ketoacids (KAs) and hydroxylamines (HAs) (Scheme 3-1a). KAHA ligation is comparable with NCL regarding both reaction rate and chemoselectivity, and superior to NCL in terms of the conjugation site, as peptide fragments can be conjugated with any amino acid residues. This reaction has been applied to the synthesis of various small proteins. KAT ligation is a chemoselective peptide-bond-forming reaction between potassium acyltrifluoroborates (KATs) and hydroxylamines that does not require condensation reagents or catalysts (Scheme 3-1b). KAT ligation proceeds under mild conditions, at diluted concentrations in aqueous media at room temperature, and tolerates unprotected functional groups. Moreover, KAT ligation does not require specific conjugation sites and exhibits a reaction rate.
that is 80 times faster than NCL.\textsuperscript{4b} KAT ligation can be used for the site-specific functionalization of side-chain of unprotected peptides, but peptide–peptide conjugation using KAT ligation has not yet been achieved.\textsuperscript{4c,d} That is due to the lack of synthetic routes to peptides that contain a KAT moiety at the C-terminus (peptide-KATs). Conventional methods for the preparation of KATs exhibit low functional-group tolerance or require multi-step reactions.\textsuperscript{5} Thus, synthetic routes to KAT-containing α-amino-acid analogues (α-amino KATs), i.e., peptide-KATs models, have not yet been reported.

\begin{align*}
\text{a) KAHA ligation} \\
\text{Ph-}\overset{\text{O}}{\text{C}}\overset{\text{O}}{\text{H}} + \overset{\text{H}}{\overset{\text{N}}{\overset{\text{Ph}}{\text{Ph}}}} \xrightarrow{\text{DMF (0.1 M), 40ºC, 15 h}} \text{Ph-}\overset{\text{N}}{\overset{\text{Ph}}{\text{Ph}}} \quad 89\% \\
\text{b) KAT ligation} \\
\text{Ph-}\overset{\text{O}}{\text{C}}\overset{\text{BF}_3\text{K}}{\text{Ph}} + \overset{\text{H}}{\overset{\text{N}}{\overset{\text{Ph}}{\text{Ph}}}} \xrightarrow{\text{H}_2\text{O} (0.1 \text{ M); rt, 30 min}} \text{Ph-}\overset{\text{N}}{\overset{\text{Ph}}{\text{Ph}}} \quad 87\%
\end{align*}

\textit{Scheme 3-1.} KAHA ligation and KAT ligation

In 2007, Molander \textit{et al.} reported ozonolysis of unsaturated organotrifluoroborates (Scheme 3-2a). They achieved the synthesis of oxo-substituted organotrifluoroborates by the ozonolysis of alkene-bearing organotrifluoroborates moiety at remote part.\textsuperscript{6a} In addition, Yudin reported the ozonolysis of allyl MIDA (N-methyliminodiacetic acid) boronates to afford α-boryl substituted aldehyde (Scheme 3-2b).\textsuperscript{6b} Taking the accessibility of alkenylboronates in consideration, ozonolysis of alkenylboronate seems one of the most effective way to synthesize acylboron species. However, there are no report on the ozonolysis of alkenes that trifluoroborate moiety is directly attached at vinylic position.

\begin{align*}
\text{a) Ozonolysis of unsturated organotrifluoroborates} \\
\text{\begin{align*}
\begin{array}{c}
\text{\text{BF}_3\text{K}} \\
\text{or}
\end{array}
\end{align*}} \xrightarrow{\text{Ozonolysis}} \text{\begin{align*}
\begin{array}{c}
\text{\text{BF}_3\text{K}} \\
\text{or}
\end{array}
\end{align*}}
\end{align*}

\begin{align*}
\text{b) Ozonolysis of allyl MIDA boronate} \\
\text{BrMg} \xrightarrow{\text{1. B(OMe)\textsubscript{3}}} \text{(MIDA)B\textbackslash\textbackslash}_\text{detected by NMR}
\end{align*}

\textit{Scheme 3-2.} Ozonolysis of unsaturated organoboron compounds. a) Ozonolysis of unsturated organotrifluoroborates. b) Ozonolysis of allyl MIDA boronate.
Herein, we report a concise acylboron synthesis by the ozonolysis of alkenyl MIDA boronates (Scheme 3-3). This new method has the following two important features; (a) synthesis of alkenyl boronates are well-studied, they can be readily available by hydroboration of alkynes, cross-coupling of alkenyl halides or C–H borylation of alkenes, and they are transformed to MIDA boronates easily by Burke’s method; and (b) ozonolysis can be conducted under mild reaction conditions and exhibits good functional group tolerance. As a result, this method was applied for the synthesis of various functionalized acylborons, including the first synthesis of glycine and L-alanine type α-amino acylborons. Furthermore, oligopeptide synthesis by amide forming reaction between α-amino acylborons and amino acid derivatives in diluted aqueous media was also investigated.

Scheme 3-3. Acyl MIDA boronate synthesis by ozonolysis of alkenyl MIDA boronates.
Results and Discussion

We first examined the ozonolysis of potassium alkenyltrifluoroborate considering the stability of trifluoroborates under the conditions of ozonolysis. The crude solution contained a complex mixture and we could not detect the desired acyl trifluoroborates. Next, we investigated the ozonolysis of alkenyl MIDA boronate based on the known tolerance of MIDA boronates to ozonolysis. 1a can be easily prepared by Cu(I)-catalyzed protoboration of alkyne, followed by conversion of pinacol boronate to MIDA boronate, according to a modified procedure based on the Burke’s method (Scheme 3-4).

When the ozonolysis of 1a was conducted in acetone at −78°C, the substrate was consumed within 1 minute and the desired acylboron 4a was obtained in good yield (Table 1, entry 1). In the crude reaction mixture of ozonolysis, we detected acyloxyboronate 5a as a minor side-product in 11B NMR spectrum in addition to 4a. Based on the 11B NMR and HRMS, we elucidated this side-product as acyloxyboronate 5a, generated by over-oxidation. The ratio of acylboronate 4a and acyloxyboronate 5a was determined by 11B NMR as 87:13. Unfortunately, we found that it was difficult to isolate 4a from 5a by column chromatography. Despite all our effort such as investigation of condition of acidic quenching or recrystallization, we could not establish method to separate 4a and 5a. In 2012, Yudin previously reported that this species could be synthesized by the oxidation of acyl MIDA boronates using m-CPBA. Even though the mechanism of this over-oxidation is not clear, a similar reaction is known in the ozonolysis of alkenylsilanes.

To improve the yield and selectivity of 4a over 5a, we next investigated the reaction conditions (Table 1, entries 1–9). As a result of solvent screening (entries 1–4), the ozonolysis in acetone gave the best yield and selectivity (85%, 4a:5a = 87:13). Ozonolysis in acetonitrile or EtOAc decreased the ratio of 4a:5a (entry 2: 70:30, and entry 3: 56:44). On the other hand, When the ozonolysis was conducted in methanol, a complex mixture with 4a as a minor product was obtained (entry 4). The use of PPh3 or Zn instead of Me2S resulted in low yield and low selectivity (entries 5 and 6), however reduction with pyridine resulted in high yield of 4a of 94% as sole product (entry 7). It is noteworthy that side-product 5a was not detected at all in the ozonolysis of tetra-substituted alkenylboronate. This feature is interesting to investigate the mechanism of the generation of 5a. However, this route has poor synthetic applicability because there are few general methods to synthesize tetra-substituted alkenyl pinacol boronates and transesterification to MIDA boronate is very low yield (ca. 5%).
Taking the accessibility of substrate in consideration, we next investigated the scope of this reaction in terms of the alkenyl MIDA boronates using the reaction conditions of entries 1 and 7 in Table 3-2. The substrates were prepared from alkynes according to the procedure depicted in Scheme 3-4. The ozonolysis of 1b proceeded in high yield with high selectivity (Table 3-2, 87%, 94:6), and ozonolysis of 1c, which had a sterically hindered secondary alkyl group also proceeded in high yield with high selectivity (84%, >95:<5). This method can also be applied to a styrene derivative; ozonolysis of 1d gave acylboron in high yield with high selectivity with pyridine as the reducing agent (90%, >95:<5); the same reaction using Me2S gave low selectivity (64:36). Acylborons bearing a chloride group 4e or ketone group 4f can also be synthesized by this reaction conditions in high yield with good selectivity (4e: 94%, 84:16, 4f: 88%, >95:<5). The functional group compatibility was investigated by the ozonolysis of β-borylated allyl alcohol bearing various protecting group on hydroxyl group such as acetyl, benzyl, or TIPS group. The ozonolysis proceeded in good to high yield with high selectivity with alkenyl MIDA boronate with ether and ester (4g: 85%, 93:7, 4h: 84%, 82:18). On the other hand, silyl protected α-hydroxy acylboron 4i was obtained with medium selectivity (66%, 74:26). Synthesis of such α-hydroxy acylboronates has not been achieved by any known preparation approach because their synthetic intermediate may decompose through rapid β-elimination. These results also indicate that substituent R1 give not so important effect on the yields and selectivities; substrates bearing phenyl group can be used in this reaction, and exomethylene-type substrates that do not bear any substituent at R1 moiety can also be employed for this reaction.

Next, synthesis of α-amino alkenyl boronates were investigated. Alkenyl boronates bearing
amines at allylic position can easily be prepared in high yield and high regioselectivity by Cu(I)-catalyzed hydroboration of propargyl amine reported by Hoveyda. As a result, N-Phth, N-Cbz, N-Boc and N-Fmoc protected α-amino alkenyl MIDA boronate can be used in this reaction and gave the desired glycine acylboron analogues in good yields and high selectivity (4j: 90%, >95:5, 4k: 88%, 90:10, 4l: 91%, 95:5, 4m: 65%, 93:7). The structure of 4j was confirmed by X-ray crystallography (Figure 3-1).

Table 3-3. Substrate Scope[a]

<table>
<thead>
<tr>
<th>Substrate Structure</th>
<th>Conditions A</th>
<th>Conditions B</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1=Ph (A)</td>
<td>Ozone bubbling then SMe2 (excess)</td>
<td></td>
</tr>
<tr>
<td>R1=H (A)</td>
<td>Ozone bubbling Pyridine (3.0 equiv)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>R1</th>
<th>Product</th>
<th>Ratio</th>
<th>Isolated Yield</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>4b</td>
<td>90%</td>
<td>94:6</td>
<td>87%</td>
</tr>
<tr>
<td>Ph</td>
<td>4c</td>
<td>&gt;95:5</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>4d</td>
<td>&gt;95:5</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>4e</td>
<td>94:16</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>4f</td>
<td>&gt;95:5</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>4g</td>
<td>95:5</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>4h</td>
<td>85:15</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>4i</td>
<td>74:26</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>TMS</td>
<td>4j</td>
<td>&gt;95:5</td>
<td>90%</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>4k</td>
<td>95:5</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>4l</td>
<td>95:5</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>4m</td>
<td>93:7</td>
<td>65%</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction condition A: a) 1 (0.3 mmol), O3, acetone, –78ºC. b) Me2S (excess), acetone, –78ºC, 5 min. Reaction condition B: 1 (0.3 mmol), O3, pyridine (3.0 equiv), acetone, –78ºC. [b] Combined isolated yields of products (4+5) are reported. [c] Product ratio (4:5) in the crude reaction mixture were determined by 11B NMR spectroscopy analysis. [d] 0.03 mol% of Sudan III was added as an indicator.

Figure 3-1. Crystal Structure of 4j-CH3CN. CH3CN was omitted for clarification.
Next, we tried to synthesize other optically active \( \alpha \)-amino acylboron, L-alanine type acyl boron (Scheme 3-5). Enantiopure active propargyl amine (S)-7 was obtained from the commercially available propargyl alcohol (R)-6 (>98% ee) by Mitsunobu reaction with CbzNHNs \((\text{Ns} = \text{2-nitrobenzenesulfonyl})\) and Ns deprotection (60%, two steps). Cu(I)-catalyzed protoboration proceeded smoothly to give alkenyl pinacol boronate (S)-8 in 69% yield without any loss of enantiopurity. Then, transformation of ligands on boron atom was investigated. At first, alkenyl pinacol boronate (S)-8 was reacted with MIDA in DMSO at 100 °C for 24h according to the Burke’s procedure, but alkenyl MIDA boronate obtained very low yield and substrate was recovered in ca 50%. In order to improve this yield, some pinacol trapping agent, which are generally used for protection of 1,2-diol, were investigated. As a result, addition of trimethyl orthoformate gave alkenyl MIDA boronate (S)-1n in relatively high yield (39%). Ozonolysis of (S)-1n gave alanine acylboron analogue (S)-4n in 93% yield with high chemoselectivity (>95:<5) and high enantiospecificity (99% ee). This compound may be difficult to synthesize by conventional methods which require boryl metal species or \( n \)-BuLi because their harsh condition will cause racemization at \( \alpha \)-position.

\[
\begin{align*}
\text{HO} & \quad \text{CbzNHNs} \\
\text{Me} & \quad \text{DIAD, PPh}_3 \\
\text{CH}_2\text{Cl}_2 & \quad \text{thioglycolic acid} \\
\text{DMF, 60% (2 steps)} & \quad \text{CBzHN} \\
\text{(S)-7} & \quad \text{B}_2\text{(pin)}_2 \\
\text{MeOH} & \quad \text{THF, 78%} \\
\end{align*}
\]

\[
\begin{align*}
\text{Sudan III} & \quad \text{acetone, –78ºC, 1 min} \\
\text{then Me}_2\text{S} & \quad \text{MeOH} \\
\text{93% (4n:5n = >95:<5)} & \quad \text{THF, 78%} \\
\text{14} & \quad \text{Sudan III} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 3-5. Synthesis of L-Alanine type acyl MIDA boronates}
\end{align*}
\]

\( \alpha \)-Amino acylboron compounds could potentially be used as a building block in peptide conjugation using KAT ligation. As a preliminary investigation towards this goal, we investigated oligopeptide synthesis using the amide-forming reaction of KATs and amines in the presence of a chlorinating agent reported by Bode (Scheme 3-6).\(^{14}\) According to the reported procedure, MIDA-protected 4n could easily be converted to potassium acyltrifluoroborate 9 in 85% yield (Scheme 4A).\(^ {15}\) The reaction between 9 and glycine benzyl ester 10 in the presence of DCH (1,3-dichloro-5,5-dimethylhydantoin) was performed in aqueous solvent at room temperature. The reaction finished within 1 h at a concentration of 0.1 M, and the ligation product 11 was obtained in 72% yield; even at a concentration of 1.0 mM, 11 was obtained in 50% yield. Tetrapeptide synthesis from dipeptide KAT 12 and dipeptide 13 afforded 14 in 61% (Scheme 3-6b). The diastereomeric ratio of 14 was 98:2, indicating that \( \alpha \)-amino acylborons have configurational stability under the ligation conditions.
Scheme 3-6. Oligopeptide synthesis between the α-amino KAT and amino acid using chlorinating agent in water.

a) Dipeptide synthesis in highly diluted solution. b) Preservation of stereochemistry in tetrapeptide synthesis.

Summary

In summary, we have developed a concise synthesis of functionalized acylboronates by the ozonolysis of alkenyl MIDA boronates. Ozonolysis of substrates containing various functional groups such as chlorides, ketones, esters, benzyl ether, amino groups afforded the corresponding products. Importantly, α-amino acylboron which bearing asymmetric carbon at α-position, could be synthesized with high enantiospecificity and found to be configurationally stable. Furthermore, peptide synthesis by amide-forming reaction between α-amino acylboron and amino acid revealed this reaction proceed even in highly diluted concentration and proceed without racemization at adjacent position of reaction site.
Experimental

General and Materials.

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers, and dried over molecular sieves (MS 4A). $^1$H NMR spectra were recorded on JEOL JNM-ECX400P (400 MHz) and JNM-ECS400 (400 MHz) spectrometer and spectra are referenced to Tetramethylsilane (0.00 ppm) or residual protonated solvent (acetone-d$_6$: 2.05 ppm; CD$_3$CN: 1.94 ppm; DMSO-d$_6$: 2.50 ppm). $^{13}$C NMR spectra were recorded on JEOL JNM-ECX400P (100 MHz) and JNM-ECS400 (100 MHz) spectrometer and spectra are referenced to the solvent (CDCl$_3$: 77.0 ppm; acetone-d$_6$: 29.92 ppm; CD$_3$CN: 1.39 ppm; DMSO-d$_6$: 39.52 ppm). $^{11}$B NMR spectra were recorded on JEOL JNM-ECX400P (128 MHz) and JNM-ECS400 (128 MHz) spectrometer and spectra are referenced to an external sample (BF$_3$·Et$_2$O: 0.0 ppm). Chemoselctivities were determined by $^{11}$B NMR analysis. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with a ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and a FID detector. HPLC analyses with chiral stationary phase were carried out using a Hitachi LaChrome Elite HPLC system with a L-2400 UV detector and a Jasco LC-2000Plus HPLC system with a UV-2075 detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University. (SIMes)CuCl and (IMes)CuCl were synthesized according to the reported procedure.

General Experimental Procedures.

A General Procedure for the Ozonolysis of Alkenyl MIDA Boronates 1a with Me$_2$S as a Reductant. (Reaction Condition A).

Alkenyl MIDA boronate 1a (108.9 mg, 0.30 mmol) were placed in an oven-dried reaction vial. The vial was filled with nitrogen gas and then sealed with a screw cap containing a Teflon-coated rubber septum. Dry acetone (2.00 mL) was added in the vial through the rubber septum using a syringe. The solution was cooled to −78°C, at which point a stream of O$_3$/O$_2$ was introduced through a needle until which time the reaction mixture started to turn blue. The ozone was then stopped and O$_2$ gas was bubbled through the solution for 5 minutes to remove remained O$_3$ gas. The vial was charged with Me$_2$S (0.30 mL) and stirred at −78°C for 5 minutes. The reaction mixture was then warmed to room temperature and stirred for 5 minutes. The solvent was then removed in vacuo. The resulting oil was reprecipitated with EtOAc/Et$_2$O to yield a white solid.

A General Procedure for the Ozonolysis of Alkenyl MIDA Boronates 1a with Pyridine as a Reductant. (Reaction Condition B).

Alkenyl MIDA boronate 1a (108.9 mg, 0.30 mmol) were placed in an oven-dried reaction vial. The vial was filled with nitrogen gas and then sealed with a screw cap containing a Teflon-coated rubber septum. Dry acetone (2.00 mL) and pyridine (72.5 µL, 0.90 mmol) were added in the vial through the rubber septum using syringes. The solution was cooled to −78°C, at which point a stream of O$_3$/O$_2$ was introduced through a needle until which time the reaction mixture started to turn blue. The ozone was then stopped and O$_2$ gas was bubbled through the solution for 5 minutes
to remove remained O₃ gas. The vial was then warmed to room temperature and stirred for 5 minutes. The solvent was then removed in vacuo. The resulting oil was reprecipitated with EtOAc/Et₂O to yield a white solid.

**Stability and Isolation of Acylboron Compounds.**

The obtained acyl MIDA boronates (4a–4n, and S25) are fairly stable. Although we stock them in nitrogen-purged vial in refrigerator for several months and use them in air, we detected no significant decomposition. However, acyl MIDA boronates are unstable to water or methanol, and gradually decompose as described in the previous report.¹⁵ They are soluble in THF, EtOAc, CH₃CN and acetone, but Et₂O does not solubilize them. In addition, they are also unstable to silica gel chromatography. We found that the ratio of acylboron to over-oxidized product deceased after silica gel chromatography.

**Preparation of Substrates.**

**Preparation of (Z)-2-(1,4-diphenylbut-1-en-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1a).**

B₂(pin)₂ (2.51 g, 9.9 mmol), (IMes)CuCl (36.4 mg, 0.09 mmol), NaOH (18.0 mg, 0.45 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Cyclopentyl Methyl Ether (CPME, 9.9 mL), 2 (1.86 g, 9.0 mmol), and MeOH (728 µL, 18.0 mmol) were then added in the flask through the rubber septum using syringes, and the resultant solution was then stirred at room temperature for 22 h. The resulting mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography to obtain 3 (2.61 g, 7.81 mmol, 87%) as a white solid.⁸c ¹H NMR (396 MHz, CDCl₃, δ): 1.31 (s, 12H), 2.69 (dd, J = 5.9, 10.0 Hz, 2H), 2.79 (dd, J = 5.6, 10.2 Hz, 2H), 7.14–7.33 (m, 11H). ¹³C NMR (100 MHz, CDCl₃, δ): 24.8 (CH₃), 31.3 (CH₂), 36.0 (CH₂), 83.4 (C), 125.6 (CH), 127.1 (CH), 128.1 (CH), 128.2 (CH), 128.5 (CH), 128.8 (CH), 137.7 (C), 142.3 (C), 142.6 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-El (m/z): [M⁺] calc for C₂₂H₂₇BO₃, 333.21404; found, 333.21428.

3 (2.34 g, 7.0 mmol) and MIDA (6.39 g, 43.4 mmol) was placed in an oven-dried two-neck equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DMSO (70 mL) and CH(OEt)₃ (2.99 mL, 28.0 mmol) were then added in the flask through the rubber septum using syringes, and then the resultant solution was stirred at 100°C for 48 h. The reaction mixture was then cooled to room temperature, the resulting solution was poured into 630 mL H₂O. The mixture was diluted with 210 mL EtOAc and shaken. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 210 mL). The combined organic phases were washed with H₂O and brine, and then dried over MgSO₄, filtered, and concentrated in vacuo. The crude product was washed with Et₂O three times to obtain 1a (1.08 g, 2.97 mmol, 42%) as a white solid.⁸c
\(^1\)H NMR (396 MHz, CD\(_3\)CN, \(\delta\)): 2.43–2.48 (m, 2H), 2.70–2.74 (m, 2H), 2.83 (s, 3H), 3.91 (d, \(J = 17.4\) Hz, 2H), 4.03 (d, \(J = 17.0\) Hz, 2H), 6.86 (s, 1H), 7.12–7.17 (m, 3H), 7.23–7.29 (m, 3H), 7.38 (d, \(J = 4.4\) Hz, 4H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN, \(\delta\)): 33.8 (CH\(_2\)), 36.8 (CH\(_2\)), 47.9 (CH\(_2\)), 63.0 (CH\(_2\)), 126.7 (CH), 127.8 (CH), 129.1 (CH), 129.2 (CH), 129.3 (CH), 129.5 (CH), 138.8 (CH), 139.4 (C), 143.6 (C), 169.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-\(E^+\) (m/z): [M]+ calcd for C\(_{21}\)H\(_{32}\)BNO\(_4\), 362.16782; found, 362.16654.

**Preparation of (Z)-6-methyl-2-(1-phenylhex-1-en-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (1b).**

S\(_1\) (2.19 g, 7.64 mmol) was prepared in 85% yield from hex-1-yn-1-ylbenzene (1.42 g, 9.0 mmol) according to the procedure for the synthesis of 3. The spectral data was consistent with those reported in the literature.\(^{17}\) 1b (891 mg, 2.83 mmol, white solid) was prepared in 40% yield from S\(_1\) (2.00 g, 7.0 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, CD\(_3\)CN, \(\delta\)): 0.85 (t, \(J = 7.1\) Hz, 3H), 1.29 (sxt, \(J = 7.3\) Hz, 2H), 1.38–1.46 (m, 2H), 2.18–2.22 (m, 2H), 2.81 (s, 3H), 3.88 (d, \(J = 17.0\) Hz, 2H), 3.99 (d, \(J = 16.6\) Hz, 2H), 6.75 (s, 1H), 7.22–7.26 (m, 1H), 7.32–7.38 (m, 4H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN, \(\delta\)): 14.1 (CH\(_3\)), 23.8 (CH\(_2\)), 30.8 (CH\(_2\)), 32.9 (CH\(_2\)), 47.8 (CH\(_3\)), 63.0 (CH\(_2\)), 127.6 (CH), 129.2 (CH), 129.6 (CH), 137.9 (CH), 139.5 (C), 169.6 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-\(E^+\) (m/z): [M]+ calcd for C\(_{17}\)H\(_{22}\)BNO\(_4\), 314.16782; found, 314.16791.

**Preparation of (Z)-2-(1-cyclohexyl-2-phenylvinyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1c).**

S\(_2\) (2.32 g, 7.43 mmol) was prepared in 83% yield from (cyclohexylethynyl)benzene (1.66 g, 9.0 mmol) according to the procedure for the synthesis of 3. The spectral data was consistent with those reported in the literature.\(^{17}\) 1c (322.0 mg, 0.94 mmol, white solid) was prepared in 14% yield from S\(_2\) (2.19 g, 7.0 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, CD\(_3\)CN, \(\delta\)): 1.07–1.16 (m, 3H), 1.49–1.70 (m, 7H), 2.62–2.70 (m, 1H), 2.86 (s, 3H), 3.89 (d, \(J = 17.0\) Hz, 2H), 3.99 (d, \(J = 17.4\) Hz, 2H), 6.70 (s, 1H), 7.22–7.26 (m, 3H), 7.35 (t, \(J = 7.5\) Hz, 2H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN, \(\delta\)): 26.9 (CH\(_2\)), 27.4 (CH\(_2\)), 32.8 (CH\(_2\)), 42.1 (CH), 49.0 (CH\(_3\)), 63.4 (CH\(_2\)), 127.5 (CH), 129.0 (CH), 129.6 (CH), 138.4 (CH), 140.1 (C), 169.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-\(E^+\) (m/z): [M]+ calcd for C\(_{19}\)H\(_{24}\)BNO\(_4\), 340.18347; found, 340.18250.

81
Preparation of (Z)-2-(1,2-diphenylprop-1-en-1-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1d).

S3 (4.04 g, 13.2 mmol) was prepared in 66% yield from 1,2-diphenylethyne (3.56 g, 20.0 mmol) according to the reported procedure.\(^{18}\) 1d (751 mg, 2.45 mmol, white solid) was prepared in 38% yield from S3 (1.80 g, 5.9 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, CD\(_2\)CN, \(\delta\)): 2.83 (s, 3H), 3.55 (d, \(J = 16.6\) Hz, 2H), 3.93 (d, \(J = 17.4\) Hz, 2H), 6.90–7.07 (m, 2H), 7.05 (s, 1H), 7.09–7.15 (m, 5H), 7.21–7.31 (m, 3H). \(^13\)C NMR (100 MHz, CD\(_2\)CN, \(\delta\)): 47.6 (CH), 63.0 (CH\(_2\)), 127.2 (CH), 128.0 (CH), 128.8 (CH), 129.5 (CH), 130.1 (CH), 130.4 (CH), 138.5 (C), 138.5 (CH), 139.1 (CH), 142.5 (C), 169.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]+ calcd for C\(_{15}\)H\(_{18}\)BNO\(_4\), 334.13652; found, 334.13602.

Preparation of (Z)-2-(5-chloro-1-phenylpent-1-en-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1e).

S4 (2.71 g, 8.83 mmol) was prepared in 88% yield from (5-chloropent-1-yn-1-yl)benzene (1.79 g, 10.0 mmol) according to the procedure for the synthesis of 3. S4 (346 mg, 1.13 mmol) and KHF\(_2\) (398 mg, 5.09 mmol) was placed in a flask equipped with a stir bar. MeOH (4.52 mL) and H\(_2\)O (2.26 mL) were then added in the flask using syringes, and then the resultant solution was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo. The resulting solid was washed with hexane, Et\(_2\)O, and then filtered with EtOAc. The filtrate was concentrated in vacuo. The product S5 was used in the next reaction without further purification.

S5 (185 mg, 0.65 mmol) was placed in an oven-dried two-neck flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. CH\(_3\)CN (6.5 mL), (TMS)$_2$MIDA (188 mg, 0.65 mmol), and BF$_3$·Et\(_2\)O (81.2 \(\mu\)L, 0.65 mmol), and then the resultant solution was stirred at 80ºC for 7 h. The reaction mixture was concentrated in vacuo. The crude product was purified by flash column chromatography to obtain 1e (139 mg, 0.42 mmol) in 64% (2 steps) as a white solid. \(^1\)H NMR (396 MHz, CD\(_2\)CN, \(\delta\)): 1.85–1.93 (m, 2H), 2.37 (t, \(J = 7.9\) Hz, 2H), 2.84 (s, 3H), 3.54 (t, \(J = 6.7\) Hz, 2H), 3.90 (d, \(J = 17.0\) Hz, 2H), 4.02 (d, \(J = 17.0\) Hz, 2H), 6.84 (s, 1H), 7.23–7.29 (m, 1H), 7.34–7.36 (m, 4H). \(^13\)C NMR (100 MHz, CD\(_2\)CN, \(\delta\)): 28.4 (CH\(_2\)), 33.5 (CH\(_2\)), 46.4 (CH\(_2\)), 47.8 (CH\(_3\)), 62.9 (CH\(_2\)), 127.8 (CH), 129.2 (CH), 129.6 (CH), 139.0 (CH), 139.2 (C), 169.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS–EI (m/z): [M]+ calcd for C\(_{16}\)H\(_{19}\)BClNO\(_4\), 334.11320; found, 334.11211.
Preparation of (Z)-6-methyl-2-(6-oxo-1-phenylhept-1-en-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (1f).

\[
\begin{align*}
\text{S6} & \overset{\text{KHF}_2 (4.5 \text{ equiv})}{\longrightarrow} \overset{\text{MeOH/H}_2\text{O}}{\text{rt}, 15 \text{ min}} \overset{\text{BF}_3\text{K}}{\longrightarrow} \overset{\text{CH}_3\text{CN, 80ºC, 7 h}}{\text{79%}} \overset{(\text{TMS})_2\text{MIDA (1 equiv)}}{\text{BF}_3\text{Et}_2\text{O (1 equiv)}} \overset{\text{79%}}{\longrightarrow} \text{1f}
\end{align*}
\]

S6 (630 mg, 2.0 mmol) was prepared in 80% yield from 7-phenyleth-6-yn-2-one (465 mg, 2.5 mmol) according to the procedure for the synthesis of 3. \(^\text{1}^H\) NMR (392 MHz, CDCl\(_3\), \(\delta\)): 1.31 (s, 12H), 1.76 (quint, \(J = 7.6\) Hz, 2H), 2.07 (s, 3H), 2.39 (quint, \(J = 7.4\) Hz, 4H), 7.22–7.26 (m, 2H), 7.30–7.36 (m, 4H). \(^{13}C\) NMR (99 MHz, CDCl\(_3\), \(\delta\)): 23.9 (CH\(_2\)), 24.7 (CH\(_3\)), 28.5 (CH\(_2\)), 29.6 (CH\(_3\)), 43.5 (CH\(_2\)), 83.4 (C), 127.1 (CH), 128.1 (CH), 128.8 (CH), 137.6 (C), 142.8 (CH), 209.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): [M]\(^+\) calcd for C\(_{19}\)H\(_{27}\)BO\(_3\), 313.20896; found, 313.20944.

S7 (756 mg, 2.57 mmol, white solid) was prepared in 86% yield from S6 (693 mg, 3.0 mmol) according to the procedure for the synthesis of S5. 1F (404 mg, 1.18 mmol, white solid) was prepared in 79% yield from S7 (441 mg, 1.50 mmol) according to the procedure for the synthesis of 1E. \(^\text{1}^H\) NMR (392 MHz, CDCl\(_3\), \(\delta\)): 1.57–1.65 (m, 2H), 2.14–2.19 (m, 2H), 2.35 (t, \(J = 7.2\) Hz, 2H), 2.78 (s, 3H), 3.85 (d, \(J = 17.0\) Hz, 2H), 3.96 (d, \(J = 17.0\) Hz, 2H), 6.76 (s, 1H), 7.19–7.25 (m, 1H), 7.33 (d, \(J = 4.5\) Hz, 4H). \(^{13}C\) NMR (99 MHz, CDCl\(_3\), \(\delta\)): 24.8 (CH\(_2\)), 29.9 (CH\(_3\)), 30.2 (CH\(_2\)), 44.1 (CH\(_3\)), 47.8 (CH\(_3\)), 63.0 (CH\(_2\)), 127.8 (CH), 129.3 (CH), 129.7 (CH), 138.6 (CH), 139.4 (C), 169.7 (C), 209.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): [M]\(^+\) calcd for C\(_{19}\)H\(_{27}\)BO\(_3\), 342.16273; found, 342.16225.

Preparation of 2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)allyl acetate (1g).

\[
\begin{align*}
\text{S8} & \overset{\text{MIDA (6.2 equiv)}}{\longrightarrow} \overset{\text{HC(OEt)}_3 (4.0 \text{ equiv})}{\text{DMSO, 100ºC, 22 h}} \overset{\text{57%}}{\longrightarrow} \text{1g}
\end{align*}
\]

S8 was prepared from prop-2-yn-1-yl acetate according to the reported procedure. \(^\text{1}^H\) NMR (396 MHz, CD\(_2\)CN, \(\delta\)): 2.02 (s, 3H), 2.83 (s, 3H), 3.84 (d, \(J = 17.4\) Hz, 2H), 4.01 (d, \(J = 17.4\) Hz, 2H), 4.59 (s, 2H), 5.23 (s, 1H), 5.71 (s, 1H). \(^{13}C\) NMR (100 MHz, CD\(_2\)CN, \(\delta\)): 21.0 (CH\(_3\)), 48.2 (CH\(_3\)), 62.9 (CH\(_2\)), 68.3 (CH\(_2\)), 126.5 (CH\(_2\)), 169.6 (C), 171.2 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): [M]\(^+\) calcd for C\(_{10}\)H\(_{14}\)BO\(_3\), 254.09505; found, 254.09496.

Preparation of 2-[3-(benzyloxy)prop-1-en-2-yl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1h).

\[
\begin{align*}
\text{S9} & \overset{\text{MIDA (6.2 equiv)}}{\longrightarrow} \overset{\text{HC(OEt)}_3 (4.0 \text{ equiv})}{\text{DMSO, 100ºC}} \overset{\text{82%}}{\longrightarrow} \text{1h}
\end{align*}
\]

S9 was prepared in from [(prop-2-yn-1-lyloxy)methyl]benzene according to the reported procedure. \(^\text{8f}\) 1H (742 mg,
2.45 mmol, white solid) was prepared in 82% yield from $\text{S9}$ (823 g, 3.0 mmol) according to the procedure for the synthesis of $\text{1a}$. $^1\text{H NMR}$ (396 MHz, CD$_3$CN, $\delta$): 2.75 (s, 3H), 3.74 (d, $J = 17.4$ Hz, 2H), 3.87 (d, $J = 17.0$ Hz, 2H), 4.05 (s, 2H), 4.45 (s, 2H), 5.51 (d, $J = 3.2$ Hz, 1H), 5.65 (s, 1H), 7.30–7.39 (m, 5H). $^{13}\text{C NMR}$ (100 MHz, CD$_3$CN, $\delta$): 48.3 (C$_7$H$_3$), 63.3 (C$_8$H$_2$), 73.8 (C$_8$H$_2$), 76.1 (C$_8$H$_2$), 126.1 (C$_7$H$_2$), 128.7 (C$_7$H), 129.1 (C$_7$H), 129.4 (C$_7$H), 139.0 (C), 169.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{15}$H$_{18}$BNO$_5$, 302.13143; found, 302.13070.

Preparation of 6-methyl-2-[3-[(triisopropylsilyl)oxy]prop-1-en-2-yl]-1,3,6,2-dioxazaborocane-4,8-dione ($\text{1i}$).

$\text{S10}$ was prepared from propargylalcohol according to the reported procedure.$^8$ $\text{S10}$ (737 mg, 4.00 mmol) and imidazole (817 mg, 12.0 mmol) were placed in an oven-dried two-neck flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. CH$_2$Cl$_2$ (8.0 mL), TIPS–Cl (771 mg, 400 mmol) were then added in the flask through the rubber septum using syringes. After stirred for 3 h, the mixture was passed through a short silica gel column eluting with EtOAc. The crude material was purified by flash column chromatography to give $\text{S11}$ (885 mg, 2.46 mmol, 61%) as a colorless oil.

$\text{1i}$ (124 mg, 0.336 mmol, white solid) was prepared in 56% yield from $\text{S11}$ (204 mg, 0.60 mmol) according to the procedure for the synthesis of $\text{1a}$. $^1\text{H NMR}$ (392 MHz, CDCl$_3$, $\delta$): 1.04–1.18 (m, 21H), 2.91 (s, 3H), 3.77 (d, $J = 15.7$ Hz, 2H), 3.96 (d, $J = 15.7$ Hz, 2H), 4.28 (s, 2H), 5.63 (d, $J = 2.7$ Hz, 1H), 5.71 (s,1H). $^{13}\text{C NMR}$ (99 MHz, CDCl$_3$, $\delta$): 11.9 (C), 18.0 (C$_7$H$_3$), 47.1 (C$_7$H$_3$), 61.9 (C$_7$H$_2$), 68.2 (C$_7$H$_2$), 126.3 (C$_7$H), 168.2 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{17}$H$_{32}$O$_5$N$_{10}$BNaSi, 391.20713; found, 391.20766.

Preparation of (Z)-2-[3-(1,3-dioxoisindolin-2-yl)-1-phenylprop-1-en-2-yl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione ($\text{1j}$).

$\text{S12}$

$\text{S13}$

$\text{S14}$

$\text{S15}$

$\text{1j}$
Phthalimide (2.94 g, 20 mmol) and PPh₃ (6.30 g, 24 mmol) was placed in an oven-dried two-neck flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (20 mL) and S₁₂ (2.56 g, 20.0 mmol) were added in the flask through the rubber septum using syringes, and then DIAD (5.26 g, 26.0 mmol) was added dropwise at 0°C. After stirring for 1 h, the solution was diluted with water and extracted with Et₂O three times, and then washed with brine, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain S₁₃ (2.21 g, 8.60 mmol) in 43%. B₃(pin)₂ (1.52 g, 6.00 mmol), CuCl (24.8 mg, 0.25 mmol), ICy·HCl (67.2 mg, 0.25 mmol) were then added in the flask through the rubber septum using syringes. The resultant solution was allowed to warm to 0°C, µL, 10.0 mmol) were then added in the flask through the rubber septum using syringes. The resultant solution was allowed to warm to 0°C, and then stirred for 15 h. After passing through a short silica gel column eluting with EtOAc, the crude product was purified by flash column chromatography to obtain S₁₄ (1.30 g, 3.36 mmol, 67%). S₁₅ (897.1 mg, 2.46 mmol, white solid) was prepared in 91% yield from S₁₄ (1.04 g, 2.70 mmol) according to the procedure for the synthesis of S₅. 1j (596.3 mg, 1.44 mmol, white solid) was prepared in 72% yield from S₁₅ (730 mg, 2.00 mmol) according to the procedure for the synthesis of 1e. ¹H NMR (392 MHz, Acetone-d₆, δ): 0.29 (s, 9H), 3.22 (s, 3H), 3.99 (d, J = 16.6 Hz, 2H), 4.15 (d, J = 17.0 Hz, 2H), 4.62 (d, J = 1.3 Hz, 2H), 6.30 (s, 1H), 7.82 (s, 4H). ¹³C NMR (100 MHz, Acetone-d₆, δ): 0.42 (CH₃), 43.7 (CH₂), 47.6 (CH₃), 62.5 (CH₂), 123.7 (CH), 133.5 (C), 134.8 (CH), 145.7 (CH), 168.9 (C), 169.4 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (m/z): [M]+ calcd for C₁₉H₂₅BN₂O₃Si, 413.14547; found, 413.14413.

**Preparation of benzyl [2-(6-methyl-1,3-dioxo-1,3,6,2-dioxazaborocan-2-yl)allyl]carbamate (1k).**

S₁₆ (8.68 g, ca. 70% purity) was prepared from benzyl prop-2-yn-1-ylcarbamate (5.68 g, 30.0 mmol) according to the procedure for the synthesis of S₈. The borylation product was used in the next reaction without further purification. S₁₇ (7.07 g, 23.8 mmol, white solid) was prepared in 79% yield (2 steps) from S₁₆ (8.53 g, ca. 70% purity) according to the procedure for the synthesis of S₅. 1k (721 mg, 2.07 mmol, white solid) was prepared in 69% yield from S₁₇ (891 mg, 3.00 mmol) according to the procedure for the synthesis of 1e. ¹H NMR (396 MHz, CD₂CN, δ): 2.82 (s, 3H), 3.73 (dt, J = 1.8, 6.3 Hz, 2H), 3.82 (d, J = 16.6 Hz, 2H), 3.96 (d, J = 16.6 Hz, 2H), 5.05 (s, 2H), 5.39 (s, 1H), 5.56 (s, 1H), 5.81 (brs, 1H), 7.32–7.38 (m, 5H). ¹³C NMR (100 MHz, CD₂CN, δ): 45.1 (CH₃), 47.6 (CH₂), 62.6 (CH₂), 66.9 (CH₂), 123.3 (CH₂), 128.7 (CH), 128.8 (CH), 129.4 (CH), 138.4 (C), 157.4 (C), 169.4 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (m/z): [M]+ calcd for C₁₆H₁₉¹⁰BN₂O₆, 345.13725; found, 345.13631.
Preparation of tert-butyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)allyl]carbamate (1I).

S18 was prepared from tert-butyl prop-2-yn-1-ylcarbamate (15.5 g, 100.0 mmol) according to the reported procedure.8f After passing through a short silica gel column eluting with EtOAc, the obtained mixture was used in the next reaction without further purification. S19 (19.1 g, 67.3 mmol) was prepared in 67% according to the procedure for the synthesis of S5. 

\[
\text{1H NMR (392 MHz, CD}_2\text{CN, }\delta): 1.40 (s, 9H), 3.60 (d, J = 5.4 Hz, 2H), 4.93 (s, 1H), 4.98 (s, 1H), 5.26 (brs, 1H). \text{13C NMR (99 MHz, CD}_2\text{CN, }\delta): 28.7 (CH}_3\text{), 45.5 (CH}_2\text{), 79.1 (C), 113.5 (CH}_2\text{), 153.4 (br, B–C), 157.4 (C). \text{11B NMR (127 MHz, CD}_2\text{CN, }\delta): 3.63 (s). \text{HRMS-ESI (m/z): [M–K]+ calced for C}_9\text{H}_{16}\text{O}_2\text{N}_1\text{BF}_3\text{, 223.11115; found, 223.11140.}
\]

1I (17.1 g, 65.0 mmol) was prepared in 84% according to the procedure for the synthesis of 1e. 

\[
\text{1H NMR (396 MHz, CD}_2\text{CN, }\delta): 1.40 (s, 9H), 2.82 (s, 3H), 3.65 (dt, J = 1.8, 6.3 Hz, 2H), 3.83 (d, J = 17.2 Hz, 2H), 3.97 (d, J = 16.8 Hz, 2H), 5.39 (s, 1H), 5.45 (brs, 1H), 5.54 (s, 1H). \text{13C NMR (99 MHz, CD}_2\text{CN, }\delta): 28.7 (CH}_3\text{), 44.6 (CH}_2\text{), 47.6 (CH}_2\text{), 62.7 (CH}_2\text{), 79.3 (C), 123.1 (CH}_2\text{), 145.2 (br, B–C), 157.0 (C), 169.4 (C). \text{11B NMR (127 MHz, CD}_2\text{CN, }\delta): 11.19 (s). \text{HRMS-ESI (m/z: [M+Na]+ calced for C}_{10}\text{H}_{21}\text{O}_6\text{N}_2\text{BF}_3\text{, 334.14212; found, 334.14221.}
\]

Preparation of (9H-Fluoren-9-yl)methyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)allyl] carbamate (1m).

1I (1.57 g, 5.02 mmol) was placed in an oven-dried two-neck flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dioxane (25 mL) were then added in the flask using syringes, and then the solution was cooled to 0°C. 4 M HCl in dioxane (25 mL) was then added to the solution and the resultant solution was stirred at room temperature for 30 min. The resultant suspension was then diluted with EtOAc and the precipitated solid was collected by decantation, and dried in vacuo. The resultant solid (1.24 g) and Fmoc–OSu (1.68 g, 5.0 mmol) was placed in an oven-dried two-neck flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Dioxane (33 mL), and DIPEA (1.74 mL, 10 mmol) were then added in the flask using syringes, and then the solution was stirred at room temperature for 20 h. The reaction mixture was passed through a short silica gel column eluting with EtOAc, and washed with aqueous NH₄Cl solution. The obtained organic layer was dried over MgSO₄, filtered, and concentrated in vacuo to obtain 1m (1.65 g, 3.80 mmol, 76%) as a white solid. 

\[
\text{1H NMR (392 MHz, CD}_2\text{CN, }\delta): 2.81 (s, 3H), 3.71 (d, J = 5.8 Hz, 2H), 3.81 (d, J = 17.0 Hz, 2H), 3.96 (d, J = 17.1 Hz, 2H), 4.23 (t, J =}
\]

86
Preparation of benzyl (S)-[3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)but-3-en-2-yl]carbamate (1n).

NsHNCbz (6.34 g, 21.0 mmol) and PPh₃ (4.41 g, 16.8 mmol) was placed in an oven-dried two-neck equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (42 mL) and (R)-6 (981 mg, 14.0 mmol, >98% ee, TCI, B2909) were added in the flask through the rubber septum using syringes, and then DIAD (6.87 mL, 35.0 mmol) was added dropwise at 0°C. After stirring for 1 h, the mixture was concentrated in vacuo. The residue was purified by column chromatography to give S20 in 83% (containing small amount of impurities). The obtained S20 was used in the next reaction without further purification.

S20 (4.50 g, 11.6 mmol) and LiOH·H₂O (1.95 g, 46.4 mmol) was placed in an oven-dried two-neck equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DMF (89 mL) and thioglycolic acid (1.62 mL, 23.2 mmol) were added in the flask through the rubber septum using syringes, and then DIAD (8.37 mL, 50.5 mmol) was added dropwise at 0°C. After stirring for 30 min, the solution was diluted with saturated NaHCO₃ solution and extracted with Et₂O four times, and then washed with brine, and dried over MgSO₄. After filtration, the solvents were removed by evaporation. The crude product was purified by flash column chromatography to obtain 7 (1.70 g, 8.36 mmol) in 60% (2 steps). ¹H NMR (392 MHz, CDCl₃, δ): 1.43 (d, J = 6.7 Hz, 3H), 2.29 (d, J = 2.7 Hz, 1H), 4.55–4.59 (m, 1H), 4.92 (brs, 1H), 5.12 (s, 2H), 7.30–7.39 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 22.3 (CH₃), 38.7 (CH), 66.8 (CH₂), 70.5 (C), 84.0 (CH), 128.1 (CH), 128.4 (CH), 136.1 (C), 155.1 (C). HRMS-EI (m/z): [M]+ calc for C₁₂H₁₃NO₄, 203.09463; found, 203.09526. [α]D²⁷.⁸ −38.0 (c 1.0 in CHCl₃).

8 (304 mg, 1.01 mmol) was prepared in 78% from 7 (264 mg, 1.30 mmol) according to the procedure for the synthesis of S8. ¹H NMR (392 MHz, CD₂CN, δ): 1.19 (d, J = 6.7 Hz, 3H), 1.24 (s, 12H), 4.27 (quint, J = 7.4 Hz, 1H), 5.01 (d, J = 12.5 Hz, 1H), 5.06 (d, J = 12.6 Hz, 1H), 5.69 (s, 3H), 7.29–7.39 (m, 5H). ¹³C NMR (99 MHz, CDCl₃, δ): 22.2 (CH₃), 24.5 (CH₃), 24.7 (CH₃), 52.2 (CH), 66.2 (CH₂), 83.5 (C), 127.8 (CH), 127.9 (CH), 128.3 (CH), 129.0 (CH₂), 129.7 (CH), 136.1 (C), 155.1 (C).
136.7 (C), 142.2 (br, B–C), 155.4 (C). HRMS-EI (m/z): [M]+ cale for C_{18}H_{26}^{10}BNO_{6}, 330.19912; found, 330.19877. \([\alpha]_D^{24} +3.80 (c 0.9 in CHCl_3, 98% ee). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 100/0, 0.5 mL/min, 40 °C, (R)-isomer: \(t_R = 57.57 \text{ min.}, (S)-isomer: \(t_R = 44.00 \text{ min.}

**1n** (312 mg, 0.31 mmol) was prepared in 39% from **8** (265 mg, 0.80 mmol) according to the procedure for the synthesis of **1a**. \(^{1}H\) NMR (392 MHz, CD_{3}CN, \(\delta\)): 1.21 (d, \(J = 7.2 \text{ Hz}, 3H\)), 2.81 (s, 3H), 3.75 (d, \(J = 17.0 \text{ Hz}, 1H\)), 3.86–3.99 (m, 3H), 4.11 (quint, \(J = 7.1 \text{ Hz, 1H}\)), 5.02 (s, 2H), 5.38 (s, 1H), 5.67 (s, 1H), 5.81 (brd, \(J = 6.3 \text{ Hz, 1H}\)), 7.29–7.39 (m, 5H). \(^{13}C\) NMR (99 MHz, CD_{3}CN, \(\delta\)): 22.4 (CH_{3}), 47.7 (CH_{3}), 50.8 (CH), 62.6 (CH_{2}), 62.8 (CH_{2}), 66.8 (CH_{2}), 122.7 (CH_{2}), 128.6 (CH), 129.9 (CH), 138.5 (C), 151.7 (br, B–C), 156.7 (C), 169.4 (C), 169.6 (C). HRMS-EI (m/z): [M]+ cale for C_{17}H_{21}^{10}BNO_{6}, 359.15290; found, 359.15409. \([\alpha]_D^{27.7} -10.8 (c 1.0 in CH_{3}CN, 98% ee). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 30/70, 0.5 mL/min, 40 °C, (R)-isomer: \(t_R = 45.57 \text{ min.}, (S)-isomer: \(t_R = 52.59 \text{ min.}

**Preparation of (9H-fluoren-9-yl)methyl(S)-(2-[[3-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)but-3-en-2-yl]amino]-2-oxoethyl)carbamate (S24).**

\[
\begin{align*}
\text{HO} & \quad \text{BocNHNs (1.5 equiv)} \\
\text{(R)-6} & \quad \text{DIAD (2.5 equiv)} \\
>98% \text{ ee} & \quad \text{PPH}_{3} (3.0 \text{ equiv}) \\
\text{CH}_{2}Cl_{2}, \text{rt, 1 h} & \quad \text{Boc}^{+} \\
\text{MeOH (1.5 equiv)} & \quad \text{thioglycolic acid (2.0 equiv)} \\
\text{THF, -30°C, 4 h} & \quad \text{LiOH·H}_{2}O (4.0 \text{ equiv}) \\
72\% & \quad \text{DMF, rt, 30 min} \\
& \quad 44\% (2 \text{ steps}) \\
\text{B}_{2}(pin)_{2} (1.1 \text{ equiv}) & \quad \text{MIDA (6.4 equiv)} \\
1 \text{ mol% SmI}{\text{MesCuI}} & \quad \text{HC(OEt)}_{2} (4.0 \text{ equiv}) \\
1 \text{ mol% Na(O}{\text{Bu})} & \quad \text{DMSO, 100°C} \\
& \quad 24 \text{ h, 48\%} \\
\text{HCl (4 M in dioxane)} & \quad \text{Fmoc–Gly–OH (2.0 equiv)} \\
\text{0°C to rt, 30 min} & \quad \text{EDCI (1.5 equiv)} \\
& \quad \text{HOBr (1.7 equiv)} \\
& \quad \text{DIPEA (1.2 equiv)} \\
& \quad \text{DMF, 0°C to rt, 21 h} \\
64\% (2 \text{ steps}) & \quad \text{FmocHN} \\
\text{B(MIDA)} & \quad \text{B(MIDA)} \\
\text{(S)-S23, 99\% ee} & \quad \text{(S)-S24, >99\% ee} \\
\text{BocNH} \quad \text{BocNH} & \quad \text{BocNH} \\
\end{align*}
\]

**S21** (1.64 mg, 9.72 mmol, white solid) was prepared in 44% yield (2 steps) from (R)-6 (1.05 g, 22.2 mmol, >98% ee, TCI, B2909) according to the procedure for the synthesis of 7. \(^{1}H\) NMR (401 MHz, CDCl_{3}, \(\delta\)): 1.40 (d, \(J = 7.2 \text{ Hz, 3H}\)), 1.45 (s, 9H), 2.26 (d, \(J = 2.4 \text{ Hz, 1H}\)), 4.50 (brs, 1H), 4.71 (brs, 1H). \(^{13}C\) NMR (100 MHz, CDCl_{3}, \(\delta\)): 22.4 (CH_{3}), 28.3 (CH_{3}), 38.1 (CH), 70.1 (C), 79.8 (C), 84.5 (CH), 154.6 (C). HRMS-ESI (m/z): [M+Na]+ cale for C_{9}H_{13}O_{2}NNa, 192.09950; found, 192.10017. \([\alpha]_D^{25.1} -57.3 (c 1.1 in CHCl_{3}, 99% ee).

**S22** (2.08 g, 7.00 mmol) was prepared in 72% from **S21** (1.69 g, 9.76 mmol) according to the procedure for the synthesis of **S8**. \(^{1}H\) NMR (401 MHz, CDCl_{3}, \(\delta\)): 1.22 (d, \(J = 6.4 \text{ Hz, 3H}\)), 1.27 (s, 12H), 1.44 (s, 9H), 4.32 (m, 1H), 5.02 (brd, \(J = 7.2 \text{ Hz, 1H}\)), 5.72 (s, 1H), 5.79 (s, 1H). \(^{13}C\) NMR (99 MHz, CDCl_{3}, \(\delta\)): 22.2 (CH_{3}), 24.6 (CH_{3}), 28.3 (CH_{3}), 51.4 (CH), 78.6 (C), 83.4 (C), 128.4 (CH_{2}), 143.0 (br, B–C), 155.0 (C). HRMS-ESI (m/z): [M–CH_{3}]^{+} cale for
\[
\text{C}_{14}\text{H}_{23}\text{NO}_4, \text{281.19129;} \text{ found, 281.19103. } [\alpha]_D^{27.2} = 12.0 \text{ (c 1.1 in CHCl}_3, \text{ 99% ee). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, (R)-isomer: } t_R = 12.27 \text{ min., (S)-isomer: } t_R = 16.56 \text{ min.}
\]

**S23** (398 mg, 1.22 mmol) was prepared in 48% from **S22** (751 mg, 2.53 mmol) according to the procedure for the synthesis of **1a**. Unreacted starting material was recovered in 19%. 1H NMR (401 MHz, CD$_3$CN, δ): 1.16 (d, J = 6.8 Hz, 3H), 1.37 (s, 9H), 2.83 (s, 3H), 3.79 (d, J = 7.2 Hz, 2H), 4.36 (m, 4H), 5.37 (d, J = 1.8 Hz, 1H), 5.63 (s, 1H), 5.94 (brt, J = 5.6 Hz, 1H), 6.76 (brd, J = 6.7 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 7.6 Hz, 2H). 13C NMR (99 MHz, CD$_3$CN, δ): 22.2 (CH$_3$), 44.8 (CH$_2$), 47.7 (CH$_2$), 47.9 (CH), 48.9 (CH), 62.8 (CH$_2$), 67.3 (CH$_2$), 121.0 (CH), 122.9 (CH), 126.2 (CH), 128.7 (CH), 142.1 (C), 145.1 (C), 157.6 (C), 169.3 (C), 169.4 (C), 169.7 (C). 11B NMR (127 MHz, acetone-de$_6$, δ): 11.36 (s). HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{14}$H$_{23}$O$_3$N$_2$Na, 348.15777; found, 348.15828. [α]$_D^{24.0} = +3.0$ (c 0.7 in CH$_3$CN, 99% ee). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 15/85, 0.5 mL/min, 40 °C, (R)-isomer: $t_R = 55.01$ min., (S)-isomer: $t_R = 46.16$ min.

**S23** (878.8 mg, 2.70 mmol) was placed in an oven-dried two-neck flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. 4 M HCl in dioxane (27 mL) was then added to the solution and the resultant solution was stirred at room temperature for 30 min. The resultant suspension was then diluted with Et$_2$O and the precipitated solid was collected by decantation, and dried in vacuo. The ammonium salt (673.8 mg, 2.70 mmol) and Fmoc-Gly-OH (1.6055 g, 5.4 mmol), EDC (0.7764 g, 4.1 mmol), and HOBt (0.6202 g, 4.6 mmol) were placed in an oven-dried two-neck flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DMF (21 mL) and DIPEA (0.56 mL, 3.2 mmol) were then added in the flask using syringes at 0°C, and then the solution was allowed to warm to room temperature and stirred for 17 h. Then aq. NH$_3$Cl was added to the reaction mixture and separated. The aqueous layer was further extracted with AcOEt three times. The combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (AcOEt/Acetone 100:0–80:20) to afford **S24** (833.8 mg, 1.65 mmol) in 64% yield (2 steps) as a white solid. 1H NMR (392 MHz, CD$_3$CN, δ): 1.20 (d, J = 6.7 Hz, 3H), 2.82 (s, 3H), 3.66 (d, J = 6.3 Hz, 2H), 3.79 (d, J = 17.0 Hz, 1H), 3.91 (s, 1H), 3.96 (d, J = 1.8 Hz, 2H), 4.23–4.36 (m, 4H), 5.37 (d, J = 1.8 Hz, 1H), 5.63 (s, 1H), 5.94 (bdt, J = 5.6 Hz, 1H), 6.76 (brd, J = 6.7 Hz, 1H), 7.34 (t, J = 7.4 Hz, 2H), 7.42 (t, J = 7.4 Hz, 2H), 7.67 (d, J = 7.2 Hz, 2H), 7.84 (d, J = 7.6 Hz, 2H). 13C NMR (99 MHz, CD$_3$CN, δ): 22.2 (CH$_3$), 44.8 (CH$_2$), 47.7 (CH$_2$), 47.9 (CH), 48.9 (CH), 62.8 (CH$_2$), 67.3 (CH$_2$), 121.0 (CH), 122.9 (CH), 126.2 (CH), 128.1 (CH), 128.7 (CH), 142.1 (C), 145.1 (C), 157.6 (C), 169.3 (C), 169.4 (C), 169.7 (C). 11B NMR (127 MHz, CD$_3$CN): 11.03 (s). HRMS-ESI: [M+Na]$^+$ calculated for C$_{12}$H$_{25}$O$_7$N$_3$Na, 527.19488; found, 527.19522. [α]$_D^{24.0} = +25.3$ (c 1.0 in CH$_3$CN, 99% ee). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 100/0, 0.5 mL/min, 40 °C, (R)-isomer: $t_R = 49.65$ min., (S)-isomer: $t_R = 44.72$ min.
Characterization of Acylboron Compounds.

6-Methyl-2-(3-phenylpropanoyl)-1,3,6,2-dioxazaborocane-4,8-dione (4a).

![4a](image)

4a (81.5 mg, 0.28 mmol, white solid) was prepared in 94% yield (4a:5a = >95:<5) from 1a (108.9 mg, 0.30 mmol). The NMR spectra of 4a are consistent with those reported. ¹H NMR (396 MHz, CD₃CN, δ): 2.75 (s, 3H), 2.82 (t, J = 7.5 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H), 3.87 (d, J = 17.2 Hz, 2H), 4.02 (d, J = 16.7 Hz, 2H), 7.14–7.28 (m, 5H).

¹³C NMR (100 MHz, CD₃CN, δ): 28.7 (C₆H₂), 47.4 (C₆H₃), 48.9 (C₆H₂), 63.1 (C₆H₂), 126.8 (CH), 129.3 (CH), 129.4 (CH), 143.0 (C), 169.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ¹¹B NMR (127 MHz, CD₃CN, δ): 4.80 (s). HRMS-ESI (m/z): [M+Na]^+ calcd for C₁₄H₁₆O₅N₁₀BNa, 311.10501; found, 311.10499.

6-Methyl-2-pentanoyl-1,3,6,2-dioxazaborocane-4,8-dione (4b).

![4b](image)

4b (63.1 mg, 0.26 mmol, white solid) was prepared in 87% yield (4b:5b = 94:6) from 1b (94.6 mg, 0.3 mmol). The NMR spectra of 4b are consistent with those reported. ¹H NMR (396 MHz, CD₃CN, δ): 0.89 (t, J = 7.3 Hz, 3H), 1.24–1.33 (m, 2H), 1.48 (quint, J = 7.3 Hz, 2H), 2.63 (t, J = 7.3 Hz, 2H), 2.80 (s, 3H), 3.88 (d, J = 17.4 Hz, 2H), 4.02 (d, J = 17.0 Hz, 2H). ¹³C NMR (100 MHz, CD₃CN, δ): 14.3 (CH₃), 23.1 (CH₂), 24.9 (CH₂), 47.2 (CH₂), 47.3 (CH₃), 63.0 (CH₂), 169.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ¹¹B NMR (127 MHz, CD₃CN, δ): 4.80 (s). HRMS-ESI (m/z): [M]^+ calcd for C₁₀H₁₆O₅BNO₅, 240.11578; found, 240.11555.

2-(Cyclohexanecarbonyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4c).

![4c](image)

4c (67.5 mg, 0.25 mmol, white solid) was prepared in 84% yield (4c:5c = >95:<5) from 1c (102.4 mg, 0.30 mmol). The NMR spectra of 4c are consistent with those reported. ¹H NMR (396 MHz, CD₃CN, δ): 1.10–1.38 (m, 5H), 1.63–1.82 (m, 5H), 2.72–2.80 (m, 1H), 2.78 (s, 3H), 3.89 (d, J = 16.6 Hz, 2H), 4.01 (d, J = 17.0 Hz, 2H). ¹³C NMR (100 MHz, CD₃CN, δ): 26.4 (CH₂), 26.8 (CH₂), 27.3 (CH₃), 47.4 (CH₃), 53.7 (CH), 62.9 (CH₂), 169.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ¹¹B NMR (127 MHz, CD₃CN, δ): 4.98 (s). HRMS-ESI (m/z): [M]^+ calcd for C₁₂H₁₈O₅BNO₅, 266.13143; found, 266.13137.
2-Benzoyl-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4d).

\[
\begin{align*}
&\text{4d} \\
&\text{4d (70.5 mg, 0.27 mmol, white solid) was prepared in 90% yield (4d:5d = >95:<5) from 1d (100.5 mg, 0.30 mmol). The NMR spectra of 4d are consistent with those reported.}^{10} \text{ } \text{ } \text{1H NMR (396 MHz, CD}_2\text{CN, } \delta) \text{: 2.94 (s, 3H), 3.99 (d, } J = 17.2 \text{ Hz, 2H), 4.10 (d, } J = 16.7 \text{ Hz, 2H), 7.50–7.54 (m, 2H), 7.61 (tt, } J = 1.7, 7.2 \text{ Hz, 2H), 8.04–8.07 (m, 2H).}^{13} \text{ } \text{C NMR (100 MHz, CD}_2\text{CN, } \delta): 47.5 (\text{C}_3\text{H}), 63.0 (\text{C}_2\text{H}), 129.2 (\text{C}_\text{H}), 129.7 (\text{C}_\text{H}), 134.2 (\text{C}_\text{H}), 141.7 (\text{C}), 169.0 (\text{C}). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. }^{11} \text{ } \text{B NMR (127 MHz, CDCl}_3, \delta): 5.96 (s). HRMS-ESI (m/z): [M+Na]^+ \text{ calcd for C}_{12}\text{H}_{12}\text{O}_{5}\text{BNO}_5, 260.08448; found, 260.08411.}
\end{align*}
\]

2-(4-Chlorobutanoyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4e).

\[
\begin{align*}
&\text{4e} \\
&\text{4e (73.6 mg, 0.28 mmol, white solid) was prepared in 94% yield (4e:5e = 84:16) from 1e (100.7 mg, 0.30 mmol). This product contains small amount of impurities. }^{1} \text{ } \text{1H NMR (396 MHz, CD}_2\text{CN, } \delta) \text{: 1.95–1.99 (m, 2H), 2.80 (t, } J = 7.1 \text{ Hz, 2H), 2.82 (s, 3H), 3.58 (t, } J = 6.7 \text{ Hz, 2H), 3.89 (d, } J = 17.0 \text{ Hz, 2H), 4.03 (d, } J = 17.4 \text{ Hz, 2H).}^{13} \text{ } \text{C NMR (100 MHz, CD}_2\text{CN, } \delta): 25.9 (\text{C}_2\text{H}), 44.4 (\text{C}_2\text{H}), 45.8 (\text{C}_2\text{H}), 47.4 (\text{C}_3\text{H}), 63.0 (\text{C}_2\text{H}), 169.1 (\text{C}). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. }^{11} \text{ } \text{B NMR (127 MHz, CDCl}_3, \delta): 4.76 (s). HRMS-ESI (m/z): [M+Na]^+ \text{ calcd for C}_{9}\text{H}_{13}\text{O}_{5}\text{N}_{10}\text{BClNa, 283.05038; found, 283.05038.}
\end{align*}
\]

6-Methyl-2-(5-oxohexanoyl)-1,3,6,2-dioxazaborocane-4,8-dione (4f).

\[
\begin{align*}
&\text{4f} \\
&\text{4f (71.4 mg, 0.27 mmol, white solid) was prepared in 88% yield (4f:5f = >95:<5) from 1f (102.9 mg, 0.30 mmol). }^{1} \text{ } \text{1H NMR (396 MHz, CD}_2\text{CN, } \delta) \text{: 1.69 (quint, } J = 7.3 \text{ Hz, 2H), 2.05 (s, 3H), 2.40 (t, } J = 7.3 \text{ Hz, 2H), 2.64 (t, } J = 7.2 \text{ Hz, 2H), 2.81 (s, 3H), 3.88 (d, } J = 16.7 \text{ Hz, 2H), 4.02 (d, } J = 17.2 \text{ Hz, 2H).}^{13} \text{ } \text{C NMR (100 MHz, CD}_2\text{CN, } \delta): 17.0 (\text{CH}_2), 30.0 (\text{CH}_3), 43.2 (\text{CH}_2), 46.6 (\text{CH}_2), 47.5 (\text{CH}_3), 63.1 (\text{CH}_2), 169.2 (\text{C}), 209.6 (\text{C}). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. }^{11} \text{ } \text{B NMR (127 MHz, acetone-d}_6, \delta): 5.14 (s). HRMS-ESI (m/z): [M]^+ \text{ calcd for C}_{11}\text{H}_{16}\text{BNO}_6, 268.11070; found, 268.10983.}
\end{align*}
\]

2-(6-Methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl acetate (4g).

\[
\begin{align*}
&\text{4g} \\
&\text{AcO} \quad \text{B(MIDA)} \\
\end{align*}
\]
4g (65.2 mg, 0.25 mmol, white solid) was prepared in 85% yield (4g:5g = 93:7) from 1g (76.5 mg, 0.30 mmol). \(^1\)H NMR (396 MHz, CD\(_2\)CN, \(\delta\)): 2.08 (s, 3H), 2.86 (s, 3H), 3.92 (d, \(J = 17.0\) Hz, 2H), 4.07 (d, \(J = 16.6\) Hz, 2H), 4.92 (s, 2H). \(^1\)C NMR (100 MHz, CD\(_2\)CN, \(\delta\)): 20.6 (CH\(_3\)), 47.8 (CH\(_3\)), 63.0 (CH\(_2\)), 73.8 (CH\(_2\)), 168.9 (C), 171.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(^1\)B NMR (127 MHz, CD\(_2\)CN, \(\delta\)): 4.90 (s, 1B). HRMS-ESI (m/z): [M+Na]\(^+\) calcd for C\(_9\)H\(_{17}\)O\(_3\)N\(_{10}\)BNa, 279.06353; found, 279.06353.

2-[(Benzyloxy)acetyl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4h).

6-Methyl-2-[(triisopropylsilyl)oxy]acyetyl]-1,3,6,2-dioxazaborocane-4,8-dione (4i).

2-[(1,3-Dioxiisoindolin-2-yl)acetyl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4j).
Benzyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl]carbamate (4k).

4k (91.9 mg, 0.26 mmol, white solid) was prepared in 88% yield (4k:5k = 90:10) from 1k (103.8 mg, 0.30 mmol). 

\[ \text{1H NMR} (396 MHz, CD}_3\text{CN, } \delta: 2.84 (s, 3H), 3.91 (d, } J = 17.0 \text{ Hz, 2H), 4.05 (d, } J = 16.6 \text{ Hz, 2H), 4.19 (d, } J = 5.5 \text{ Hz, 2H), 5.06 (s, 2H), 5.77 (brs, 1H), 7.32–7.38 (m, 5H).} \]

\[ \text{13C NMR} (100 MHz, CD}_3\text{CN, } \delta: 47.7 (\text{C}_3\text{H}_3), 55.4 (\text{C}_2\text{H}_2), 63.1 (\text{C}_2\text{H}_2), 67.1 (\text{C}_2\text{H}), 128.7 (\text{CH}), 128.9 (\text{CH}), 129.4 (\text{CH}), 138.3 (\text{C}), 157.4 (\text{C}) 168.9 (\text{C}). \]

The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. 

\[ \text{11B NMR} (127 MHz, CD}_3\text{CN, } \delta): 5.01 (s). \]

HRMS-ESI (m/z): [M+Na]⁺ calcd for C_{15}H_{17}O_7N_210BNa, 370.10573; found, 370.10557.

**tert-Butyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl]carbamate (4l).**

4l (857.6 mg, 2.73 mmol, white solid) was prepared in 91% yield (4l:5l = 95:5) from 1l (936.5 mg, 2.99 mmol). 

\[ \text{1H NMR} (396 MHz, acetone-d}_6, \delta: 1.40 (s, 9H), 3.09 (s, 3H), 4.16 (d, } J = 17.2 \text{ Hz, 2H), 4.17 (d, } J = 4.9 \text{ Hz, 2H), 4.38 (d, } J = 17.2 \text{ Hz, 2H), 5.89 (brs, 1H).} \]

\[ \text{13C NMR} (99 MHz, acetone-d}_6, \delta: 28.9 (\text{C}_3\text{H}_3), 47.8 (\text{C}_3\text{H}_3), 55.5 (\text{C}_2\text{H}_2), 63.4 (\text{C}_2\text{H}_2), 79.3 (\text{C}), 156.9 (\text{C}), 169.1 (\text{C}). \]

The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. 

\[ \text{11B NMR} (127 MHz, acetone-d}_6, \delta): 5.38 (s). \]

HRMS-ESI (m/z): [M+Na]⁺ calcd for C_{12}H_{19}O_7N_210BNa, 336.12138; found, 336.12209.

**(9H-Fluoren-9-yl)methyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl]carbamate (4m).**

4m (85.1 mg, 0.20 mmol, white solid) was prepared in 65% yield (4m:5m = 93:7) from 1m (130.2 mg, 0.30 mmol). 

\[ \text{1H NMR} (396 MHz, acetone-d}_6, \delta: 3.10 (s, 3H), 4.17 (d, } J = 17.2 \text{ Hz, 2H), 4.23–4.35 (m, 5H), 4.39 (d, } J = 16.7 \text{ Hz, 2H), 6.51 (brt, } J = 4.8 \text{ Hz, 1H), 7.34 (t, } J = 7.5 \text{ Hz, 2H), 7.42 (t, } J = 7.2 \text{ Hz, 2H), 7.74 (d, } J = 7.7 \text{ Hz, 2H), 7.87 (d, } J = 7.7 \text{ Hz, 2H).} \]

\[ \text{13C NMR} (99 MHz, acetone-d}_6, \delta: 47.5 (\text{CH}_3), 47.9 (\text{CH}), 55.4 (\text{CH}_2), 63.1 (\text{CH}_2), 67.2 (\text{CH}_2), 120.8 (\text{CH}), 126.2 (\text{CH}), 128.0 (\text{CH}), 128.5 (\text{CH}), 141.2 (\text{C}), 145.1 (\text{C}), 157.3 (\text{C}), 168.9 (\text{C}). \]

The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. 

\[ \text{11B NMR} (127 MHz, acetone-d}_6, \delta): 5.35 (s). \]

HRMS-ESI (m/z): [M+Na]⁺ calcd for C_{22}H_{21}O_7N_210BNa, 458.13703; found, 458.13718.
Benzyl (S)-[1-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-1-oxopropan-2-yl]carbamate (4n).

\[
\text{CbzHN} \quad \begin{array}{c}
\text{O} \\
\end{array} \quad \begin{array}{c}
\text{B(MIDA)} \\
\end{array} \\
\text{Me} \\
\]

\(4n\) (336.8 mg, 0.93 mmol, white solid) was prepared in 93% yield (\(4n:5n = >95:<5\)) from \(1n\) (360.2 mg, 1.00 mmol).

\(^1\)H NMR (396 MHz, acetone-\(d_6\), \(\delta\)): 1.30 (d, \(J = 7.3\) Hz, 3H), 3.05 (s, 3H), 4.11 (d, \(J = 16.8\) Hz, 1H), 4.18 (d, \(J = 17.2\) Hz, 1H), 4.38 (t, \(J = 17.4\) Hz, 2H), 4.59 (quint, \(J = 7.4\) Hz, 1H), 5.04 (s, 2H), 6.44 (brd, \(J = 6.3\) Hz, 1H), 7.29–7.38 (m, 5H). \(^13\)C NMR (99 MHz, acetone-\(d_6\), \(\delta\)): 15.6 (\(\text{C}_3\)H₃), 47.9 (\(\text{C}_3\)H₃), 59.3 (CH), 63.3 (CH₂), 63.4 (CH₂), 67.0 (CH₂), 129.0 (CH), 129.6 (CH), 138.6 (C), 157.2 (C), 168.8 (C), 169.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(^{11}\)B NMR (127 MHz, acetone-\(d_6\), \(\delta\)): 5.52 (s). HRMS-ESI (m/z): [M+Na]\(^+\) calculated for C\(^{16}\)H\(^{19}\)O\(^7\)N\(^2\)10BNa, 384.12138; found, 384.12228. [\(\alpha\)]\(^D\) \(27.6^+81.3\ (c 1.0 \text{ in CH}_3\text{CN, 99% ee}).\]

The ee value was determined by HPLC analysis. Daicel CHIRALPAK® IC, AcOEt/Hexane = 33:67, 0.8 mL/min, 40 °C, (\(R\))-isomer: \(t_R = 17.13\) min., (\(S\))-isomer: \(t_R = 20.42\) min.

(9H-Fluoren-9-yl)methyl(\(S\))-(2-[1-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-1-oxopropan-2-yl]amino)-2-oxoethyl)carbamate (S25).

\[
\text{FmocHN} \quad \begin{array}{c}
\text{N} \\
\end{array} \quad \begin{array}{c}
\text{O} \\
\end{array} \quad \begin{array}{c}
\text{Me} \\
\end{array} \quad \begin{array}{c}
\text{B(MIDA)} \\
\end{array} \\
\]

\(S25\) (702.4 mg, 1.38 mmol, white solid) was prepared in 76% yield (\(S25:acyloxyboron = 96:4\)) from \(S24\) (923.3 mg, 1.83 mmol).

\(^1\)H NMR (396 MHz, DMSO-\(d_6\), \(\delta\)): 1.15 (d, \(J = 7.2\) Hz, 3H), 2.79 (s, 3H), 3.57–3.70 (m, 2H), 4.05 (dd, \(J = 4.9, 17.2\) Hz, 2H), 4.20–4.40 (m, 5H), 4.61 (quint, \(J = 7.5\) Hz, 1H), 7.32 (t, \(J = 7.5\) Hz, 2H), 7.41 (t, \(J = 7.2\) Hz, 2H), 7.53 (t, \(J = 6.1\) Hz, 1H), 7.71 (d, \(J = 7.2\) Hz, 2H), 7.89 (d, \(J = 7.1\) Hz, 2H), 8.02 (d, \(J = 6.3\) Hz, 1H). \(^13\)C NMR (100 MHz, DMSO-\(d_6\), \(\delta\)): 14.5 (CH₃), 43.1 (CH₂), 46.7 (CH₂), 47.0 (CH₃), 56.1 (CH), 62.1 (CH₂), 65.8 (CH₂), 120.2 (CH), 125.3 (CH), 127.2 (CH), 140.8 (C), 143.9 (C), 156.5 (C), 168.7 (C), 168.8 (C), 169.2 (C). \(^{11}\)B NMR (127 MHz, DMSO-\(d_6\), \(\delta\)): 4.77 (s). HRMS-ESI: [M+Na]\(^+\) calculated for C\(^{25}\)H\(^{26}\)O\(^8\)N\(^3\)10BNa, 529.17415; found, 529.17476. [\(\alpha\)]\(^D\) \(23.9^+28.3\ (c 1.0 \text{ in CH}_3\text{CN}).\)

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Oligopeptide Synthesis by Ligation between KAT and Amino Acid

Preparation of potassium ([[(9H-fluoren-9-yl)methoxy]carbonyl]glycyl)trifluoroborate (9)

4m (436.1 mg, 1.00 mmol) and KHF$_2$ (351.0 mg, 4.50 mmol) was placed in a flask equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (2.0 mL) and H$_2$O (1.0 mL) were then added in the flask using syringes, and then the resultant solution was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo. The resulting solid was washed with Et$_2$O, and then filtered with DMF. The filtrate was concentrated in vacuo to obtain 9 (328.6 mg, 0.849 mmol, 85%) as a white solid.

$^1$H NMR (396 MHz, DMSO-d$_6$, $\delta$): 3.83 (d, $J$ = 5.9 Hz, 3H), 4.12–4.21 (m, 2H), 6.80 (t, $J$ = 5.4 Hz, 1H), 7.33 (t, $J$ = 7.2 Hz, 1H), 7.42 (t, $J$ = 7.2 Hz, 2H), 7.73 (d, $J$ = 7.7 Hz, 2H), 7.89 (d, $J$ = 7.7 Hz, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$, $\delta$): 46.7 (C), 52.5 (CH$_2$), 65.6 (CH$_2$), 120.1 (CH), 125.4 (CH), 127.1 (CH), 127.7 (CH), 140.7 (C), 144.0 (C), 156.2 (C). $^{11}$B NMR (127 MHz, DMSO-d$_6$): –1.58 (s). HRMS-ESI: [M + K]$^-$ calculated for C$_{17}$H$_{14}$O$_3$N$_1$O$^{10}$BF$_3$, 347.10606; found, 347.10653.

Potassium ([(9H-fluoren-9-yl)methoxy]carbonyl-L-alanyl)trifluoroborate (12)

12 (346.5 mg, 0.76 mmol) was prepared in 64% from S25 (600.4 mg, 1.18 mmol) according to the procedure for the synthesis of 9. $^1$H NMR (396 MHz, acetone-d$_6$, $\delta$): 1.23 (d, $J$ = 7.1 Hz, 3H), 3.82–3.88 (m, 2H), 4.23–4.34 (m, 3H), 4.59 (quint, $J$ = 6.8 Hz, 1H), 6.89 (brt, $J$ = 4.8 Hz, 1H), 7.31–7.35 (m, 2H), 7.41 (t, $J$ = 7.5 Hz, 2H), 7.74 (d, $J$ = 7.1 Hz, 2H), 7.86 (d, $J$ = 7.1 Hz, 2H). $^{13}$C NMR (99 MHz, CD$_3$CN, $\delta$): 16.3 (CH$_3$), 44.8 (CH$_2$), 47.8 (CH), 56.5 (CH), 67.4 (CH$_2$), 120.9 (CH), 126.1 (CH), 128.0 (CH), 128.6 (CH), 142.0 (C), 144.97 (C), 154.00 (C), 167.6 (C), 194.9 (C). $^{11}$B NMR (127 MHz, acetone-d$_6$): 0.00 (s). HRMS-ESI: [M + K]$^-$ calculated for C$_{20}$H$_{16}$O$_3$N$_2$BF$_3$, 418.14318; found, 418.14391. $[\alpha]_D^{24.5} +17.5$ (c 1.0 in MeOH).
Dipeptide 11 synthesis between α-amino KAT 9 and amino acid 10 in water.\textsuperscript{14}

\[
\begin{align*}
\text{FmocHN} & \quad \text{Cl} \quad \text{OBn} \\
\text{BF}_3 \text{K} & + \quad \text{TfO\textsuperscript{-}H}_3 \text{N}^\text{+} \quad \text{OBn} \\
9 & \quad 10 \quad 11
\end{align*}
\]

9 (116.6 mg, 0.30 mmol) and 10 (102.3 mg, 0.30 mmol) were dissolved in 300 mL of a 1:1 mixture of THF and aq. pH 3 buffer (prepared by dissolving citric acid monohydrate (4.48 g, 21.35 mmol) and trisodium citrate dihydrate (1.07 g, 3.64 mmol) in distilled water (1 L), final pH was adjusted using 0.1 M NaOH and HCl solutions). Then, 1,3-dichloro-5,5-dimethylhydantoin (DCH, 64.9 mg, 0.33 mmol) was added and the mixture was stirred for 24 h at room temperature. The solution was quenched with sat. aq. Na\textsubscript{2}SO\textsubscript{3}, concentrated in vacuo, and poured into brine and extracted with EtOAc (3 x 3 mL). The organic layers were dried over MgSO\textsubscript{4}, filtered and evaporated in vacuo. The residue was purified by column chromatography (AcOEt/Hex 30:70–50:50) to afford the desired dipeptide 11 (67.2 mg, 50%).

\[
\begin{align*}
\text{1}^\text{H} \text{NMR (392 MHz, CDCl}_3, \delta): & \text{ 3.93 (d, } J = 5.0 \text{ Hz, 2H), 4.10 (d, } J = 5.0 \text{ Hz, 2H), 4.23 (t, } J = 6.8 \text{ Hz, 1H), 4.45 (d, } J = 6.8 \text{ Hz, 2H), 5.19 (s, 2H), 5.38 (brs, 1H), 6.41 (brs, 1H), 7.26–7.42 (m, 9H), 7.59 (d, } J = 7.2 \text{ Hz, 2H), 7.76 (d, } J = 7.3 \text{ Hz, 2H).} \\
\text{1}^\text{3} \text{C NMR (100 MHz, CDCl}_3, \delta): & \text{ 41.2 (C}_2\text{H}, 44.2 (C}_2\text{H}, 47.0 (CH), 67.1 (CH}_2, 119.9 (CH), 125.0 (CH), 127.0 (CH), 127.7 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 134.9 (C), 141.2 (C), 143.6 (C), 156.6 (C), 169.4 (C), 169.6 (C). HRMS-ESI: [M+Na]^{+} \text{calculated for C}_{26}H_{24}O_{5}N_{2}Na, 467.15774; found, 467.15823.}
\end{align*}
\]

Tetrapeptide 14 synthesis between 12 and 13 in water.\textsuperscript{14}

\[
\begin{align*}
\text{FmocHN} & \quad \text{Cl} \quad \text{OBn} \\
\text{BF}_3 \text{K} & + \quad \text{Cl\textsuperscript{-}H}_3 \text{N}^\text{+} \quad \text{COOBn} \\
12 & \quad 13 \quad 14
\end{align*}
\]

KAT 12 (136.2 mg, 0.30 mmol) and 13 (89.6 mg, 0.30 mmol) were dissolved in 3.0 mL of a 1:1 mixture of THF and aq. pH 3 buffer. Then, DCH (65.2 mg, 0.33 mmol) was added and the mixture stirred for 1 h at room temperature. The solution was quenched with sat. aq. Na\textsubscript{2}SO\textsubscript{3}, poured into brine and extracted with EtOAc (3 x 3 mL). The organic layers were dried over MgSO\textsubscript{4}, filtered and evaporated in vacuo. The residue was purified by column chromatography (AcOEt/Hex 50:50–AcOEt/Acetone 80:20) to afford the desired tetrapeptide 14 (111.6 mg, 0.18 mmol, 61%, containing small amount of chlorinated product). \textsuperscript{1}H NMR (392 MHz, CDCl\textsubscript{3}, \delta): 1.41 (d, \textit{J} = 6.7 Hz, 3H), 1.98–2.23 (m, 4H), 3.44–3.67 (m, 2H), 3.92 (s, 2H), 4.05 (s, 2H), 4.23 (t, \textit{J} = 7.2 Hz, 1H), 4.41 (d, \textit{J} = 7.2 Hz, 2H), 4.56–4.61 (m, 2H), 5.13 (d, \textit{J} = 12.1 Hz, 1H), 5.18 (d, \textit{J} = 12.5 Hz, 1H), 5.63 (brs, 1H), 6.73 (brs, 1H), 6.94 (brs, 1H), 7.29–
7.42 (m, 9H), 7.60 (d, J = 7.2 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H). $^{13}$C NMR (99 MHz, CDCl$_3$, δ): 18.5 (CH$_3$), 24.4 (CH$_2$), 28.8 (CH$_2$), 41.8 (CH$_2$), 44.1 (CH$_2$), 45.9 (CH$_2$), 46.9 (CH), 48.7 (CH), 58.9 (CH), 66.8 (CH$_2$), 67.0 (CH$_2$), 119.7 (CH), 125.1 (CH), 126.9 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 128.4 (CH), 135.3 (C), 141.0 (C), 143.7 (C), 156.6 (C), 166.9 (C), 169.1 (C), 171.5 (C), 172.5 (C). HRMS-ESI: [M+Na]$^+$ calculated for C$_{34}$H$_{36}$O$_7$N$_4$Na, 635.24762; found, 635.24799. $[\alpha]_{D}^{24.0}$ –45.0 (c 1.0 in CH$_3$CN).

14 was separated from chlorinated product by reverse-phase HPLC. HPLC conditions were as follows: Shimadzu Prominence HPLC with PDA detector; Mighysil RP-18 GP Aqua column (250 mm L × 4.6 mm ID, 5 µm, Kanto Chemical Co., Inc.); flow rate, 1 mL min$^{-1}$; temperature, 30°C; mobile phase A, water + 0.05% TFA, mobile phase B, acetonitrile + 0.05% TFA; gradient conditions, 40% B, 0–30 min; 40%–100% B, 30–40 min; 100% B, 40–50 min; detection, 254 nm; injection volume, 25 µL (1mg/mL in acetonitrile/H$_2$O (1:1), 5 cycles).

The diastereomeric ratio was determined by HPLC analysis. Daiel CHIRALPAK® IC-3, MeOH/CHCl$_3$ = 100/0, 0.5 mL/min, 40 °C, (L,L)-isomer: $t_R$ = 8.59 min., (D,L)-isomer: $t_R$ = 12.13 min.
### X-ray Crystal Structure of 4j.

**Table 3-4. Summary of X-ray crystallographic data of 4j.**

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<th>Value</th>
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<td>Crystal Size / mm</td>
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<td>a / Å</td>
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<tr>
<td>b / Å</td>
<td>9.9748(16)</td>
</tr>
<tr>
<td>c / Å</td>
<td>12.737(2)</td>
</tr>
<tr>
<td>α / ‡</td>
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</tr>
<tr>
<td>β / ‡</td>
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<td>Temperature / K</td>
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</tr>
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<tr>
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</tr>
</tbody>
</table>

<sup>a</sup>: I > 2.00σ(I). <sup>b</sup>: All reflections. <sup>c</sup>: Goodness of Fit Indicator. <sup>d</sup>: in Final Diff. Map.
The References


13) The enantiomeric excess of (S)-4n slightly increased from (S)-1n. This would be caused by precipitation in the purification process of (S)-4n.


Chapter 4.

Synthesis of Potassium Acyltrifluoroborates from Aldehydes by a Cu(I)-catalyzed Borylation/Oxidation Protocol
Abstract
Preparation of potassium acyltrifluoroborates (KATs) was achieved by copper(I)-catalyzed borylation of aldehydes and following oxidation. Commercially availability of aldehydes, step- and redox-economical protocol, and mild reaction conditions enabled the preparation of wide range of KATs bearing functional groups such as halides, acetal, and ester, sulfide group. Moreover, this method was applied to the three-step synthesis of various α-amino acid analogues that bear a KAT moiety on the C-terminus by using naturally-occurring amino acids as starting materials.

Introduction
The chemistry of acylboron compounds represents a rapidly growing research theme in organic synthesis. Among these acylboron species, potassium acyltrifluoroborates (KATs) are of particular interest due to their unique reactivities and remarkable stabilities toward air and moisture. In 2012, Dumas, Bode, and Molander reported KAT ligation. Although other acylboron species such as acyl MIDA boronates and monofluoro acylborates have also been used in this amide-bond-formation reaction, all these reagents can be derived from KATs; in other words: strategic importance should be attributed to KATs as precursors to a wide variety of acylboron species. In addition, Bode recently reported that KATs react with amines to give trifluoroborate iminiums (TIMs) and subsequent reaction with organometal reagents to give α-amino boron compounds, which are significantly important structures in pharmaceuticals as bio-isosteres of α-amino acids.

Scheme 4-1. Transformation reaction of KATs. a) KAT ligation. b) Interconversion of KATs and acyl MIDA boronates and acyl monofluoroborates. c) TIM formation and subsequent addition of organometal reagents.
Furthermore, α-amino trifluoroborate also react with second organometal reagent in the presence of iodonium ion to afford tertiary amine. Thus, KATs are significantly important as a precursor as various valuable organic compounds.

In chapter 3, we reported the ozonolysis of alkenyl MIDA boronates, which afford acyl MIDA boronates.\textsuperscript{5a} Just after our publication, Perrin also reported the dihydroxylation/oxidative cleavage of alkenyl MIDA boronates to afford acyl MIDA boronates.\textsuperscript{5b} These approaches are conducted under relatively mild conditions and are suitable for the preparation of highly functionalized acylboronates including the first examples of enantioenriched α-amino acylboron compounds. However, there are still room for improvement because the additional steps needed to protect boronate moiety with MIDA and sometimes the yields of this step are low. Especially, it required optically active propargyl amines as a starting material for L-alanine type acylboron, so this approach is difficult to apply to the synthesis of other amino acid analogues when the synthesis of the corresponding optically active propargylamine is difficult.

Yudin and co-workers reported Dess-Martin oxidation of α-hydroxy MIDA boronates, which affords acyl MIDA boronates in 2012. Although this reaction is attractive because of the mild conditions, functional group tolerance was not examined in this study (Scheme 4-2).\textsuperscript{6} This is because preparation of α-hydroxy MIDA boronates required multiple steps from easily available alkenyl boronates and MIDA protection of the boronate moiety against oxidative conditions, which equates to additional steps.

![Scheme 4-2. Oxidation of α-hydroxy MIDA boronates](image)

As a possible route to KATs, the oxidation of α-hydroxy trifluoroborates seems to be one of the most straightforward methods. Such oxidation, however, has never been achieved yet. Herein, we report the KAT synthesis by oxidation of potassium α-hydroxy trifluoroborates using 9-azanoradamantane-N-oxyl (nor-AZADO) or DMSO/\textsubscript{2}O under optimized conditions (Scheme 4-3).\textsuperscript{7} The starting α-hydroxy boronates can directly be prepared from the corresponding aldehydes by Cu(I)-catalyzed borylation, followed by a treatment with KHF\textsubscript{2} in a one-pot fashion.\textsuperscript{8} This MIDA-free approach drastically reduces the number of preparation steps and enables the shortest and scalable approach to
KATs with keeping high functional compatibility. The important features of this approach are the commercial availability of a wide variety of aldehydes, its step-economy, and a wide product scope including KATs derived from biologically-related molecules including carbohydrate, steroid, and α-amino acids. Especially, we can use naturally occurring α-amino acid as starting materials for α-amino KATs. The high generality of this method for the synthesis of α-amino acylboron was demonstrated by the synthesis of various α-amino KATs including glycine type-, phenyl alanine type- and leucine type KATs.

Scheme 4-3. This work: KAT synthesis by Cu(I)-catalyzed borylation of aldehyde/Oxidation.
**Results and Discussion**

Aryl substituted α-hydroxy trifluoroborate 1a was prepared from o-tolualdehyde according to the procedure reported by Molander (Scheme 4-4).\(^{3b}\) Our initial attempt to synthesize α-hydroxy MIDA boronates via the reaction between 1a and (TMS)\(_2\)MIDA/BF\(_3\)-Et\(_2\)O was unsuccessful.\(^{3b}\) Therefore, we investigated the direct oxidation of 1a.\(^9\) When 1a was subjected to a Dess-Martin oxidation under reaction conditions similar to those for the oxidation of α-hydroxy MIDA boronates reported by Yudin, the reaction afforded a complex mixture, in which the desired KAT 2a was not detected. Subsequently, we investigated standard Swern oxidation conditions using DMSO/(COCl)\(_2\); alas, the low solubility of 1a hampered the reaction. Then we exchanged potassium cation to tetrabutylammonium (TBA) cation using TBAOH to increase the solubility of α-hydroxy trifluoroborates. Swern oxidation of obtained TBA α-hydroxy trifluoroborates 3a successfully detected TBA acyltrifluoroborates 4a by \(^{11}\)B NMR.

Encouraged by these results, we next investigated Albright-Goldman oxidation of potassium salt 1a using DMSO/Ac\(_2\)O at room temperature (Table 4-1, entry 1). This reaction furnished 2a in good yield (85%).\(^{10}\) Oxidation using catalytic amounts of nor-AZADO or AZADOL and a stoichiometric amount of the co-oxidant NaNO\(_2\) with acetic acid also afforded 2a in 92% and 66% yield (entries 2, 3), respectively, while other co-oxidants such as NaOCl or PhI(OAc)\(_2\) generated complex mixtures (entries 4, 5).\(^{11}\) The oxidation with tetrapropylammonium perruthenate (TPAP)/NMO afforded 2a in lower yield (38%, entry 6).

![Scheme 4-4. Initial investigation of oxidation of α-hydroxy trifluoroborate.](image-url)
Then, we investigated the scope of this reaction using two favorable procedures: oxidation with reaction conditions A) DMSO/Ac₂O and B) nor-AZADO catalyst (Scheme 4-5). The reaction exhibited high functional-group tolerance and afforded KATs containing methoxy (2b), halide (2c–2e), trifluoromethyl (2f), and sulfide (2g) moieties in good to high yield (64–93%). Sterically hindered aryl acylboron 2h was also prepared in good yield (47%). This method can also be applied to the preparation of an acylboron bearing thiophene (2i: 68%). In addition to aryl or heteroaryl KATs, this method was also effective for the preparation of alkyl KATs. α-Hydroxy trifluoroborates bearing primary (2j), secondary (2k), and tertiary alkyl groups (2l) can also be used in this method and afford the corresponding KATs in good to high yield (69–77%). Acylboron species bearing alkene (2m), ester (2n), and acetal moieties (2o) were also obtained in 30–67% yield. KATs 2g, 2m, and 2o are particularly important as their synthesis via the oxidative cleavage of alkenyl MIDA boronates is nontrivial.⁵a,b Based on the versatility of this method, we applied it to the preparation of KATs bearing biological molecules, which afforded glucose-bearing KAT 2p and estrone-bearing KAT 2q in 70% and 74% yield, respectively. This late-stage modification of bio-active molecules to the corresponding KATs has significant potential for the preparation of glycopeptide and antibody-drug conjugates.
Substrate Scope. Reaction conditions A: 1 (0.3 mmol), Ac₂O (20 equiv), DMSO, r. Reaction conditions B: 1 (0.3 mmol), nor-AZADO (10 mol%), NaNO₂ (1.5 equiv), AcOH (2.0 equiv), CH₃CN, rt. Isolated product yields are reported.

Subsequently, we investigated the synthesis of α-amino acid-derived KATs (Scheme 4-6). This class of compounds is very attractive due to its potential use as a building block in peptide conjugation using KAT ligation.¹ᵇ,³ᵃ N-Boc glycinal can be synthesized by the oxidation of N-Boc-protected 1,2-amino ethanol. Cu(I)-catalyzed borylation afforded α-hydroxy trifluoroborate 5a in 52% and followed by nor-AZADO oxidation afforded N-Boc glycine type KAT 6a in 76%. Next, we investigated the synthesis of enantioenriched amino acid analogues. The corresponding starting materials, i.e., the α-amino aldehydes, can be prepared from commercially available α-amino acids in one step.¹² Cu(I)-catalyzed borylation of N-Fmoc-protected leucinal afforded α-hydroxy trifluoroborate 5b in 62%. The
oxidation of 5b furnished N-Fmoc-protected leucine type KAT 6b in excellent yield with high enantiomeric purity (71%, 99% ee). Leucine-type KATs are important for peptide–peptide ligation due to its frequent appearance in natural proteins. This method can also be applied to the preparation of phenylalanine-type KAT (6c) in high yield excellent enantiopurity (borylation: 70%; oxidation: 80%; 99% ee). Considering the accessibility of α-amino aldehydes from α-amino acids, this chiral-pool-based synthetic strategy provides a general, and scalable approach to α-amino KATs that is much more advantageous than the reported oxidative cleavage of alkenyl MIDA boronates, which requires enantioenriched propargyl amine as starting materials.\textsuperscript{5a,b}

**Scheme 4-6.** Preparation of α-amino KATs. [a] Borylation conditions: aldehydes, B\textsubscript{3}pin\textsubscript{2} (1.1 equiv), (ICy)CuCl. Oxidation conditions: 1 (0.3 mmol), nor-AZADO (10 mol%), NaNO\textsubscript{2} (1.5 equiv), AcOH (2.0 equiv), CH\textsubscript{3}CN, rt, 6–7 h. Isolated product yields are reported.

This borylation/oxidation protocol is especially amenable to a gram-scale synthesis of KATs (Scheme 4-7). Borylation of 10 mmols of 4-fluorobenzaldehyde with 1.5 mol% of (ICy)CuCl catalyst followed by oxidation with 5.0 mol% nor-AZADO afforded KAT 2c in 62% yield (2.1 g). It is the simplicity of the synthetic protocol that renders it suitable for upscaling: the oxidation does not require an inert atmosphere and the products in each step can be easily isolated by filtration. Furthermore, phenylalanine-derived α-hydroxy trifluoroborate 5b was obtained in 53% yield from commercially available N-Boc-protected phenylalanine in two steps. And following oxidation of 5b (5.0 mmol) with 2.0 mol% nor-AZADO affords the corresponding phenylalanine-type KAT 6b in 82% yield (1.45 g) without any loss of enantiopurity.


**Scheme 4-7. Gram-scale synthesis of 2c and 6b.**

**Summary**

In summary, we have developed an operationally simple preparation of KATs in two steps from aldehydes. This borylation and oxidation reaction proceeds under mild conditions and exhibits high functional group tolerance, such as halides, acetal, and ester group. The oxidation can be accomplished with i) DMSO/Ac₂O or ii) nor-AZADO catalyst, and the conditions for either oxidation are practical as the use of expensive stoichiometric oxidants is not required. Importantly, various α-amino-acid analogues containing a KAT moiety, which is expected to be essential for peptide-peptide conjugation, can be prepared from naturally occurring α-amino aldehydes without racemization. The utility of this method was demonstrated by the synthesis of a KAT-containing carbohydrate and estrone, and a column-chromatography-free gram-scale synthesis.
**Experimental**

**General and Materials.**

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. Solvents were also purchased from commercial suppliers and dried over molecular sieves (MS 3A for CH$_3$CN or MS 4A for other solvents). $^1$H NMR spectra were recorded on JEOL JNM-ECX400P (400 MHz) and JNM-ECS400 (400 MHz) spectrometer and spectra are referenced to Tetramethylsilane (0.0 ppm) or residual protonated solvent (acetone-d$_6$: 2.05 ppm; CD$_3$CN: 1.94 ppm; DMSO-d$_6$: 2.50 ppm; CD$_3$OD: 3.31 ppm). $^{13}$C NMR spectra were recorded on JEOL JNM-ECX400P (100 MHz) and JNM-ECS400 (100 MHz) spectrometer and spectra are referenced to the solvent (CDCl$_3$: 77.0 ppm; acetone-d$_6$: 29.92 ppm; CD$_3$CN: 1.39 ppm; DMSO-d$_6$: 39.52 ppm; CD$_3$OD: 49.00 ppm). $^{11}$B NMR spectra were recorded on JEOL JNM-ECX400P (128 MHz) spectrometer and spectra are referenced to an external sample (BF$_3$·Et$_2$O: 0.0 ppm). $^{19}$F NMR spectra were recorded on JEOL JNM-ECX400P (376 MHz) spectrometer and spectra are referenced to an internal sample (fluorobenzene: –113.6 ppm). HPLC analyses with chiral stationary phase were carried out using a Hitachi LaChrome Elite HPLC system with a L-2400 UV detector and a Hitachi Chromaster HPLC system with a 5430 diode array detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University. (ICy)CuCl was synthesized according to the reported procedure.[1]

**General Experimental Procedures.**

**A General Procedure of Oxidation of Potassium α-Hydroxytrifluoroborate 1a with DMSO/Ac$_2$O.**

**(Reaction Condition A)**

Potassium α-hydroxytrifluoroborate 1a (114.3 mg, 0.5 mmol) was placed in an oven-dried screw neck reaction vial. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. Then DMSO (8.3 mL) and Ac$_2$O (950 µL, 10.0 mmol) were added in the vial through the rubber septum using syringes. And the resultant solution was stirred at room temperature for 2 h. Then, reaction mixture was quenched with H$_2$O (360 µL) and concentrated in vacuo. The resultant solid was washed with Et$_2$O to give KAT 2a as a white solid.
A General Procedure of Oxidation of Potassium α-Hydroxyrifluoroborate 1a with nor-AZADO/NaNO₂. (Reaction Condition B)

Potassium α-hydroxyrifluoroborate 1a (114.2 mg, 0.5 mmol), nor-AZADO (6.8 mg, 0.05 mmol) and NaNO₂ (57.1 mg, 0.75 mmol) were placed in an oven-dried screw neck reaction vial. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, CH₃CN (0.5 mL) and AcOH (57 µL, 1.0 mmol) were added in the vial through the rubber septum using syringes. And the resultant solution was stirred at room temperature for 18 h. Then, reaction mixture was concentrated in vacuo. The resultant solid was dissolved in acetone and filtered. Filtrate was concentrated in vacuo. The resultant solid was washed with Et₂O to give KAT 2a as a white solid.

Preparation of Substrates.
The aldehydes for the synthesis of 1a–1m, 1o were purchased from commercial suppliers. The received aldehydes from the suppliers were subjected to purification by distillation under reduced pressure before use.

Preparation of potassium trifluoro[hydroxy(o-tolyl)methyl]borate (1a).[2]

Bis(pinacolato)diboron (2.54 g, 10 mmol), (ICy)CuCl (49.9 mg, 0.15 mmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (20.0 mL) and K(O-t-Bu)/THF (1.0 M, 300 µL, 0.30 mmol) were then added in the flask through the rubber septum using syringes, and the resultant solution was then stirred at room temperature for 15 min. The solution was cooled to 0°C, at which 2-methylbenzaldehyde (1.19 g, 10 mmol) and MeOH (810 µL, 20 mmol) were then added in the flask through the rubber septum using syringes, and the resultant solution was then warmed to room temperature and stirred for 1.5 h. The resulting mixture was quenched with 4.5 M aqueous KHF₂ solution (18 ml, 80 mmol) and stirred for 2 h. The resulting mixture was concentrated under reduced pressure. The resultant solid was dissolved in acetone and filtered. The filtrate was concentrated in vacuo. The resultant solid was washed with Et₂O to give 1a (1.97 g, 86%) as a white solid. ¹H NMR (396 MHz, acetone-d₆, δ): 2.24 (s, 3H), 2.62 (brs, 1H), 4.26 (s, 1H), 6.78–7.05 (m, 3H), 7.46 (d,  J = 7.1 Hz, 1H). ¹³C NMR (100 MHz, acetone-d₆, δ): 20.1 (CH₃), 124.1 (CH), 125.5 (CH), 126.8 (CH), 129.5 (CH), 134.7 (C), 149.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ¹¹B NMR (127
MHz, acetone-d₆, δ): 3.98 (q, \( J = 55.5 \) Hz). \(^{19}\)F NMR (373 MHz, acetone-d₆, δ): –147.7 (q, \( J = 49.9 \) Hz). HRMS-ESI (m/z): \([\text{M–K}]^-\) calcd for \( \text{C}_8\text{H}_9\text{O}_{10}\text{BF}_3 \), 188.07403; found, 188.07393.

Preparation of potassium trifluoro[hydroxy(4-methoxyphenyl)methyl]borate (1b).

![Image of 1b](image)

1b (407.6 mg, 1.67 mmol, white solid) was prepared in 84% yield from 4-methoxybenzaldehyde (275.6 mg, 2.00 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, acetone-d₆, δ): 2.67 (brs, 1H), 3.71 (s, 3H), 3.95 (brs, 1H), 6.71 (d, \( J = 9.1 \) Hz, 2H), 7.21 (d, \( J = 8.7 \) Hz, 2H). \(^{13}\)C NMR (100 MHz, acetone-d₆, δ): 55.3 (CH₃), 113.3 (CH), 113.5 (C), 127.7 (CH), 129.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(^{11}\)B NMR (127 MHz, acetone-d₆, δ): 4.00 (q, \( J = 62.8 \) Hz). \(^{19}\)F NMR (373 MHz, acetone-d₆, δ): –148.8 (d, \( J = 56.9 \) Hz). HRMS-ESI (m/z): \([\text{M–K}]^-\) calcd for \( \text{C}_8\text{H}_9\text{O}_{10}\text{BF}_3 \), 204.06895; found, 204.06876.

Preparation of potassium trifluoro[(4-fluorophenyl)(hydroxy)methyl]borate (1c).

![Image of 1c](image)

1c (830.9 mg, 3.58 mmol, white solid) was prepared in 90% yield from 4-fluorobenzaldehyde (490.2 g, 3.95 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, acetone-d₆, δ): 2.89 (s, 1H), 4.00 (brs, 1H), 6.85 (dt, \( J = 2.3, 8.9 \) Hz, 2H), 7.28 (t, \( J = 7.3 \) Hz, 2H). \(^{13}\)C NMR (100 MHz, acetone-d₆, δ): 114.1 (d, \( J_{C\text{-F}} = 20.0 \) Hz, CH), 127.9 (d, \( J_{C\text{-F}} = 6.7 \) Hz, CH), 146.3 (C), 161.2 (d, \( J_{C\text{-F}} = 238.4 \) Hz, C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(^{11}\)B NMR (127 MHz, acetone-d₆, δ): 3.82 (q, \( J = 52.2 \) Hz). \(^{19}\)F NMR (373 MHz, acetone-d₆, δ): –122.0 (s, 1F), –149.3 (d, \( J = 56.9 \) Hz, 3F). HRMS-ESI (m/z): \([\text{M–K}]^-\) calcd for \( \text{C}_7\text{H}_6\text{O}_{10}\text{BF}_4 \), 192.04896; found, 192.04897.

Preparation of potassium [(4-chlorophenyl)(hydroxy)methyl]trifluoroborate (1d).

![Image of 1d](image)

1d (424.4 mg, 1.71 mmol, white solid) was prepared in 85% yield from 4-chlorobenzaldehyde (281.7 g, 2.00 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, acetone-d₆, δ): 4.01 (s, 1H), 7.11 (d, \( J = 8.3 \) Hz, 2H), 7.28 (d, \( J = 8.7 \) Hz, 2H). \(^{13}\)C NMR (100 MHz, acetone-d₆, δ): 127.7 (CH), 128.1 (CH), 129.5 (C), 149.2 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(^{11}\)B NMR
(127 MHz, acetone-d$_6$, $\delta$): 3.93 (brs). $^{19}$F NMR (373 MHz, acetone-d$_6$, $\delta$): −149.0 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_7$H$_6$O$_{10}$BClF$_3$, 208.01941; found, 208.01927.

**Preparation of potassium [(4-bromophenyl)(hydroxy)methyl]trifluoroborate (1e).**

![Diagram of 1e]

1e (970.1 mg, 3.31 mmol, white solid) was prepared in 81% yield from 4-bromobenzaldehyde (750.4 mg, 4.08 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (396 MHz, acetone-d$_6$, $\delta$): 4.00 (s, 1H), 7.25 (q, $J = 7.9$ Hz, 4H). $^{13}$C NMR (100 MHz, acetone-d$_6$, $\delta$): 117.4 (C), 128.5 (CH), 130.6 (CH), 150.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, $\delta$): 3.89 (s). $^{19}$F NMR (373 MHz, acetone-d$_6$, $\delta$): −148.8 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_7$H$_6$O$_{10}$BBrF$_3$, 251.96890; found, 251.96896.

**Preparation of potassium trifluoro{hydroxy[4-(trifluoromethyl)phenyl]methyl}borate (1f).**

![Diagram of 1f]

1f (600.3 mg, 2.13 mmol, white solid) was prepared in 53% yield from 4-(trifluoromethyl)benzaldehyde (698.0 mg, 4.01 mmol) according to the procedure for the synthesis of 1a. This product contains small amount of impurities. $^1$H NMR (392 MHz, acetone-d$_6$, $\delta$): 3.02 (brs, 1H), 4.12 (brs, 1H), 7.43 (d, $J = 8.5$ Hz, 2H), 7.47 (d, $J = 8.1$ Hz, 2H). $^{13}$C NMR (99 MHz, DMSO-d$_6$, $\delta$): 70.5 (br, B–C), 123.5 (q, $J_{C–F} = 3.8$ Hz, CH), 124.1 (q, $J_{C–F} = 31.0$ Hz, C), 125.1 (q, $J_{C–F} = 271.2$ Hz, C), 125.6 (CH), 155.6 (C). $^{11}$B NMR (127 MHz, acetone-d$_6$, $\delta$): 3.66 (q, $J = 53.4$ Hz). $^{19}$F NMR (373 MHz, acetone-d$_6$, $\delta$): −61.0 (s, 3F), −149.2 (s, 3F). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_8$H$_6$O$_{10}$BF$_6$, 242.04577; found, 242.04582.

**Preparation of potassium trifluoro{hydroxy[4-(methylthio)phenyl]methyl}borate (1g).**

![Diagram of 1g]

1g (819.9 mg, 3.15 mmol, white solid) was prepared in 79% yield from 4-(methylthio)benzaldehyde (607.9 mg, 3.99 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (396 MHz, acetone-d$_6$, $\delta$): 2.41 (s, 3H), 2.72 (brd, $J = 3.2$ Hz, 1H), 3.99 (brs, 1H), 7.09 (dt, $J = 2.1$, 8.4 Hz, 2H), 7.24 (d, $J = 8.3$ Hz, 2H). $^{13}$C NMR (100 MHz, acetone-d$_6$, $\delta$): 17.0 (CH$_3$), 103.4 (C), 127.2 (CH), 127.5 (CH), 132.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, $\delta$): 3.79 (q, $J = 54.7$ Hz).
$^{19}$F NMR (373 MHz, acetone-d₆, δ): –149.0 (d, J = 57.0 Hz). HRMS-ESI (m/z): [M−K]$^-$ calcd for C₈H₉OBF₃S, 220.04611; found, 220.04601.

Preparation of potassium trifluoro[hydroxy(mesityl)methyl]borate (1h).

1h (836.2 mg, 3.27 mmol, white solid) was prepared in 82% yield from 2,4,6-trimethylbenzaldehyde (593.5 mg, 4.01 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (401 MHz, acetone-d₆, δ): 2.13 (s, 3H), 2.33 (s, 6H), 4.50 (brs, 1H), 6.569 (s, 2H).

$^{13}$C NMR (100 MHz, acetone-d₆, δ): 20.8 (CH₃), 21.9 (CH₃), 69.3 (br, B–CH), 129.7 (CH), 133.1 (C), 136.7 (C), 142.2 (C). $^{11}$B NMR (127 MHz, acetone-d₆, δ): 4.41 (q, J = 54.7 Hz).

$^{19}$F NMR (372 MHz, acetone-d₆, δ): –144.0 (s). HRMS-ESI (m/z): [M−K]$^-$ calcd for C₁₀H₁₃OBF₃, 216.10533; found, 216.10522.

Preparation of potassium trifluoro[hydroxy(thiophene-2-yl)methyl]borate (1i).

1i (613 mg, 2.79 mmol, brown solid) was prepared in 69% yield from thiophene-2-carbaldehyde (452 mg, 4.03 mmol) according to the procedure for the synthesis of 1a. This product contains small amount of impurities. $^1$H NMR (396 MHz, acetone-d₆, δ): 4.17 (brs, 1H), 6.76–6.82 (m, 2H), 7.01 (d, J = 4.6 Hz, 1H). $^{13}$C NMR (100 MHz, acetone-d₆, δ): 122.4 (CH), 126.8 (CH), 153.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{11}$B NMR (127 MHz, acetone-d₆, δ): 3.76 (brs). $^{19}$F NMR (373 MHz, acetone-d₆, δ): –149.0 (s). HRMS-ESI (m/z): [M−K]$^-$ calcd for C₅H₅OBF₃S, 180.01481; found, 180.01455.

Preparation of potassium trifluoro(1-hydroxy-3-phenylpropyl)borate (1j).

1j (396.8 mg, 1.64 mmol, white solid) was prepared in 82% yield from 3-phenylpropanal (268.6 mg, 2.0 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (396 MHz, acetone-d₆, δ): 1.62–1.83 (m, 2H), 2.40 (brs, 1H), 2.54–2.64 (m, 1H), 2.74–3.00 (m, 2H), 7.03–7.13 (m, 1H), 7.13–7.25 (m, 4H). $^{13}$C NMR (100 MHz, acetone-d₆, δ): 34.4 (CH₂), 37.7 (CH₂), 125.9 (CH), 128.9 (CH), 129.4 (CH), 145.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. $^{11}$B NMR (127 MHz, acetone-d₆, δ): 4.64 (brs). $^{19}$F NMR (373 MHz, acetone-d₆, δ): –149.1 (s). HRMS-ESI (m/z): [M−K]$^-$ calcd for C₉H₁₀OBF₃, 202.08968; found, 202.08949.
Preparation of potassium [cyclohexyl(hydroxy)methyl]trifluoroborate (1k).

1k (618.8 mg, 2.81 mmol, white solid) was prepared in 70% yield from cyclohexanecarbaldehyde (448.2 mg, 4.0 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (396 MHz, CD$_3$OD, $\delta$): 0.96–1.31 (m, 5H), 1.36–1.50 (m, 1H), 1.58–1.81 (m, 5H), 1.93 (d, $J = 12.7$ Hz, 1H), 2.69 (quint, $J = 4.9$ Hz, 1H). $^{13}$C NMR (100 MHz, CD$_3$OD, $\delta$): 28.0 (CH$_2$), 28.09 (CH$_2$), 28.11 (CH$_2$), 30.8 (CH$_2$), 31.5 (CH$_2$), 43.1 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, CD$_3$OD, $\delta$): 4.11 (q, $J = 47.0$ Hz). $^{19}$F NMR (373 MHz, CD$_3$OD, $\delta$): –146.4 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_7$H$_{13}$O$_{10}$BF$_3$, 180.10533; found, 180.10509.

Preparation of potassium trifluoro(1-hydroxy-2,2-dimethylpropyl)borate (1l).

1l (480.2 mg, 2.48 mmol, white solid) was prepared in 63% yield from pivalaldehyde (339.3 g, 3.9 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (396 MHz, acetone-d$_6$, $\delta$): 0.89 (s, 9H). $^{13}$C NMR (100 MHz, DMSO-d$_6$, $\delta$): 27.7 (CH$_3$), 33.9 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, $\delta$): 3.68 (q, $J = 57.5$ Hz). $^{19}$F NMR (373 MHz, acetone-d$_6$, $\delta$): –142.6 (q, $J = 56.9$ Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_5$H$_{11}$O$_{10}$BF$_3$, 154.08968; found, 154.08950.

Preparation of potassium trifluoro(1-hydroxyundec-10-en-1-yl)borate (1m).

1m (289.3 mg, 1.05 mmol, white solid) was prepared in 26% yield from undec-10-enal (673.6 mg, 4.0 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (396 MHz, acetone-d$_6$, $\delta$): 1.19–1.54 (m, 14H), 1.78 (brs, 1H), 2.01 (s, 1H), 2.79 (t, $J = 0.8$ Hz, 2H), 4.90 (doublet of quintet, $J = 1.2$, 10.1 Hz, 1H), 4.99 (dq, $J = 1.8$, 17.0 Hz, 1H), 5.75–5.87 (m, 1H). $^{13}$C NMR (100 MHz, DMSO-d$_6$, $\delta$): 26.9 (CH$_2$), 28.4 (CH$_2$), 28.6 (CH$_2$), 29.1 (CH$_2$), 29.4 (CH$_2$), 29.8 (CH$_2$), 33.3 (CH$_2$), 34.3 (CH$_2$), 66.8 (br, B–CH), 114.7 (CH$_2$), 138.9 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, $\delta$): 4.48 (q, $J = 58.3$ Hz). $^{19}$F NMR (372 MHz, acetone-d$_6$, $\delta$): –149.7 (d, $J = 68.5$ Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_{11}$H$_{21}$O$_{10}$BF$_3$, 236.16794; found, 236.16800.
Preparation of potassium [5-(benzoyloxy)-1-hydroxypentyl]trifluoroborate (1n).

5-Oxopentyl benzoate was prepared according to the reported procedure.\[^{[3]}\] 1n (1.25 g, 3.98 mmol, white solid) was prepared in 99% yield from 5-oxopentyl benzoate (814.2 g, 3.95 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, acetone-d\(_6\), \(\delta\)): 1.36–1.84 (m, 6H), 2.89 (brs, 1H), 4.28 (t, \(J = 6.7\) Hz, 2H), 7.49 (t, \(J = 7.1\) Hz, 2H), 7.60 (t, \(J = 7.3\) Hz, 1H), 8.15 (d, \(J = 7.9\) Hz, 2H). \(^13\)C NMR (100 MHz, acetone-d\(_6\), \(\delta\)): 24.2 (CH\(_2\)), 30.0 (CH\(_2\)), 34.6 (CH\(_2\)), 66.1 (CH\(_2\)), 129.4 (CH), 130.2 (CH), 131.7 (C), 133.7 (CH), 166.9 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. \(^{11}\)B NMR (127 MHz, acetone-d\(_6\), \(\delta\)): 5.05 (brs). \(^{19}\)F NMR (373 MHz, acetone-d\(_6\), \(\delta\)): –149.2 (s). HRMS-ESI (m/z): [M–K]\(^+\) calcd for C\(_{12}\)H\(_{15}\)O\(_3\)BF\(_3\), 274.11081; found, 274.11112.

Preparation of potassium [4-(5,5-dimethyl-1,3-dioxan-2-yl)-1-hydroxybutyl]trifluoroborate (1o).

1o (293.3 mg, 1.00 mmol, white solid) was prepared in 58% yield from 4-(5,5-dimethyl-1,3-dioxan-2-yl)butanal (317.9 mg, 1.7 mmol) according to the procedure for the synthesis of 1a. \(^1\)H NMR (396 MHz, acetone-d\(_6\), \(\delta\)): 0.70 (s, 3H), 1.13 (s, 3H), 1.28–1.65 (m, 6H), 2.40 (brs, 1H), 3.41 (d, \(J = 10.7\) Hz, 2H), 3.53 (d, \(J = 11.1\) Hz, 2H), 4.39 (t, \(J = 4.6\) Hz, 1H). \(^13\)C NMR (100 MHz, acetone-d\(_6\), \(\delta\)): 22.1 (CH\(_3\)), 22.4 (CH\(_2\)), 23.5 (CH\(_3\)), 30.7 (C), 35.0 (CH\(_2\)), 36.3 (CH\(_2\)), 77.6 (CH\(_2\)), 103.4 (CH\(_2\)). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. \(^{11}\)B NMR (127 MHz, acetone-d\(_6\), \(\delta\)): 4.60 (brs). \(^{19}\)F NMR (373 MHz, acetone-d\(_6\), \(\delta\)): –149.2 (s). HRMS-ESI (m/z): [M–K]\(^+\) calcd for C\(_{10}\)H\(_{19}\)O\(_3\)BF\(_3\), 254.14211; found, 254.14224.


2,3,4,6-Tetra-O-acetyl-1-bromo-\(\alpha\)-D-glucose (4.12 g, 10 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. CH\(_3\)CN (100.0 mL) was then added in the flask through the rubber septum using syringe. Silver(I) oxide (9.31 g, 40 mmol) and 4-hydroxybenzaldehyde (1.22 g, 10 mmol) were then added in the flask, and the resultant solution was stirred at room temperature for 5 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and filtered through a thin Celite
layer. Then the Celite was washed twice with ethyl acetate. The filtrate was purified in vacuo. The resultant oil was purified by silica gel column chromatography to obtain S1 (3.47 g, 7.68 mmol) in 77% yield.

1p (1.017 g, 1.81 mmol, white solid) was prepared in 91% yield from S1 (905.4 mg, 2.0 mmol) according to the procedure for the synthesis of 1a. 1H NMR (396 MHz, acetone-d6, δ): 1.96 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 2.65 (brs, 1H), 3.97 (s, 1H), 4.11–4.21 (m, 2H), 4.30 (dd, J = 5.9, 12.7 Hz, 1H), 5.06–5.19 (m, 2H), 5.27 (dd, J = 3.2, 8.3 Hz, 1H), 5.37 (t, J = 9.7 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H). 13C NMR (100 MHz, acetone-d6, δ): 20.6 (CH3), 20.7 (CH3), 20.8 (CH3), 25.3 (CH3), 62.9 (CH2), 69.5 (CH), 72.2 (CH), 72.5 (CH), 73.5 (CH), 100.4 (CH), 116.7 (CH), 127.5 (CH), 145.8 (C), 155.1 (C), 169.9 (C), 170.2 (C), 170.4 (C), 170.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. 19B NMR (127 MHz, acetone-d6, δ): 3.89 (brs). 19F NMR (373 MHz, acetone-d6, δ): −148.9 (s). HRMS-ESI (m/z): [M–K]+ calc'd for C21H23O11BF3, 520.14838; found, 520.14844.

Preparation of potassium trifluoro(1-hydroxy-6-[(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[alphenanthren-3-yl]oxy]hexyl)borate (1q).

Estrone (1.09 g, 4.0 mmol) and K2CO3 (1.66 g, 12 mmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DMF (8.0 mL) and 6-chlorohexan-1-ol (690.0 µL, 5.2 mmol) were added in the flask through the rubber septum using syringes, and the resultant solution was stirred at 120°C for 39 h. The resulting mixture was cooled down to room temperature, and then extracted with DCM three times. The combined organic layer was dried over MgSO4, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography to obtain S2 (1.23 g, 3.33 mmol) in 83% yield. 1H NMR (396 MHz, CDCl3, δ): 0.91 (s, 3H), 1.29 (brs, 1H), 1.36–1.70 (m, 12H), 1.78 (quint, J = 6.8 Hz, 2H), 1.90–2.20 (m, 4H), 2.20–2.30 (m, 1H), 2.30–2.44 (m, 1H), 2.50 (dd, J = 8.9, 18.8 Hz, 1H), 2.83–2.96 (m, 2H), 3.66 (q, J = 5.3 Hz 2H), 3.93 (t, J = 6.3 Hz, 2H), 6.64 (d, J = 2.8 Hz, 1H), 6.71 (dd, J = 2.6, 8.5 Hz, 1H), 7.19 (d, J = 9.1 Hz, 1H). 13C NMR (100 MHz, CDCl3, δ): 13.8 (CH3), 21.5 (CH3), 25.5 (CH2), 25.9 (CH2), 26.5 (CH2), 29.2 (CH2), 29.6 (CH2), 31.5 (CH2), 32.6 (CH2) 35.8 (CH2), 38.3 (CH), 43.9 (CH), 48.0 (C), 50.3 (CH), 62.8 (CH2), 67.7 (CH2), 112.0 (CH), 114.5 (CH), 126.3 (CH), 131.8 (C), 137.7 (C), 157.0 (C), 221.1 (C). HRMS-ESI (m/z): [M]+ calc'd for C23H25O3Na, 393.24002; found, 393.24045.

S2 (1.11 g, 3.0 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen
manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. DCM (150 mL) was then added in the flask through the rubber septum using syringe. Dess–Martin periodinane (3.82 g, 9.0 mmol) was then added in the flask, and the resultant solution was stirred at room temperature for 1 h. The resulting mixture was quenched by saturated aqueous NaHCO₃ solution and saturated aqueous Na₂S₂O₅ solution, and then extracted with DCM three times. The combined organic layer was washed with saturated aqueous NaHCO₃ solution, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by silica gel column chromatography to obtain S₃ (916 mg, 2.49 mmol) in 83% yield.

1H NMR (392 MHz, CDCl₃, δ): 0.91 (s, 3H), 1.36–1.84 (m, 12H), 1.89–2.20 (m, 4H), 2.20–2.30 (m, 1H), 2.36–2.56 (m, 4H), 2.82–2.97 (m, 2H), 3.94 (t, J = 6.5 Hz, 2H), 6.63 (d, J = 2.8 Hz, 1H), 6.70 (dd, J = 2.8, 8.7 Hz, 1H), 7.19 (d, J = 8.7 Hz, 1H), 9.78 (t, J = 1.6 Hz, 1H). 13C NMR (99 MHz, CDCl₃, δ): 13.8 (CH₃), 21.5 (CH₂), 21.7 (CH₂), 25.6 (CH₂), 25.8 (CH₂), 26.5 (CH₂), 29.0 (CH₂), 29.6 (CH₂), 31.5 (CH₂), 35.8 (CH₂), 38.3 (CH), 43.7 (CH₂), 43.9 (CH), 47.9 (C), 50.3 (CH), 67.3 (CH₂), 112.0 (CH), 114.4 (CH), 126.2 (CH), 131.9 (C), 137.6 (C), 156.9 (C), 202.5 (CH), 220.9 (C). HRMS-ESI (m/z): [M⁺] calcd for C₂₄H₃₃O₃Na, 391.22437; found, 391.22507.

1q (411.9 mg, 0.86 mmol, white solid) was prepared in 29% yield from S₃ (1108.2 mg, 3.0 mmol) according to the procedure for the synthesis of 1a. 1H NMR (396 MHz, acetone-d₆, δ): 2.24 (s, 3H), 2.62 (br, 1H), 4.26 (s, 1H), 6.78–7.05 (m, 3H), 7.46 (d, J = 7.1 Hz, 1H). 13C NMR (100 MHz, acetone-d₆, δ): 20.1 (CH₃), 124.1 (CH), 125.5 (CH), 126.8 (CH), 129.5 (CH), 134.7 (C), 149.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. 11B NMR (127 MHz, acetone-d₆, δ): 3.98 (q, J = 55.5 Hz). 19F NMR (372 MHz, CD₃OD, δ): −150.3 (s). HRMS-ESI (m/z): [M–K⁺] calcd for C₂₄H₃₃O₃BF₃, 189.07040; found, 189.07403.
Characterization of Acylboron Compounds.

Potassium trifluoro(2-methylbenzoyl)borate (2a).

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\text{2a (96.3 mg, 0.43 mmol, white solid) was prepared in 85\% yield from 1a (114.3 mg, 0.50 mmol) using the reaction condition A. 2a (104.3 mg, 0.46 mmol, white solid) was prepared in 92\% yield from 1a (114.2 mg, 0.50 mmol) using the reaction condition B. The NMR spectra of 2a are consistent with those reported.}^{[4]} \text{1H NMR (401 MHz, acetone-d\textsubscript{6}, } \delta \text{): 2.39 (s, 3H), 7.10 (dd, } J = 1.2, 6.7 \text{ Hz, 1H), 7.20 (quintet of doublet, } J = 1.7, 7.0 \text{ Hz, 2H), 8.05 (d, } J = 7.1 \text{ Hz, 1H). 13C NMR (100 MHz, acetone-d\textsubscript{6}, } \delta \text{): 21.3 (CH\textsubscript{3}), 125.8 (CH), 130.0 (CH), 131.7 (CH), 132.1 (CH), 136.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.}^{[4]} \text{11B NMR (127 MHz, acetone-d\textsubscript{6}, } \delta \text{): } -0.45 (q, J = 52.3 \text{ Hz). 19F NMR (372 MHz, acetone-d\textsubscript{6}, } \delta \text{): } -145.0 (q, J = 49.3 \text{ Hz). HRMS-ESI (m/z): [M–K]\textsuperscript{–} \text{calcd for C\textsubscript{8}H\textsubscript{7}O\textsubscript{10}BF\textsubscript{3}, 186.05838; found, 186.05865.} \]

Potassium trifluoro(4-methoxybenzoyl)borate (2b).

\[
\text{2b (57.6 mg, 0.24 mmol, white solid) was prepared in 80\% yield from 1b (73.1 mg, 0.30 mmol) using the reaction condition B. The NMR spectra of 2b are consistent with those reported.}^{[5]} \text{1H NMR (396 MHz, acetone-d\textsubscript{6}, } \delta \text{): 3.84 (s, 3H), 6.92 (d, } J = 9.1 \text{ Hz, 2H), 8.09 (d, } J = 9.1 \text{ Hz, 2H). 13C NMR (100 MHz, acetone-d\textsubscript{6}, } \delta \text{): 55.7 (CH\textsubscript{3}), 113.8 (CH), 131.7 (CH), 135.4 (C), 163.4 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.}^{[5]} \text{11B NMR (127 MHz, acetone-d\textsubscript{6}, } \delta \text{): } -0.08 (q, J = 49.8 \text{ Hz). 19F NMR (373 MHz, acetone-d\textsubscript{6}, } \delta \text{): } -145.8 (q, J = 41.8 \text{ Hz). HRMS-ESI (m/z): [M–K]\textsuperscript{–} \text{calcd for C\textsubscript{8}H\textsubscript{7}O\textsubscript{10}BF\textsubscript{3}, 202.05330; found, 202.05319.} \]

Potassium trifluoro(4-fluorobenzoyl)borate (2c).

\[
\text{2c (63.9 mg, 0.28 mmol, white solid) was prepared in 93\% yield from 1c (69.3 mg, 0.30 mmol) using the reaction condition A. The NMR spectra of 2c are consistent with those reported.}^{[6]} \text{1H NMR (396 MHz, acetone-d\textsubscript{6}, } \delta \text{): 7.14 (tt, } J = 2.2, 9.2 \text{ Hz, 2H), 8.15 (dd, } J = 5.9, 8.3 \text{ Hz, 2H). 13C NMR (100 MHz, acetone-d\textsubscript{6}, } \delta \text{): 115.4 (d, } J\text{C–F = 22.0 Hz, CH), 132.0 (d, } J\text{C–F = 8.6 Hz, CH), 138.7 (C), 165.6 (d, } J\text{C–F = 248.9 Hz, C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.}^{[6]} \text{11B NMR (127 MHz, acetone-d\textsubscript{6}, } \delta \text{): } -0.16 (q, J = 49.8 \text{ Hz). 19F NMR (373 MHz, acetone-d\textsubscript{6}, } \delta \text{): } -117.3 (s), -148.9 (q, J = 45.4 \text{ Hz). HRMS-ESI (m/z): [M–K]\textsuperscript{–} \text{calcd for C\textsubscript{8}H\textsubscript{7}O\textsubscript{10}BF\textsubscript{3}, 202.05330; found, 202.05319.} \]
Potassium (4-chlorobenzoyl)trifluoroborate (2d).

2d (64.5 mg, 0.26 mmol, white solid) was prepared in 87% yield from 1d (74.3 mg, 0.30 mmol) using the reaction condition A. This product contains small amount of impurities. The NMR spectra of 2d are consistent with those reported.\[^4\] ¹H NMR (396 MHz, acetone-d₆, δ): 7.41 (dt, J = 2.1, 8.8 Hz, 2H), 8.06 (d, J = 7.1 Hz, 2H). ¹³C NMR (100 MHz, acetone-d₆, δ): 128.8 (CH), 131.0 (CH), 137.4, 140.7 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ¹¹B NMR (127 MHz, acetone-d₆, δ): -0.20 (q, J = 51.4 Hz). ¹⁹F NMR (373 MHz, acetone-d₆, δ): -143.7 (q, J = 49.3 Hz). HRMS-ESI (m/z): [M-K]⁻ calcd for C₇H₄O₁₀BF₃K, 206.00376; found, 206.00363.

Potassium (4-bromobenzoyl)trifluoroborate (2e).

2e (69.1 mg, 0.24 mmol, white solid) was prepared in 79% yield from 1e (87.9 mg, 0.30 mmol) using the reaction condition B. The NMR spectra of 2e are consistent with those reported.\[^5\] ¹H NMR (396 MHz, acetone-d₆, δ): 7.57 (dt, J = 2.0, 8.4 Hz, 2H), 7.99 (dt, J = 2.2, 8.6 Hz, 2H). ¹³C NMR (100 MHz, acetone-d₆, δ): 126.1 (C), 131.2 (CH), 131.8 (CH), 141.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ¹¹B NMR (127 MHz, acetone-d₆, δ): -0.17 (q, J = 51.4 Hz). ¹⁹F NMR (373 MHz, acetone-d₆, δ): -143.9 (q, J = 49.3 Hz). HRMS-ESI (m/z): [M-K]⁻ calcd for C₇H₄O₁₀BBrF₃K, 249.95325; found, 249.95332.

Potassium trifluoro[4-(trifluoromethyl)benzoyl]borate (2f).

2f (53.4 mg, 0.19 mmol, white solid) was prepared in 64% yield from 1f (84.5 mg, 0.30 mmol) using the reaction condition A. ¹H NMR (396 MHz, acetone-d₆, δ): 7.73 (d, J = 7.1 Hz, 2H), 8.21 (d, J = 8.3 Hz, 2H). ¹³C NMR (100 MHz, acetone-d₆, δ): 125.7 (CH), 129.7 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ¹¹B NMR (127 MHz, acetone-d₆, δ): -0.19 (q, J = 51.0 Hz). ¹⁹F NMR (372 MHz, acetone-d₆, δ): -62.0 (s), -143.97 (q, J = 49.2 Hz). HRMS-ESI (m/z): [M-K]⁻ calcd for C₈H₄O₁₀BF₆K, 240.03012; found, 240.03016.
Potassium trifluoro[4-(methylthio)benzoyl]borate (2g).

2g (63.4 mg, 0.25 mmol, white solid) was prepared in 82% yield from 1g (78.0 mg, 0.30 mmol) using the reaction condition B. $^1$H NMR (396 MHz, acetone-d$_6$, δ): 2.52 (s, 3H), 7.25 (d, $J = 8.7$ Hz, 2H), 8.02 (d, $J = 8.7$ Hz, 1H). $^{13}$C NMR (100 MHz, acetone-d$_6$, δ): 14.8 (CH$_3$), 125.4 (CH), 130.0 (CH), 138.8 (C), 143.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, δ): –0.10 (q, $J = 52.2$ Hz). $^{19}$F NMR (373 MHz, acetone-d$_6$, δ): –144.44 (q, $J = 45.5$ Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_8$H$_7$O$_{10}$BF$_3$S, 218.03046; found, 218.03021.

Potassium trifluoro(2,4,6-trimethylbenzoyl)borate (2h).

2h (35.8 mg, 0.14 mmol, white solid) was prepared in 47% yield from 1h (76.2 mg, 0.30 mmol) using the reaction condition A. $^1$H NMR (396 MHz, DMSO-d$_6$, δ): 1.98 (s, 6H), 2.17 (s, 3H), 6.65 (s, 2H). $^{13}$C NMR (100 MHz, DMSO-d$_6$, δ): 18.5 (CH$_3$), 20.6 (CH$_3$), 127.3 (CH), 131.9 (C), 134.7 (C), 146.3 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, δ): –0.92 (q, $J = 49.8$ Hz). $^{19}$F NMR (373 MHz, acetone-d$_6$, δ): –149.3 (q, $J = 49.3$ Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_{10}$H$_{11}$O$_{10}$BF$_3$, 214.08968; found, 214.08949.

Potassium trifluoro(thiophene-2-carbonyl)borate (2i).

2i (44.2 mg, 0.20 mmol, white solid) was prepared in 68% yield from 1i (67.0 mg, 0.30 mmol) using the reaction condition B. The NMR spectra of 4a are consistent with those reported. $^1$H NMR (396 MHz, DMSO-d$_6$, δ): 1.98 (s, 6H), 2.17 (s, 3H), 6.65 (s, 2H). $^{13}$C NMR (100 MHz, acetone-d$_6$, δ): 128.722 (CH), 131.3 (CH), 134.6 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, δ): –0.32 (q, $J = 49.8$ Hz). $^{19}$F NMR (372 MHz, acetone-d$_6$, δ): –146.03 (q, $J = 45.5$ Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for C$_{5}$H$_{3}$O$_{10}$BF$_3$S, 177.99916; found, 177.99902.
Potassium trifluoro(3-phenylpropanoyl)borate (2j).

\[
\text{\includegraphics[width=0.1\textwidth]{borate2j.png}}
\]

2j (83.4 mg, 0.35 mmol, white solid) was prepared in 69% yield from 1j (121.5 mg, 0.50 mmol) using the reaction condition A. 2j (41.9 mg, 0.17 mmol, white solid) was prepared in 58% yield from 1j (72.6 mg, 0.30 mmol) using the reaction condition B. The NMR spectra of 4a are consistent with those reported.\(^1\) \(1^H\) NMR (396 MHz, acetone-d\(_6\), \(\delta\)): 2.73 (s, 4H), 7.09–7.27 (m, 5H). \(1^C\) NMR (100 MHz, acetone-d\(_6\), \(\delta\)): 29.3 (CH\(_2\)), 47.0 (CH\(_2\)), 126.1 (CH), 129.0 (CH), 129.2 (CH), 144.4 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(1^{11}\)B NMR (127 MHz, acetone-d\(_6\), \(\delta\)): –0.91 (q, \(J = 52.2\) Hz). \(1^{19}\)F NMR (373 MHz, acetone-d\(_6\), \(\delta\)): –149.6 (q, \(J = 49.2\) Hz). HRMS-ESI (m/z): [M–K]\(^–\) calcd for C\(_9\)H\(_9\)O\(_3\)BF\(_3\), 200.07403; found, 200.07387.

Potassium cyclohexanecarbonyl trifluoroborate (2k).

\[
\text{\includegraphics[width=0.1\textwidth]{borate2k.png}}
\]

2k (50.5 mg, 0.23 mmol, white solid) was prepared in 77% yield from 1k (66.4 mg, 0.30 mmol) using the reaction condition A. 2k (50.7 mg, 0.23 mmol, white solid) was prepared in 78% yield from 1k (66.5 mg, 0.30 mmol) using the reaction condition B. The NMR spectra of 4a are consistent with those reported.\(^7\) \(1^H\) NMR (396 MHz, acetone-d\(_6\), \(\delta\)): 1.06–1.19 (m, 3H), 1.25 (qt, \(J = 3.0, 12.3\) Hz, 2H), 1.56–1.65 (m, 1H), 1.69 (dt, \(J = 3.4, 12.4\) Hz, 2H), 1.79 (d, \(J = 11.9\) Hz, 2H), 2.55 (tt, \(J = 3.5, 11.3\) Hz, 2H). \(1^C\) NMR (100 MHz, acetone-d\(_6\), \(\delta\)): 27.0 (CH\(_2\)), 27.3 (CH\(_2\)), 28.1 (CH\(_2\)), 52.2 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(1^{11}\)B NMR (127 MHz, acetone-d\(_6\), \(\delta\)): –0.86 (q, \(J = 55.0\) Hz). \(1^{19}\)F NMR (372 MHz, acetone-d\(_6\), \(\delta\)): –147.7 (q, \(J = 53.1\) Hz). HRMS-ESI (m/z): [M–K]\(^–\) calcd for C\(_7\)H\(_{11}\)O\(_{10}\)BF\(_3\), 178.08968; found, 178.08940.

Potassium trifluoro(pivaloyl)borate (2l).

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\text{\includegraphics[width=0.1\textwidth]{borate2l.png}}
\]

2l (41.4 mg, 0.22 mmol, white solid) was prepared in 72% yield from 1l (58.1 mg, 0.30 mmol) using the reaction condition B. The NMR spectra of 4a are consistent with those reported.\(^7\) \(1^H\) NMR (396 MHz, acetone-d\(_6\), \(\delta\)): 1.01 (s, 9H). \(1^C\) NMR (99 MHz, acetone-d\(_6\), \(\delta\)): 25.6 (CH\(_3\)), 44.1 (CH\(_3\)). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. \(1^{11}\)B NMR (127 MHz, acetone-d\(_6\), \(\delta\)): –0.69 (q, \(J = 54.7\) Hz). \(1^{19}\)F NMR (373 MHz, acetone-d\(_6\), \(\delta\)): –144.1 (q, \(J = 53.1\) Hz). HRMS-ESI (m/z): [M–K]\(^–\) calcd for C\(_5\)H\(_9\)O\(_{10}\)BF\(_3\), 152.07403; found, 152.07371.
Potassium trifluoro(undec-10-enoyl)borate (2m).

2m (27.0 mg, 0.099 mmol, white solid) was prepared in 33% yield from 1m (82.9 mg, 0.30 mmol) using the reaction condition A. 2m (55.3 mg, 0.20 mmol, white solid) was prepared in 67% yield from 1m (82.5 mg, 0.30 mmol) using the reaction condition B. 

**1H NMR** (396 MHz, acetone-d6, δ): 1.17–1.50 (m, 14H), 2.38 (t, J = 7.5 Hz, 2H), 4.84–4.95 (m, 1H), 4.95–5.05 (m, 1H), 5.75–5.90 (m, 1H). 

**13C NMR** (100 MHz, DMSO-d6, δ): 22.2 (C(H2)), 28.3 (C(H2)), 28.6 (C(H2)), 28.9 (C(H2)), 29.1 (C(H2)), 29.3 (C(H2)), 33.2 (C(H2)), 44.2 (C(H2)), 114.7 (C(H2)), 138.9 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.

**11B NMR** (127 MHz, acetone-d6, δ): –0.95 (q, J = 54.3 Hz).

**19F NMR** (373 MHz, acetone-d6, δ): –149.95 (q, J = 49.4 Hz). HRMS-ESI (m/z): [M–K]– calcd for C11H19O10BF3, 234.15229; found, 234.15230.

Potassium [5-(benzoyloxy)pentanoyl]trifluoroborate (2n).

2n (54.7 mg, 0.18 mmol, white solid) was prepared in 58% yield from 1n (94.5 mg, 0.30 mmol) using the reaction condition B. 

**1H NMR** (396 MHz, acetone-d6, δ): 2.39 (s, 3H), 7.10 (dd, J = 1.2, xx Hz, 1H), 7.20 (quintet of doublet, J = 1.7, 7.0 Hz, 2H), 8.05 (d, J = 7.1 Hz, 1H). 

**13C NMR** (100 MHz, acetone-d6, δ): 21.3 (C(H3)), 125.8 (C(H)), 130.0 (C(H)), 131.7 (CH), 132.1 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.

**11B NMR** (127 MHz, acetone-d6, δ): –0.45 (q, J = 52.3 Hz).

**19F NMR** (372 MHz, acetone-d6, δ): –144.98 (q, J = 49.3 Hz). HRMS-ESI (m/z): [M–K]– calcd for C12H13O310BF3, 272.09516; found, 272.09512.

Potassium [4-(5,5-dimethyl-1,3-dioxan-2-yl)butanoyl]trifluoroborate (2o).

2o (26.0 mg, 0.09 mmol, white solid) was prepared in 30% yield from 1o (88.3 mg, 0.30 mmol) using the reaction condition A. 

**1H NMR** (396 MHz, acetone-d6, δ): 0.69 (s, 3H), 1.12 (s, 3H), 1.44–1.58 (m, 4H), 2.39 (t, J = 7.1 Hz, 2H), 3.40 (d, J = 10.3 Hz, 2H), 3.52 (d, J = 10.7 Hz, 2H), 4.38 (t, J = 4.6 Hz, 1H). 

**13C NMR** (100 MHz, acetone-d6, δ): 17.9 (CH2), 22.0 (CH3), 23.4 (CH3), 30.7 (C), 35.7 (CH2), 44.9 (C), 77.5 (CH2), 103.1 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation.

**11B NMR** (127 MHz, acetone-d6, δ): –0.94 (q, J = 56.3 Hz).

**19F NMR** (373 MHz, acetone-d6, δ): –149.8 (q, J = 49.2 Hz). HRMS-ESI (m/z): [M–K]– calcd for C10H17O310BF3, 252.12646; found, 252.12656.
Potassium trifluoro(4-\{(2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl\}oxy\}benzoyl)borate (2p).

![Diagram of 2p]

2p (117.3 mg, 0.21 mmol, white solid) was prepared in 70% yield from 1p (167.9 mg, 0.30 mmol) using the reaction condition B. 1H NMR (396 MHz, acetone-d6, δ): 1.93 (s, 3H), 1.98 (s, 9H), 4.14 (d, J = 11.9 Hz, 1H), 4.18–4.30 (m, 2H), 5.08 (t, J = 9.5 Hz, 1H), 5.37 (t, J = 9.5 Hz, 1H), 5.47 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.0 Hz, 2H), 8.03 (d, J = 8.7 Hz, 2H). 13C NMR (100 MHz, acetone-d6, δ): 20.6 (CH3), 20.7 (CH3), 62.8 (CH2), 69.3 (CH), 72.0 (CH), 72.7 (CH), 73.4 (CH), 98.9 (CH), 116.4 (CH), 131.3 (CH), 160.2 (C), 169.8 (C), 170.2 (C), 170.4 (C), 170.7 (C), 172.2 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. 11B NMR (127 MHz, acetone-d6, δ): −0.03 (q, J = 54.3 Hz). 19F NMR (373 MHz, acetone-d6, δ): −144.4 (s). HRMS-ESI (m/z): [M−K]− calcld for C21H23O11BF3, 518.13273; found, 518.13319.

Potassium trifluoro(6-\{(8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl\}oxy\}hexanoyl)borate (2q).

![Diagram of 2q]

2q (70.1 mg, 0.15 mmol, white solid) was prepared in 74% yield from 1q (95.8 mg, 0.20 mmol) using the reaction condition B. 1H NMR (396 MHz, methanol-d3, δ): 0.72 (s, 3H), 1.05–1.60 (m, 7 H), 1.62–2.10 (m, 11 H), 2.15–2.30 (m, 4H), 2.60–2.68 (m, 2H), 3.71 (t, J = 6.3 Hz, 2H), 6.40 (s, 1H), 6.45 (d, J = 7.9 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H). 13C NMR (100 MHz, methanol-d3, δ): 14.3 (CH3), 15.4 (C), 22.5 (CH2), 26.1 (CH2), 27.1 (CH2), 27.8 (CH2), 30.7 (CH2), 32.8 (CH2), 34.3 (CH2), 36.7 (CH2), 39.9 (CH), 45.4 (CH), 51.7 (CH), 66.9 (C), 68.7 (C), 113.2 (CH), 115.4 (CH), 127.2 (CH), 133.0 (C), 138.7 (C), 223.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. 11B NMR (127 MHz, methanol-d3, δ): −0.00 (q, J = 10.9 Hz). 19F NMR (372 MHz, methanol-d3, δ): −149.37 (s). HRMS-ESI (m/z): [M−K]− calcld for C24H33O11BF3, 434.23601; found, 434.23719.
Synthesis of α-amino KAT.

Potassium [(benzoxycarbonyl)glycyl]trifluoroborate (4a).

N-Cbz glycinal (1.58 g, 8.2 mmol) was prepared in 82% yield from benzyl (2-hydroxyethyl)carbamate (1.95 g, 10.0 mmol) according to the reported procedure.\(^8\) 3a (279.6 mg, 1.05 mmol) was prepared in 52% yield from N-Cbz glycinal (386.1 mg, 2.00 mmol) according to the procedure for the synthesis of 1a. 3a was isolated by extraction with THF/saturated aqueous KCl solution and followed by filtration with hot acetone.

\(^1^H\) NMR (396 MHz, DMSO-d6, \(\delta\)): 2.32–2.38 (m, 1H), 2.63–2.69 (m, 1H), 2.82–2.89 (m, 1H), 3.02–3.08 (m, 1H), 4.97 (s, 2H), 6.28 (brs, 1H), 7.27–7.38 (m, 5H). \(^1^3^C\) NMR (99 MHz, DMSO-d6, \(\delta\)): 46.0 (CH2), 64.9 (CH2), 127.7 (CH), 128.4 (CH), 137.5 (C), 156.1 (C). \(^1^1^B\) NMR (127 MHz, DMSO-d6, \(\delta\)): 3.34 (brs).

Oxidation was performed using the reaction condition B with 2 mol% of TBABr because of the low solubility of 3a to acetonitrile. 4a (113.9 mg, 0.38 mmol, white solid) was prepared in 76% yield from 3a (150.6 mg, 0.50 mmol).

6a was isolated by extraction with THF/saturated aqueous KCl solution and followed by filtration with hot acetone.

\(^1^H\) NMR (396 MHz, CD3CN, \(\delta\)): 3.97 (d, \(J = 4.6\) Hz, 2H), 5.05 (s, 2H), 5.66 (brs, 1H), 7.29–7.34 (m, 1H), 7.37 (d, \(J = 4.1\) Hz, 4H). \(^1^3^C\) NMR (99 MHz, DMSO-d6, \(\delta\)): 52.4 (CH2), 65.1 (CH2), 127.67 (CH), 128.4 (CH), 137.4 (C), 156.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. \(^1^1^B\) NMR (127 MHz, CD3CN, \(\delta\)): −1.13 (q, \(J = 49.0\) Hz). \(^1^9^F\) NMR (373 MHz, DMSO-d6, \(\delta\)): −149.3 (q, \(J = 41.7\) Hz). HRMS-ESI (m/z): [M–K]– cale for C10H10O3N10BF3, 259.07476; found, 259.07520.

Potassium [(tert-butoxycarbonyl)phenylalanyl]trifluoroborate (4b).

N-Boc phenylalaninal was prepared in 96% yield from N-Boc-Phe-OH (2.65 g, 10 mmol) according to the reported procedure. The spectra data was consistent with those reported in the literature.\(^9\) 3b (896.1 mg, 2.51 mmol) was prepared in 63% yield from N-Boc phenylalaninal (998.0 mg, 4.0 mmol) according to the procedure for the synthesis of 1a. This product contains small amount of pinacol (1a:pinacol = 95:5). \(^1^H\) NMR (396 MHz, acetone-d6, * indicates signals of the minor diastereomer, \(\delta\)): 1.31 (s, 9H), 1.35* (s, 9H), 2.67 (dd, \(J = 8.3, 13.9\) Hz, 1H), 2.90–3.16 (m, 2H), 3.81 (quin, \(J = 6.6\) Hz, 1H), 5.46 (brd, \(J = 8.3\) Hz, 1H), 7.11 (t, \(J = 6.9\) Hz, 1H), 7.16–7.32 (m, 4H). \(^1^3^C\) NMR (100 MHz, acetone-d6, \(\delta\)): 28.8 (CH3), 38.6 (CH2), 56.8 (CH), 68.0 (br, B–C), 78.2 (C), 126.2 (CH), 128.7 (CH), 130.5 (CH), 141.9 (C), 157.3 (C). \(^1^1^B\) NMR (127 MHz, acetone-d6, \(\delta\)): 4.44 (brs). \(^1^9^F\) NMR (372 MHz, acetone-d6, \(\delta\)): −143.3* (s), −145.8 (s). HRMS-ESI (m/z): [M–K]– cale for C10H10O3N10BF3, 317.15301; found, 317.15342. Specific
rotation of 3b could not be measured due to low solubility of 3b.

4b (85.2 mg, 0.24 mmol, white solid) was prepared in 80% yield from 3b (107.4 mg, 0.50 mmol). 1H NMR (396 MHz, acetone-d6, δ): 1.37 (s, 9H), 3.19 (dd, J = 4.6, 13.7 Hz, 1H), 3.32 (dd, J = 5.7, 13.7 Hz, 1H), 4.62 (q, J = 5.9 Hz, 1H), 5.41 (brd, J = 5.9 Hz, 1H), 7.06–7.23 (m, 5H). 13C NMR (100 MHz, acetone-d6, δ): 28.7 (CH2), 35.7 (CH2), 62.7 (CH), 78.4 (C), 126.6 (CH), 130.9 (CH), 139.3 (C), 155.8 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. 11B NMR (127 MHz, acetone-d6, δ): -0.30 (q, J = 45.8 Hz). 19F NMR (373 MHz, acetone-d6, δ): -147.2 (d, J = 56.9 Hz). HRMS-ESI (m/z): [M–K]+ calcd for C14H13O3N10BF3, 315.13736; found, 315.13798. [α]D 19.7 +99.0 (c 1.0 in MeOH, 99% ee).

The ee value of 4b was determined by HPLC analysis of the corresponding amide S5 after KAT ligation with hydroxylamine S4, according to the procedure of Scheme below.[10] Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = AcOEt/Hexane = 5.95, 0.8 mL/min, 40 °C, (D)-isomer: tR = 11.17 min., (L)-isomer: tR = 13.24 min.

Potassium ([(9H-fluoren-9-yl)methoxy|carbonyl]-L-leucyl)trifluoroborate (4c).

N-Fmoc leucinal (1.81 g, 5.36 mmol) was prepared in 54% yield from N-Boc-Phe-OH (3.53 g, 10 mmol) according to the procedure for the synthesis of N-Boc phenylalaninal. The NMR spectra data was consistent with those reported in the literature.[11] The ee value of Fmoc-leucinal was determined by HPLC analysis of the corresponding alcohol after reduction with NaBH₄. Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 15.0/85.0, 0.5 mL/min, 40 °C, (D)-isomer: tR = 22.05 min., (L)-isomer: tR = 26.45 min.

3c (1.10 g, 2.48 mmol) was prepared in 62% yield from N-Fmoc leucinal (1.345 g, 4.00 mmol) according to the procedure for the synthesis of 1a. 1H NMR (396 MHz, acetone-d6, * indicates signals of the minor diastereomer, δ): 0.88–0.91 (m, 6H), 1.34–1.45 (m, 1H), 1.46–1.56 (m, 1H), 1.62–1.74 (m, 1H), 2.35 (d, J = 3.6 Hz, 1H), 2.79 (brs, 1H), 2.96* (brs, 1H), 3.74–3.85 (m, 1H), 4.18–4.33 (m, 3H), 5.79 (d, J = 9.1 Hz, 1H), 5.92* (d, J = 11.3 Hz, 1H), 7.29–7.34 (m, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.69–7.73 (m, 2H), 7.85 (d, J = 7.7 Hz, 2H). 13C NMR (100 MHz, DMSO-d6, δ): 22.1* (CH3), 22.3 (CH3), 23.8 (CH3), 24.0* (CH3), 24.5 (CH), 24.6* (CH), 41.1 (CH2), 46.9 (CH), 52.8 (CH), 53.5* (CH), 65.1 (CH2), 67.9 (br, B–C), 120.1 (CH), 125.3* (CH), 125.4 (CH), 127.06 (CH), 127.11* (CH), 127.6 (CH), 140.7 (C), 144.0 (C), 144.2* (C), 155.8* (C), 156.1 (C). 11B NMR (127 MHz, DMSO-d6, δ): 3.64 (brs). 19F NMR (373 MHz, acetone-d6, δ): -146.2 (s), -143.9* (s). HRMS-ESI (m/z): [M–K]+ calcd for C24H23O3N10BF3, 405.18431; found, 405.18488. Specific rotation of 3c could not be measured due to low solubility of 3c to methanol.

4c (94.5 mg, 0.21 mmol, white solid) was prepared in 71% yield from 3c (133.7 mg, 0.30 mmol). 4c was isolated by
extraction with EtOAc and saturated aqueous KCl solution and followed by filtration with EtO. $^1$H NMR (392 MHz, acetone-d$_6$, δ): 0.89 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 6.3 Hz, 3H), 1.12–1.23 (m, 1H), 1.70–1.90 (m, 2H), 4.20–4.36 (m, 3H), 4.49–4.57 (m, 1H), 6.07 (brd, J = 7.6 Hz, 1H), 7.33 (t, J = 7.4 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.72 (t, J = 8.3 Hz, 2H), 7.86 (d, J = 7.6 Hz, 2H). $^{13}$C NMR (99 MHz, acetone-d$_6$, δ): 22.0 (CH$_3$), 24.1 (CH$_3$), 25.6 (CH), 39.9 (CH$_2$), 48.1 (CH), 61.1 (CH), 66.9 (CH$_2$), 120.8 (CH), 126.2 (d, J = 3.8 Hz, CH), 127.9 (CH), 128.5 (CH), 142.0 (C), 145.2 (d, J = 23.5 Hz, C), 157.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, δ): −0.19 (q, J = 56.7 Hz). $^{19}$F NMR (373 MHz, acetone-d$_6$, δ): −146.9 (s). HRMS-ESI (m/z): [M–K$^+$] calcd for C$_2$i$_2$H$_{18}$O$_3$N$_{10}$BF$_3$, 403.16866; found, 403.16919. [α]$_D^{22.6}$ +11.0 (c 1.0 in MeOH, 99% ee).

The ee value of 4c was determined by HPLC analysis of the corresponding amide after KAT ligation with hydroxylamine S5. Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 7.0/93.0, 0.5 mL/min, 40 °C, (L)-isomer: $t_R = 16.92$ min., (D)-isomer: $t_R = 23.17$ min.

**Potassium [(benzylxoy)carbonyl]-L-valyl]trifluoroborate (4d).**

N-Cbz valinal was prepared in 48% yield over two steps from N-Boc-Phe-OH according to the reported procedure.$^{[12]}$

The spectra data was consistent with those reported in the literature.$^{[13]}$ 3d (301 mg, 0.88 mmol) was prepared in 50% yield from N-Cbz valinal (235 mg, 1.76 mmol) according to the procedure for the synthesis of 1a. $^1$H NMR (396 MHz, acetone-d$_6$, δ): 0.85 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 2.02 (d, J = 6.4 Hz, 1H), 2.80 (s, 1H), 2.97 (brs, 1H), 3.49 (dt, J = 5.5, 9.5 Hz, 1H), 5.00 (d, J = 12.9 Hz, 1H), 5.10 (d, J = 12.8 Hz, 1H), 5.57 (d, J = 8.7 Hz, 1H), 7.24–7.42 (m, 5H). $^{13}$C NMR (100 MHz, DMSO-d$_6$, δ): 18.2 (CH$_3$), 20.9 (CH$_3$), 29.5 (CH), 59.2 (CH), 64.5 (CH$_2$), 127.3 (CH), 127.5 (CH), 128.3 (CH), 137.9 (C), 156.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, δ): 4.03 (brs). $^{19}$F NMR (373 MHz, acetone-d$_6$, δ): −147.8 (s). HRMS-ESI (m/z): [M–K$^+$] calcd for C$_{13}$H$_{10}$O$_3$N$_{10}$BF$_3$, 303.13770; found, 303.13736. Specific rotation of 3d could not be measured due to low solubility of 3d.

4d (131 mg, 0.38 mmol, white solid) was prepared in 77% yield from 3d (172 mg, 0.50 mmol). $^1$H NMR (396 MHz, acetone-d$_6$, δ): 0.61 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 2.55–2.68 (m, 1H), 4.45 (dd, J = 3.2, 8.4 Hz, 1H), 5.04 (s, 2H), 5.86 (d, J = 7.5 Hz, 1H), 7.27–7.40 (m, 5H). $^{13}$C NMR (100 MHz, acetone-d$_6$, δ): 16.6 (CH$_3$), 21.2 (CH$_3$), 29.0 (CH), 66.5 (CH$_2$), 67.2 (CH), 128.6 (CH), 128.7 (CH), 129.2 (CH), 138.5 (C), 157.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. $^{11}$B NMR (127 MHz, acetone-d$_6$, δ): −1.27 (q, J = 50.6 Hz). $^{19}$F NMR (373 MHz, acetone-d$_6$, δ): −148.0 (d, J = 57.0 Hz). HRMS-ESI (m/z): [M–K$^+$] calcd for C$_{13}$H$_{10}$O$_3$N$_{10}$BF$_3$, 301.12171; found, 301.12202. [α]$_D^{18.2}$ +68.3 (c 1.0 in MeOH, 99% ee).

The ee value of 4d was determined by HPLC analysis of the corresponding amide after KAT ligation with hydroxylamine S5, according to the procedure of Scheme S1. Daicel CHIRALPAK® IE-3, 2-PrOH/Hexane = 10.0:90.0, 0.5 mL/min, 40 °C, (L)-isomer: $t_R = 45.32$ min., (D)-isomer: $t_R = 49.96$ min.
Gram-scale synthesis of 2c and 6b.

**Gram-scale synthesis of potassium trifluoro(4-fluorobenzoyl)borate (2c)**

1c (3.45 g, 14.8 mmol) was prepared in 99% yield from 4-fluorobenzaldehyde (1.87 g, 15 mmol) according to the procedure for the synthesis of 1a. 1c (2.12 g, 9.2 mmol), nor-AZADO (103.0 mg, 0.75 mmol) and NaNO₂ (1.55 g, 22.5 mmol) were placed in an oven-dried 50 mL single-neck flask. After the flask was sealed with a rubber septum and connected to a balloon filled with dry air through needle, CH₃CN (15 mL) and AcOH (1.7 mL, 30 mmol) were added in the vial through the rubber septum using syringes. And the resultant solution was stirred at room temperature for 5 days. Then, reaction mixture was concentrated in vacuo. The resultant solid was dissolved in acetone, cooled down to 0°C and filtered. Filtrate was concentrated in vacuo. The resultant solid was washed with Et₂O to give KAT 2c (2.12 g, 62%) as a white solid.

**Gram-scale synthesis of potassium [(tert-butoxycarbonyl)phenylalanyl]trifluoroborate (4b).**

Boc-phenylalaninal (4.22 g, 16.9 mmol) was prepared in 85% yield from N-Boc-Phe-OH (5.31 g, 20.0 mmol) according to the reported procedure. Boc-phenylalaninal (3.49 g, 14.0 mmol) according to the procedure for the synthesis of 1a. Due to the high solubility of 3b to Et₂O, 3b was separated from pinacol by washing with a large amount of hexane.

3b (1.79 g, 5.0 mmol), nor-AZADO (13.8 mg, 0.10 mmol) and NaNO₂ (517.5 mg, 7.50 mmol) were placed in an oven-dried 50 mL single-neck flask. After the flask was filled with dry air, sealed with a rubber septum and connected to a balloon filled with dry air through needle, CH₂CN (15 mL) and AcOH (759 µL, 10 mmol) were added in the vial through the rubber septum using syringes. And the resultant solution was stirred at room temperature for 7 h. Then, reaction mixture was concentrated in vacuo. The resultant solid was dissolved in acetone and filtered. Filtrate was concentrated in vacuo. The resultant solid was isolated by reprecipitation with Et₂O/hexane to give KAT 4b (1.45 g, 82%) as a white solid.
References


References


List of Publications

Chapter 1
Catalyst-Controlled Regiodivergent C–H Borylation of Multifunctionalized Heteroarenes Using Iridium Complexes

Chapter 2
Iridium(I)-catalyzed C–H Borylation of α,β-Unsaturated Esters with Bis(pinacolato)diboron
Sasaki, I.; Taguchi, J.; Doi, H.; Ito, H.; Ishiyama, T.

Chapter 3
Synthesis of Acylborons by Ozonolysis of Alkenylboronates: Preparation of an Enantioenriched Amino Acid Acylboronate

Chapter 4
Concise Synthesis of Potassium Acyltrifluoroborates from Aldehydes by a Cu(I)-catalyzed Borylation/Oxidation Protocol
Taguchi, J.; Takeuchi, T.; Takahashi, R.; Ito, H.
*To be submitted.*

Other Publications

1.
Regioselective C–H Borylation of Heteroaromatic Aldimines with Iridium Complexes
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