Title	Development of Synthetic Methods for Functionalized Organoboron Compounds via Transition Metal Catalysis
Author(s)	田口, 純平
Degree Grantor	北海道大学
Degree Name	博士(工学)
Dissertation Number	甲第13687号
Issue Date	2019-03-25
DOI	https://doi.org/10.14943/doctoral.k13687
Doc URL	https://hdl.handle.net/2115/77036
Type	doctoral thesis
File Information	Jumpei_Taguchi.pdf

Ph.D. thesis

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

（遷移金属触媒を用いた官能基化有機ホウ素化合物の合成法の開発）

Hokkaido University

Graduate School of Chemical Science and Engineering

Organoelement Laboratory

Jumpei Taguchi

2019

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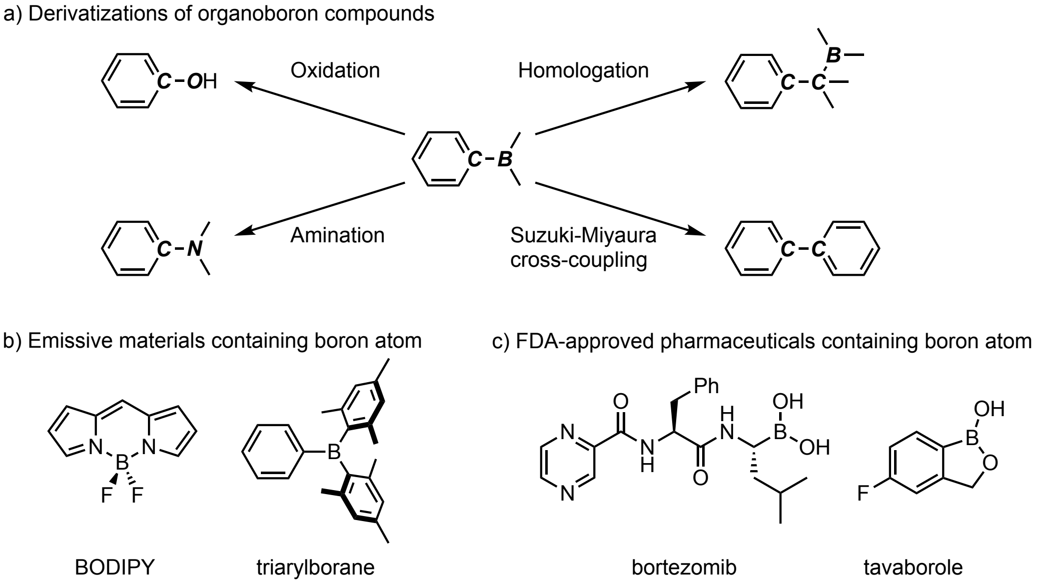
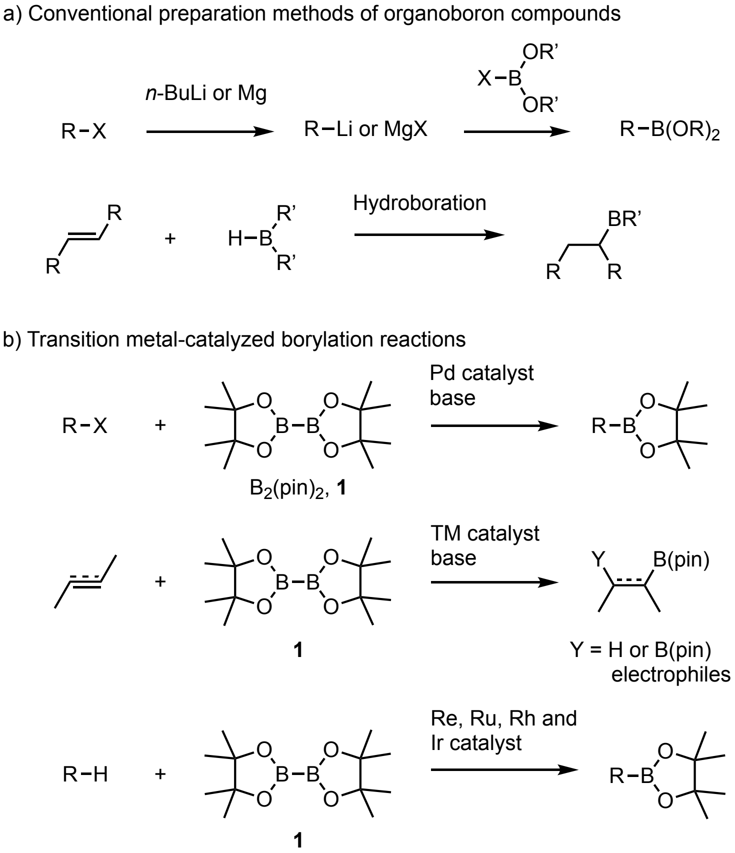
General Introduction

Organoboron compound is a significant class of compounds in synthetic organic chemistry.[1] They exhibit much higher stability against air and moisture compared with other organometallic reagents such as organolithium or Grignard reagents.[2] 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).[3] 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).[4] 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).[1] 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.



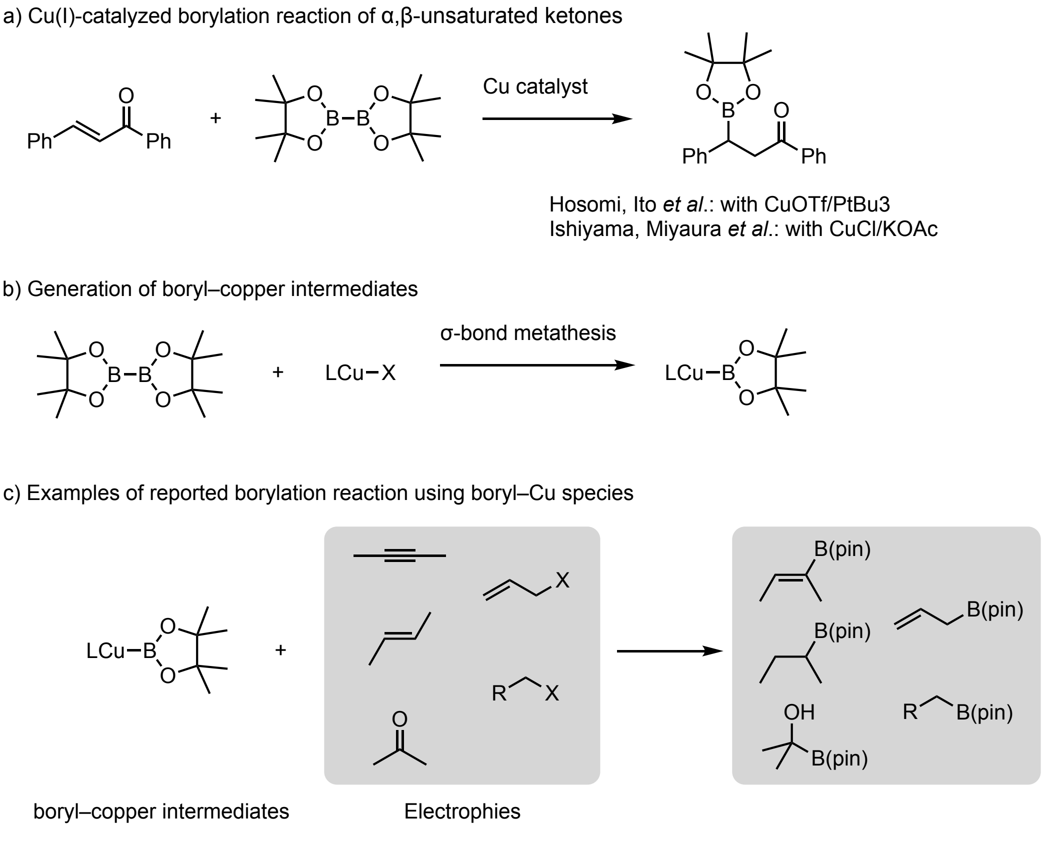
Scheme 1. Importance of organoboron compounds in organic chemistry. a) Derivatizations of organoboron compounds. b) Organic emissive materials containing boron atom. c) FDA-approved pharmaceuticals containing boron atom.

Conventional methods for the preparation of organoboron compounds had been achieved via halogen-metal exchange or metalation of aryl bromides or iodides and subsequent trapping with boron electrophiles such as BCl_3, BBr_3, $B(OMe)_3$ (Scheme 2a).[1] 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 method to synthesize alkyl or alkenyl boronates. This method also has significant limitation such as regioselectivity issue 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,[5] transition metal-catalyzed hydroboration or diboration reaction,[6] and Hartwig-Miyaura C–H borylation reaction[7] 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.



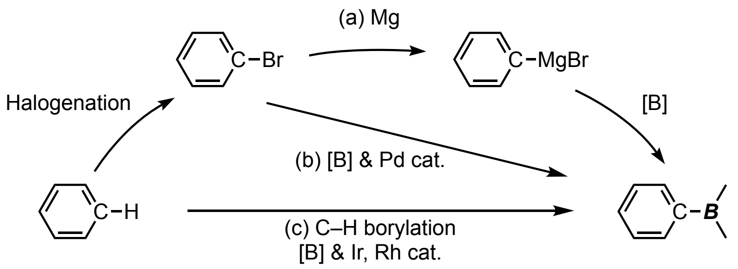
Scheme 2. Preparation methods of organoboron compounds. a) Conventional preparation methods of organoboron compounds. b) Transition metal-catalyzed borylation reactions.

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).[8] 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).[9] 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).[10] In addition, these reactions can be used in asymmetric borylation reactions under mild conditions by using chiral ligands.



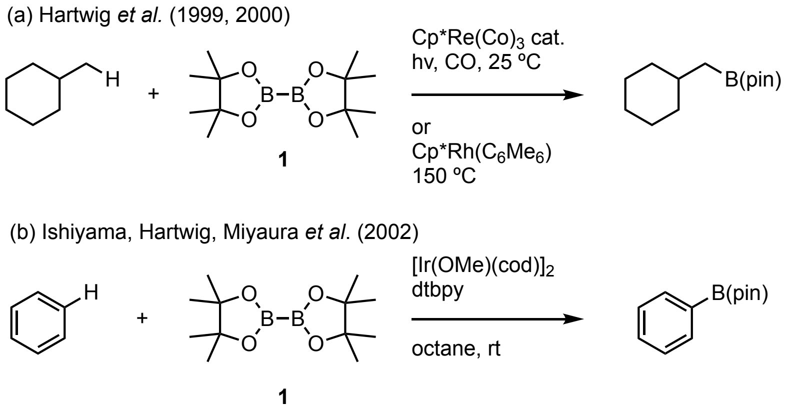
Scheme 3. Copper(I)-catalyzed nucleophilic borylation reactions. a) Cu(I)-catalyzed borylation reaction of α,β-unsaturated ketones. b) Generation of boryl–copper intermediates. c) Examples of reported borylation reaction using boryl–Cu species.

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)



Scheme 4. Transition metal-catalyzed C–H borylation reaction.

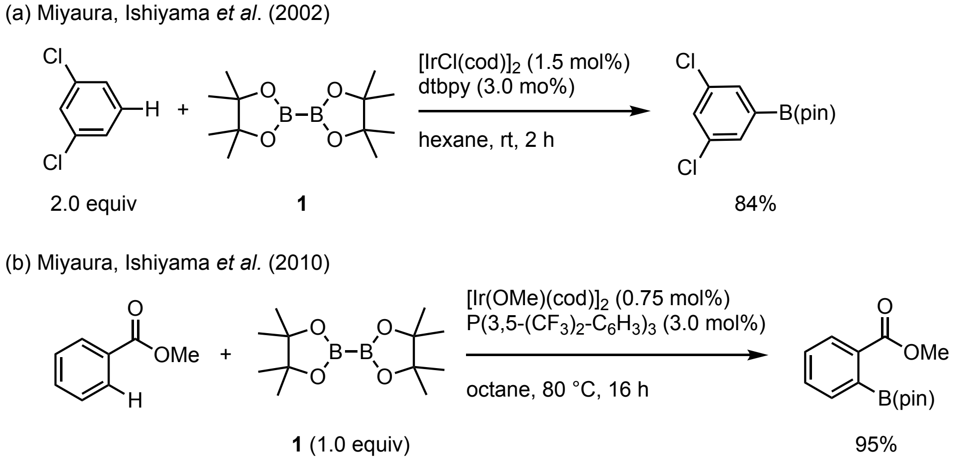
The initial example of C–H borylation was reported by Hartwig in 1999 (Scheme 5a).[11] Excess amount of alkanes react with diboron **1** in the presence of Cp*Re(CO)$_3$ under irradiation of light to afford borylated alkane. Hartwig also reported alkyl C–H bond borylation reaction using Rh catalyst at 150°C in 2000.[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.[13] In particular, reaction using [Ir(OMe)(cod)]$_2$/dtbpy (cod = 1,5-cyclooctadiene, dtbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) catalyst has significant importance because it does not require light irradiation and high reaction temperature (Scheme 5b).[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.



Scheme 5. Initial reports on transition metal-catalyzed C–H borylation reaction.

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 *meta*-positions of various substituents were reported by our group and the groups of Smith III and Hartwig (Scheme 6a).[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 *meta*- and *para*-borylated products.

Iridium-catalyzed C–H borylation at the *ortho*-position of the coordinating functionalities was reported by Ishiyama in 2010 (Scheme 6b).[13h] Carbonyl-substituted benzenes react with diboron **1** in the presence of $[\mathrm{Ir(OMe)(cod)}]_2$/2 $\mathrm{P(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_3}$ catalyst to afford *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 *ortho*-position. As a result, subsequent oxidative addition proceeds at *ortho*-position selectively.

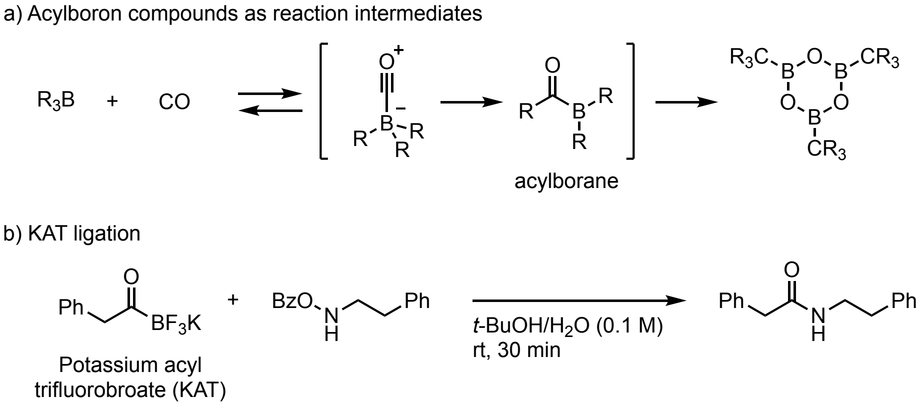


Scheme 6. Control of regioselectivity in aromatic C–H borylation reaction.

Chapter 1 describes the regiodivergent C–H borylation of 2,5-disubstituted heteroarenes with diboron **1** by using iridium catalysts formed *in situ* from $[\mathrm{Ir(OMe)(cod)}]_2$/dtbpy or $[\mathrm{Ir(OMe)(cod)}]_2$/2 $\mathrm{AsPh_3}$.[14] When $[\mathrm{Ir(OMe)(cod)}]_2$/dtbpy was used as the catalyst, borylation at the 4-position proceeded selectively to afford 4-borylated products in high yields. This regioselectivity is originated from the steric repulsion between carbonyl groups and iridium complex. The regioselectivity changed when the $[\mathrm{Ir(OMe)(cod)}]_2$/2 $\mathrm{AsPh_3}$ 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 α,β-unsaturated esters using diboron **1**.[15] These reactions proceeded in octane solvent at temperatures ranging from 80 to 120°C to give the corresponding β-borylated α,β-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.[16] 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.[17a,b] In 2010, Molander reported the first synthesis of potassium acyltrifluoroborate (KAT) and found that this compound has high stability against air and moisture.[17e] 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.[18] (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.[18b] 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

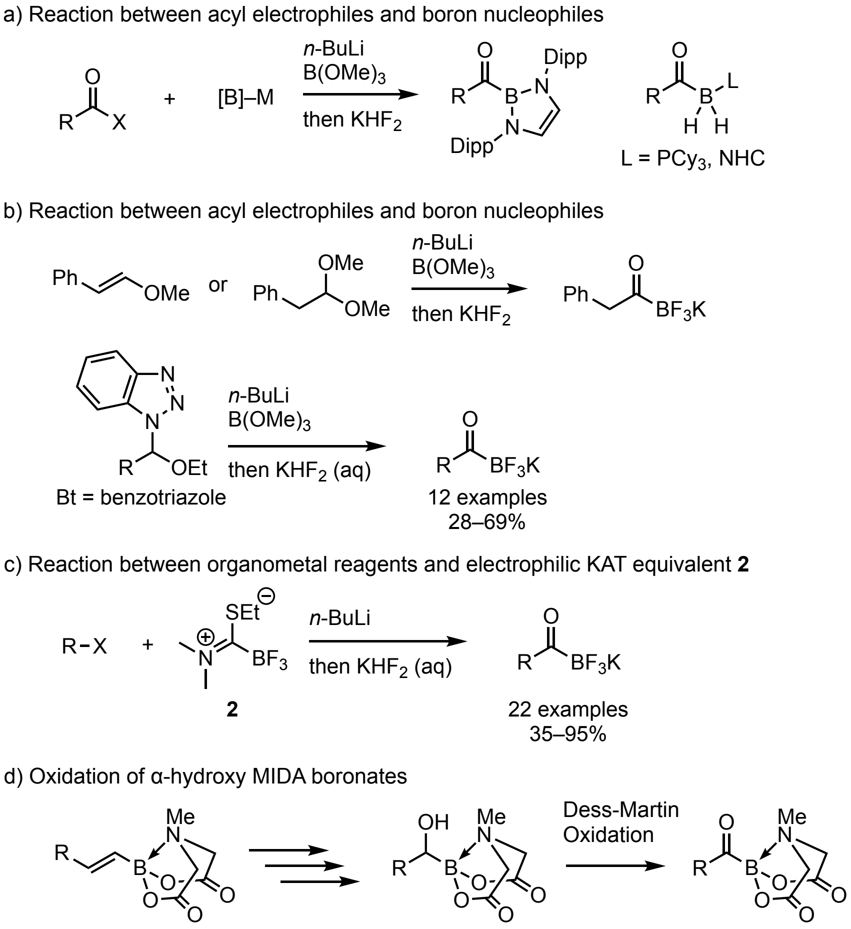
Reported methods for the preparation of acylborons can be categorized into mainly three approaches; 1) the reaction between acyl cation equivalents and boron nucleophiles, 2) the reaction between acyl anion equivalents and boron electrophiles, and 3) nucleophilic organometal reagents and electrophilic acylboron equivalent reagent. Yamashita and Nozaki's first synthesis of acylboron belongs to the first approach (Scheme 8a).[17a] In addition, Imamoto, Curran, Lacote, Grimmes, and Aldridge reported the acylboron synthesis using various boron nucleophiles such as phosphine borane–complexes, NHC–borane complex, boryl–zinc reagent and so on.[17c,d] 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).[17e] 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.[17f] 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).[17g,h] 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).[17i] 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.


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

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.

Chapter 3 describes the synthesis of acyl MIDA boronates by the ozonolysis of alkenyl MIDA boronates.[18] 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.[19] 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.

References

(1) *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine and Materials*; Hall, D. G., 2nd revised ed.; Wiley-VCH Verlag: Weinheim, **2011**.

(2) *Organic Synthesis via Boranes*; Brown, H. C.; Wiley-VCH Verlag: Weinheim, **1975**.

(3) a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; b) Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778; c) Hupe, E.; Marek, I.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861; d) Crudden, C. M.; Glasspoole, B. W.; Lata, C. J. *Chem. Commun.* **2009**, 6704.

(4) Reviews: a) Mukherjee, S.; Thilagar, P. J. *Mater. Chem. C* **2016**, *4*, 2647; b) Frath, D.; Massue, J.; Ulrich, G.; Ziessel, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2290.

(5) a) Primas, N.; Bouillon A.; Rault, S. *Tetrahedron* **2010**, *66*, 8121; b) Ishiyama, T.; Miyaura, N.; *Chem. Rec.* **2004**, *3*, 271; c) Ishiyama T.; Miyaura, N. *J. Organomet. Chem.* **2000**, *611*, 392.

(6) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179.

(7) Reviews: a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890; b) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864.

(8) a) Ito, H.; Yamanaka, H.; Tateiwa, J.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821; b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982.

(9) Laitar, D. S.; Müller P.; Sadighi, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 17196; b) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao J.; Tsuji, Y. *Chem.–Eur. J.* **2013**, *19*, 7125.

(10) Review: a) Kubota, K.; Iwamoto H.; Ito, H. *Org. Biomol. Chem.* **2017**, *15*, 285; b) Dang, L.; Lin, Z. Marder, T. B. *Chem. Commun.* **2009**, 3987; c) Yun, J. *Asian J. Org. Chem.* **2013**, *2*, 1016; d) Alfaro, R.; Parra, A.; Alemán, J.; Tortosa, M. *Synlett* **2013**, *24*, 804.

(11) Chen, H.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391

(12) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995.

(13) (a) Iverson, C. N.; Smith III, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 7696. (b) Cho, J.-Y.; Iverson, C. N.; Smith III, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 12868; (c) Tse, M. K.; Cho, J.-Y.; Smith III, M. R. *Org. Lett.* **2001**, *3*, 2831. (d) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith III, M. R. *Science* **2002**, *295*, 305. (e) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith III, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 7792. (f) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390. (g) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3056. 9. H) Ishiyama, T.; Isou, H.; Kikuchi, T.; Miyaura, N. *Chem. Commun.* **2010**, *46*, 159.

(14) Sasaki, I.; Taguchi, J.; Hiraki, S.; Ito, H.; Ishiyama, T. *Chem. Eur. J.* **2015**, *21*, 9236.

(15) Sasaki, I.; Taguchi, J.; Doi, H.; Ito, H.; Ishiyama, T. *Chem. Asian J.* **2016**, *11*, 1400.

(16) Reviews on acylboron compounds: a) Scharnagl, F. K.; Bose, S. K.; Marder, T. B. *Org. Biomol. Chem.* **2017**, *15*, 1738. b) Noda, H.; Bode, J. W. *Org. Biomol. Chem.* **2016**, *14*, 16; c) St. Denis, J. D.; He, Z.; Yudin A. K. *ACS Catal.* **2015**, *5*, 5373.

(17) a) Yamashita, M.; Suzuki, Y.; Segawa, Y.; Nozaki, K. *J. Am. Chem. Soc.* **2007**, *129*, 9570; b) Segawa, Y.; Suzuki, Y.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 16069; c) Monot, J. Solovyev, A.; Bonin-

Dubarle, H.; Derat, É.; Curran, D. P.; Robert, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 9166; d) Frank, R.; Howell, J.; Campos, J.; Tirfoin, R.; Phillips, N.; Zahn, S.; Mingos, D. M. P.; Aldridge, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 9586; e) Molander, G. A.; Raushel, J.; Ellis, N. M. *J. Org. Chem.* **2010**, *75*, 4304; f) Dumas, A. M.; Bode, J. W. *Org. Lett.* **2012**, *14*, 2138; g) Erös, G.; Kushida, Y.; Bode, J. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 7604; h) Liu, S. M.; Wu, D.; Bode, J. W. *Org. Lett.* **2018**, *20*, 2378; i) He, Z.; Trinchera, P.; Adachi, S.; St Denis, J. D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11092.

(18) a) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 5683; b) Noda, H.; Erós, G.; Bode, J. W. *J. Am. Chem. Soc.* **2014**, *136*, 5611; c) Noda, H.; Bode, J. W. *Chem. Sci.* **2014**, *5*, 4328; d) Liu, M.; Mazunin, D.; Pattabiraman, V. R.; Bode, J. W. *Org. Lett.* **2016**, *18*, 5336; e) Mazunin, D.; Broguiere, N.; Zenobi-Wong, M.; Bode, J. W. *ACS Biomater. Sci. Eng.* **2015**, *1*, 456; f) Noda, H.; Bode, J. W. *J. Am. Chem. Soc.* **2015**, *137*, 3958.

(19) Taguchi, J.; Ikeda, T.; Takahashi, R.; Sasaki, I.; Ogasawara, Y.; Dairi, T.; Kato, N.; Yamamoto, Y.; Bode, J. W.; Ito, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 13847.

(20) Taguchi, J.; Takeuchi, T.; Takahashi, R.; Ito, H. *To be submitted.*

Chapter 1.

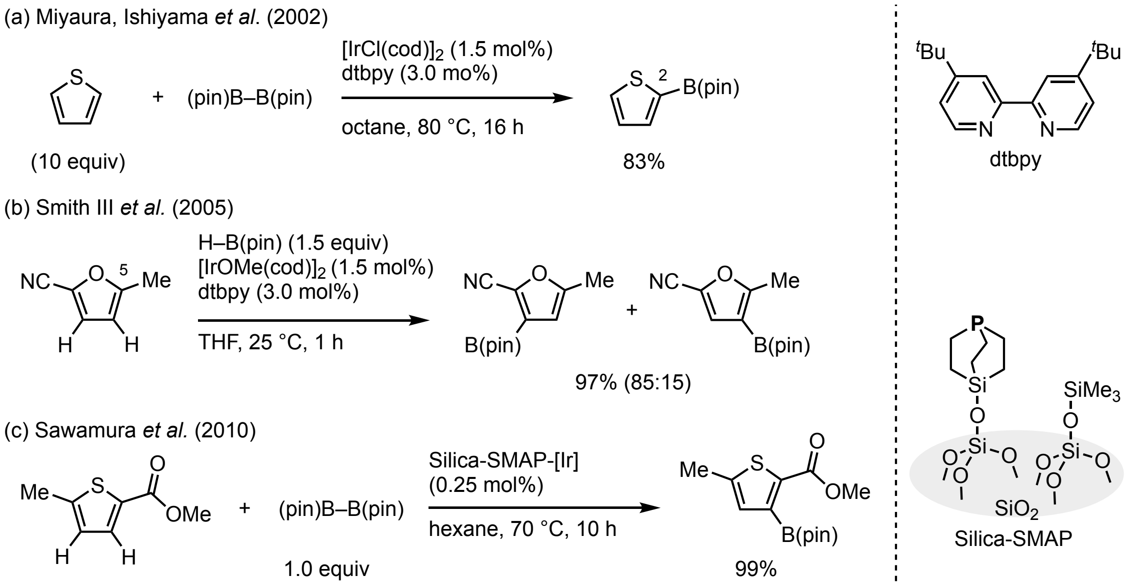
Iridium-Catalyzed Regiodivergent C–H borylation of Multifunctionalized heteroarenes

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.

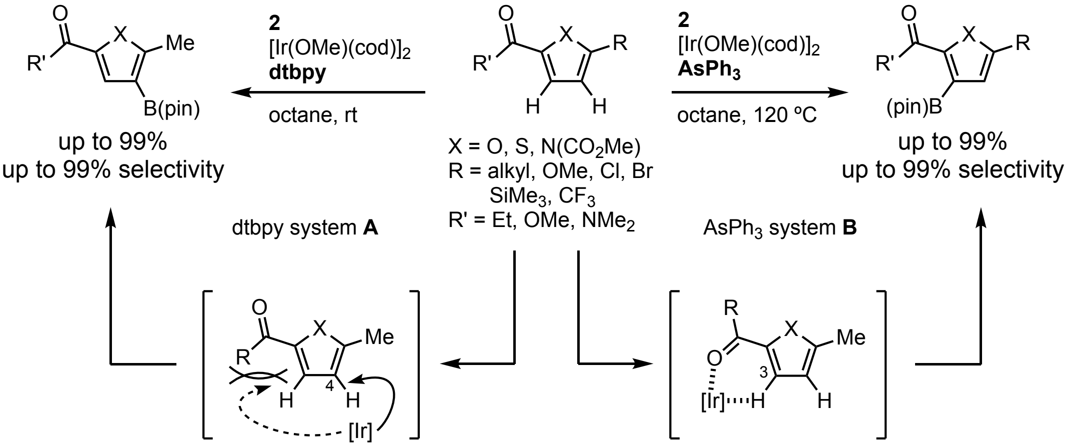
Introduction

Multi-substituted heteroarenes bearing boryl substituent are important structural motifs because they can be utilized as a 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 borylatin 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.



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

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 **1** with bis(pinacolato)diboron (B_2pin_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 $[Ir(OMe)(cod)]_2$/2 $AsPh_3$ complex afforded the 4-borylated product 4 (Scheme 1-2, $AsPh_3$ system B).

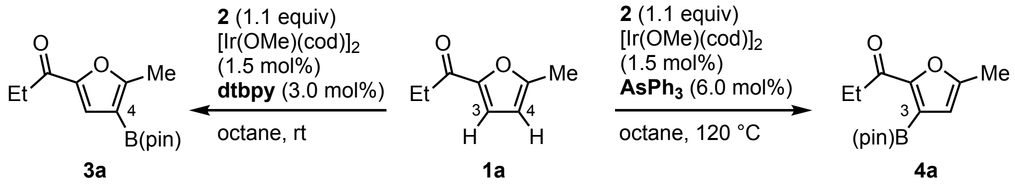


Scheme 1-2. This work: Regiodivergent C–H borylation reactions of heteroaromatic compounds.

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 AsPh$_3$ 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]

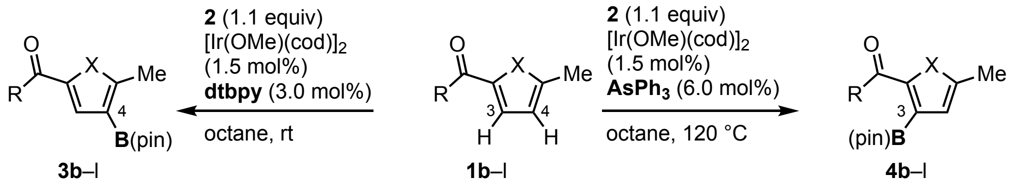


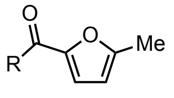
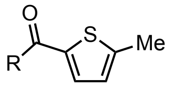
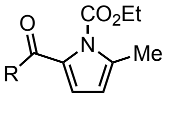
entry	Ligand (mol%)	T (°C)	Solvent	Yield (%)[b]	3a/4a[c]
1	dtbpy (3)	rt	octane	92 (76)[d]	>99:<1
2	TMphen (3)	rt	octane	82	>99:<1
3	AsPh$_3$ (6)	120	octane	74 (43)[d,e]	<1:>99
4	P[3,5-(CF$_3$)$_2$C$_6$H$_3$]$_3$ (6)	120	octane	0	-
5	P(C$_6$F$_5$)$_3$ (6)	120	octane	31	<1:>99
6	PPh$_3$ (6)	120	octane	22	<1:>99
7	PCy$_3$ (6)	120	octane	18	<1:>99
8	-	120	octane	28	<1:>99
9	AsPh$_3$ (6)	120	DMF	0	-
10	AsPh$_3$ (6)	120	diglyme	69	<1:>99
11	AsPh$_3$ (6)	120	mesitylene	72	<1:>99

[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 ^{1}H NMR spectroscopy analysis. [d] Yield of product isolated. [e] The yield of borylated product **4a** a 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 ^{1}H 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; AsPh$_3$ 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.

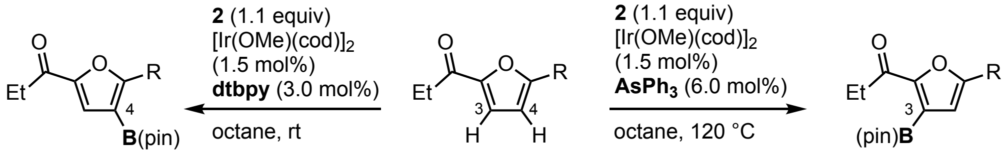


entry	Substrate	R	System	time (h)	Yield (%)[b]	3/4[c]
1		Me (**1b**)	A	2	99	>99:<1
2			B	9	56	<1:>99
3		OMe (**1c**)	A	4	98	>99:<1
4			B	4	74	<1:>99
5		NMe$_2$ (**1d**)	A	1	94	>99:<1
6			B	6	93	<1:>99
7		N(*i*-Pr)$_2$ (**1e**)	A	1	94	>99:<1
8			B	6	93	<1:>99
9		Et (**1f**)	A	2	99	>99:<1
10			B	9	56	<1:>99
11		Me (**1g**)	A	4	98	>99:<1
12			B	4	74	<1:>99
13		OMe (**1h**)	A	1	94	>99:<1
14			B	6	93	<1:>99
15		N(i-Pr)$_2$ (**1i**)	A	1	94	>99:<1
16			B	6	93	<1:>99
17		Et (**1j**)	A	2	99	>99:<1
18			B	9	56	<1:>99
19		NMe$_2$ (**1k**)	A	4	98	>99:<1
20			B	4	74	<1:>99
21		OMe (**1l**)	A	1	94	>99:<1
22			B	6	93	<1:>99

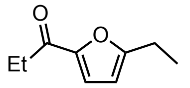
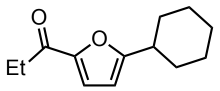
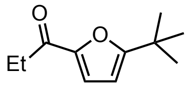
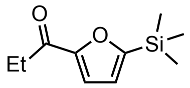
[a] System A: **1** (0.5 mmol), **2** (0.55 mmol), [Ir(OMe)(cod)]$_2$ (1.5 mol%), and dtbpy (3.0 mol %) in octane (3 mL) at room temperature for 16 h. System B: **1** (0.5 mmol), **2** (0.55 mmol), [Ir(OMe)(cod)]$_2$ (1.5 mol%), and AsPh$_3$ (6.0 mol %) in octane (3 mL) at 120°C for 16 h. [b] Yields were determined by GC analysis (internal standard: dodecane). [c] Ratios of isomers in the crude reaction mixture were determined by ^{1}H 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-substitutents 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 1-3. Scope of furanes with various alkyl and TMS group at 5-position.



3m–p **1m–p** **4m–p**

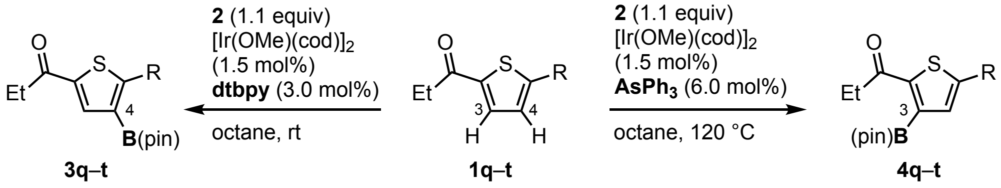
entry	Substrate	System	time (h)	Yield (%)[b]	3/4[b]
1	 **1m**	A	24	81	97:3
2		B	3	68	<1:>99
3	 **1n**	A	8	86	94:6
4		B	4	94	<1:>99
5	 **1o**	A	4	75	<1:>99
6[c]		B	3	67	<1:>99
7	 **1p**	A	3	58	<1:>99
8[d]		B	30	48	<1:>99

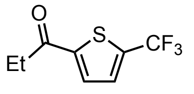
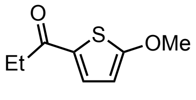
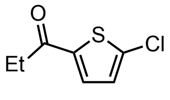
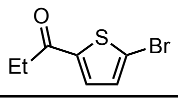
[a] System A: **1** (0.5 mmol), **2** (0.55 mmol), [Ir(OMe)(cod)]$_2$ (1.5 mol%), and dtbpy (3.0 mol%) in octane (3 mL) at room temperature. System B: **1** (0.5 mmol), **2** (0.55 mmol), [Ir(OMe)(cod)]$_2$ (1.5 mol %), and AsPh$_3$ (6.0 mol %) in octane (3 mL) at 120°C. [b] Combined yields and ratios of isomers in the crude reaction mixture were determined by ^{1}H NMR spectroscopy analysis (internal standard: dibromomethane). [c] This reaction was carried out at 60°C. [d] This reaction was carried out at 80°C.

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 $AsPh_3$ 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 CF_3 group behaved as a larger substituent than that of a Cy group in this borylation.[11] Borylation of the 5-CF_3-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 obtained selectively under $AsPh_3$ system B (entry 2). Although the methoxy-substituted thiophene **1r** reacted with **2** under dtbpy system A to afford the 4-borylated product **3r** in high yield (82 %, **3r**/**4r** = >99:<1; entry 3), no reaction occurred under $AsPh_3$ system B (entry 4). A chloro group did not interfere with the formation of 4-borylated product **3s** (dtbpy system A, 82 %, **3s**/**4s** = >99:<1; entry 5). Low reactivity and regioselectivity were observed when $AsPh_3$ was used as the ligand ($AsPh_3$ system B: 46%, **3s**/**4s** = 26:74; entry 6). This result suggests that the chloro group might weakly coordinate with the iridium center.[9f] The borylation of substrate **1t**, which had a bromo group, proceeded regioselectively at the 4-position to give **3t** in 53 % yield under dtbpy system A (Table 4, entry 7), but the 3-borylated product **4t** was not obtained ($AsPh_3$ system B; entry 8).[12] These results show that **1r** or **1t** cannot be used as substrates under $AsPh_3$ system B.

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



entry	Substrate	System	time (h)	Yield (%)[b]	3/4[b]
1[c]	 **1q**	A	20	80	56:44
2[d]		B	20	75	<1:>99
3	 **1r**	A	16	82	>99:<1
4		B	30	0	-
5	 **1s**	A	16	82	>99:<1
6		B	16	46	26:74
7	 **1t**	A	1	53	>99:<1
8		B	48	0	-

[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 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 $AsPh_3$ were used.

In the borylation of **1r** or **1t** under $AsPh_3$ 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.

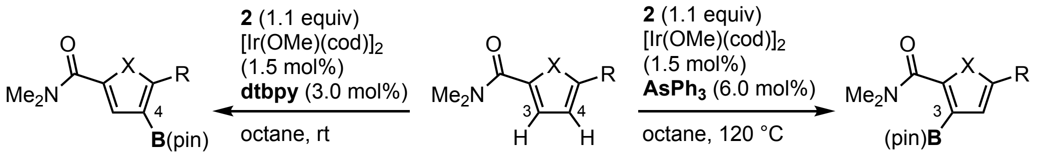
1u
dtbpy system A
80°C, 1 h, 91% (**3u**/**4u** = >99:<1)
$AsPh_3$ system B
120°C, 48 h, 20% (**3u**/**4u** = <1:>99)

1v
dtbpy system A
80°C, 1 h, 94% (**3v**/**4v** = >99:<1)
$AsPh_3$ system B
120°C, 20 h, 40% (**3v**/**4v** = <1:>99)

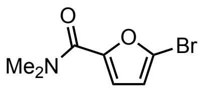
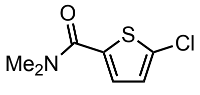
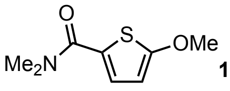
Scheme 1-3. Borylation of 5-bromothiophene with ester **1u** or amide groups **1v** at the 2-position.

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). $AsPh_3$ 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; $AsPh_3$ 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; $AsPh_3$ 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.

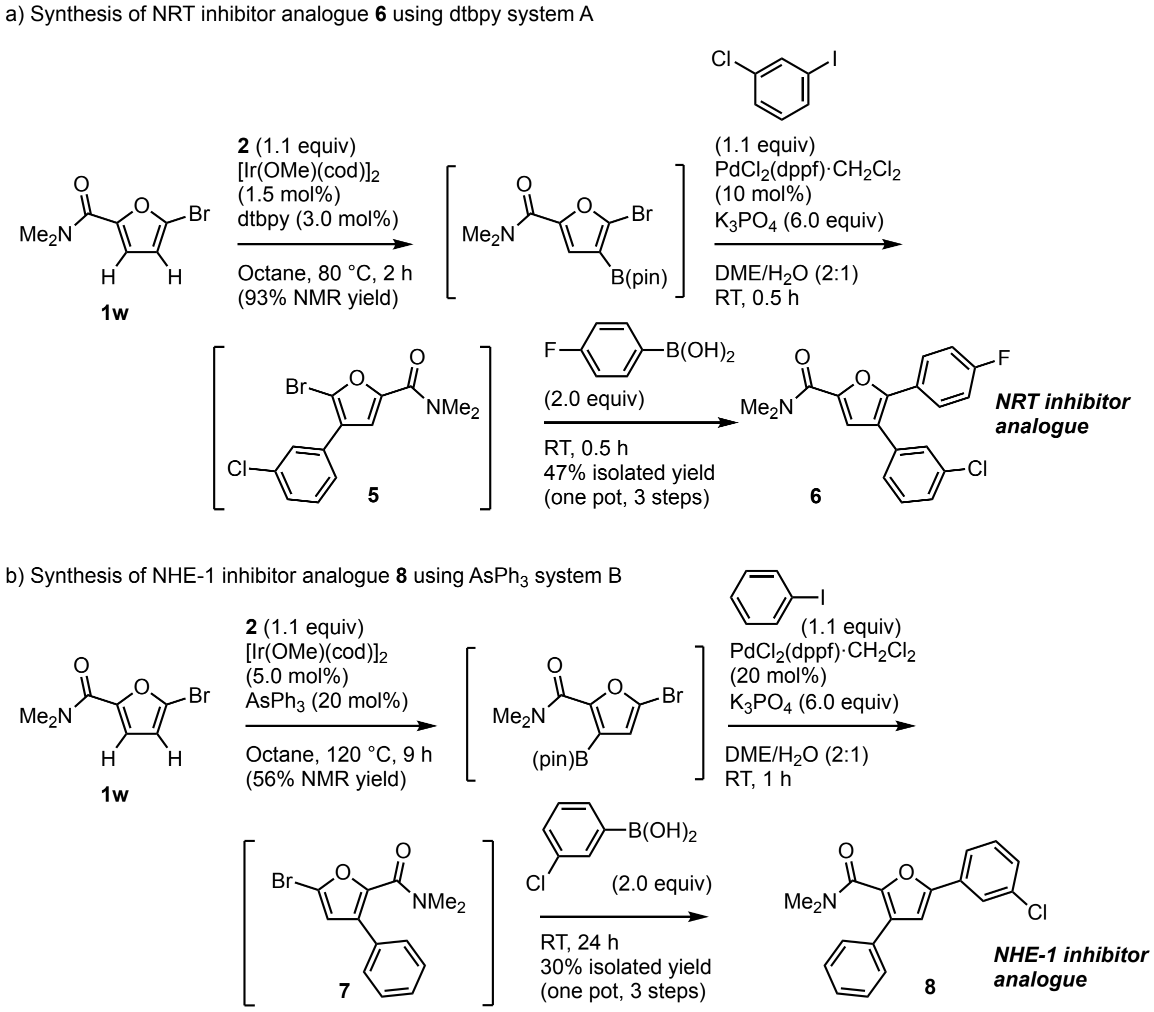


3w–y **1w-y** **4w–y**

entry	Substrate	System	time (h)	Yield (%)[b]	**3a/4a**[b]
1	 **1w**	A	2	99	95:5
2		B	9	56	>99:<1
3	 **1x**	A	4	98	<1:>99
4		B	4	74	13:87
5	 **1y**	A	1	94	<1:>99
6[c]		B	6	93	<1:>99

[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 80°C. System B: **1** (0.5 mmol), **2** (0.55 mmol), $[Ir(OMe)(cod)]_2$ (5.0 mol %), and $AsPh_3$ (20 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] 1.5 mol % of $[Ir(OMe)(cod)]_2$ and 6.0 mol % of $AsPh_3$ were used.

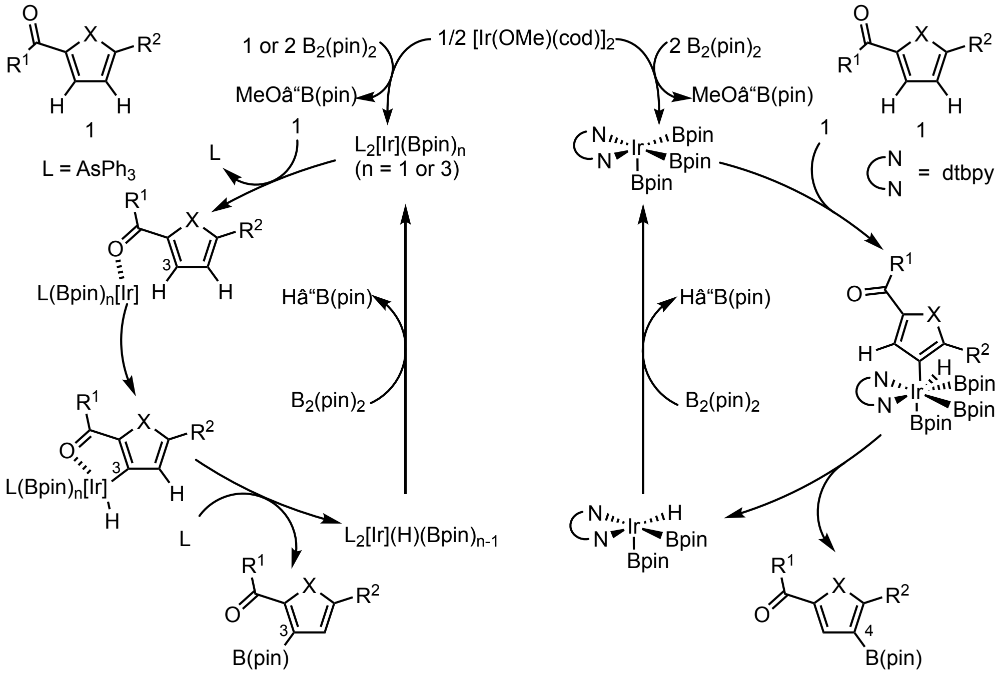
To further demonstrate the synthetic utility of this regiodivergent borylation, we synthesized two different biologically active compound analogues by using borylated furans derived from **1w** (Scheme 1-4).[1b,1g] The one-pot synthesis of **6** was achieved by using a stepwise cross-coupling strategy 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 $AsPh_3$ system B, followed by a stepwise cross-coupling procedure by using iodobenzene (1.1 equiv) and (3-chlorophenyl)boronic acid (2.0 equiv).


a) Synthesis of NRT inhibitor analogue **6** using dtbpy system A

b) Synthesis of NHE-1 inhibitor analogue **8** using $AsPh_3$ system B

Scheme 1-4. Synthesis of biologically active compound analogues.

Two proposed catalytic cycles are shown in Scheme 1-5.[13] 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 ($AsPh_3$ system B), the mono- (n=1) or tris- (n=3) boryliridium complex **D** is first produced by reactions of iridium(I) complexes containing $AsPh_3$ 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**.



Scheme 1-5. Proposed catalytic cycles

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 AsPh$_3$ catalyst (AsPh$_3$ 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.

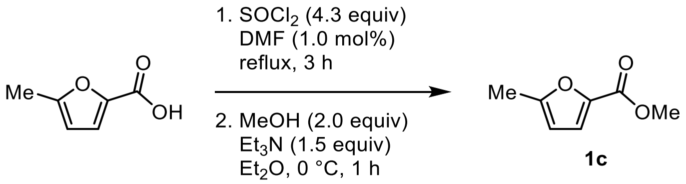
A General Procedure for the $[Ir(OMe)(cod)]_2$/$AsPh_3$-Catalyzed C–H Borylation of Heteroarenes 1a–1y (Catalytic System B).

$[Ir(OMe)(cod)]_2$ (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.

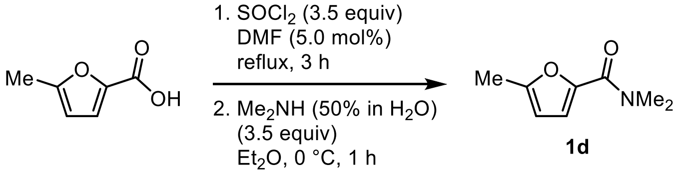
Preparation of methyl 5-methylfuran-2-carboxylate (1c).



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. $SOC1_2$ (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 $SOCl_2$ was removed under reduced pressure. Et_2O (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 Et_3N (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 Et_2O three times. The combined organic layer was washed with H_2O, and dried over $MgSO_4$. 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.

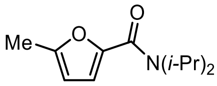
Preparation of *N*,*N*-dimethyl-5-methylfuran-2-carboxamide (1d).



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. $SOC1_2$ (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 $SOCl_2$ was removed under reduced pressure. Et_2O (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 Me_2NH (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 Et_2O three times. The combined organic layer was washed with H_2O, and dried over $MgSO_4$. 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. ^{1}H NMR (396 MHz, $CDCl_3$, δ): 2.36 (s, 3H), 3.19 (br s, 6H), 6.07–6.08 (m, 1H), 6.87 (d, J = 3.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.0 ($\mathit{C}H_3$), 35.7 (br, CH_3), 37.5 (br, $\mathit{C}H_3$), 106.8 (*C*H), 116.5 (*C*H), 145.5 (*C*), 153.5 (*C*), 159.6 (*C*). HRMS-EI (m/z): $[M]^+$ calcd for $C_8H_{11}NO_2$, 153.07898; found, 153.07863.

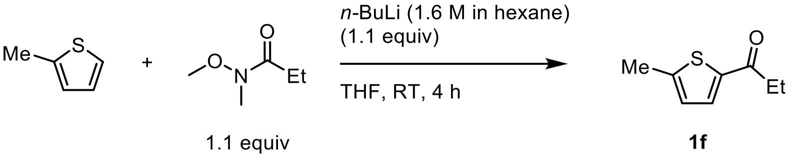
Preparation of *N*,*N*-diisopropyl-5-methylfuran-2-carboxamide (1e).



1e

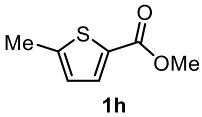
1e was prepared from 5-methylfuran-2-carboxylic acid and (*i*-Pr)$_2$NH according to the procedure for the synthesis of **1d**. ^{1}H NMR (392 MHz, CDCl$_3$, δ): 1.37 (br s, 6H), 1.38 (br s, 6H), 2.33 (s, 3H), 4.01 (br s, 2H), 6.03–6.04 (m, 1H), 6.70 (d, J =3.2 Hz, 1H). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 13.3 (CH$_3$), 20.6 (CH$_3$), 47.7 (br, CH), 106.8 (CH), 114.7 (CH), 147.2 (C), 152.9 (C), 160.1 (C). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{12}H_{19}NO_2$, 209.14158; 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 $C_8H_{10}OS$, 154.04524; found, 154.04485.

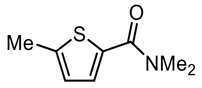
Preparation of methyl 5-methylthiophene-2-carboxylate (1h).



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.

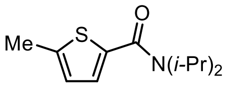
Preparation of *N*,*N*-dimethyl-5-methy-thiophene-2-carboxamide (1i).



1i

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_2NH (50%) according to the procedure for the synthesis of **1d**. ^1H NMR (392 MHz, $CDCl_3$, δ): 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, $CDCl_3$, δ): 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 $C_8H_{10}NOS$, 168.04831; found, 168.04762.

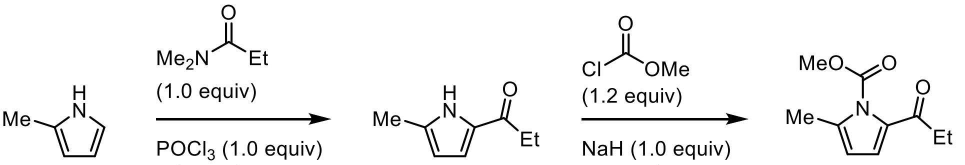
Preparation of *N*,*N*-diisopropyl-5-methylthiophene-2-carboxamide (1j).



1j

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 $(i\text{-}Pr)_2NH$ according to the procedure for the synthesis of **1d**. ^1H NMR (392 MHz, $CDCl_3$, δ): 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, $CDCl_3$, δ): 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 $C_{12}H_{19}NOS$, 225.11873; found, 225.11874.

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



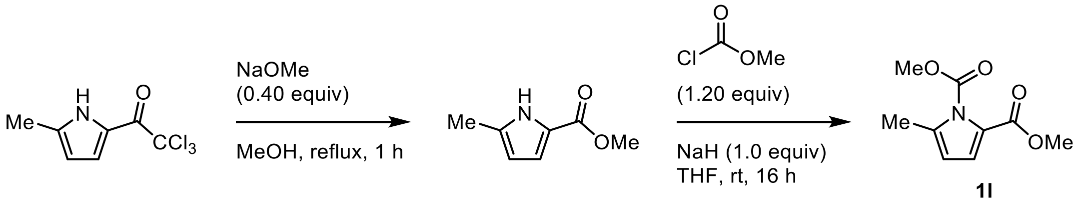
1k

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 –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_3CO_2Na (23 g) in H_2O (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 H_2O, and 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 **1k** (1.50 g, 7.68 mmol, 39%). ^{1}H NMR (392 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 8.5 (CH_3), 12.5 (CH_3), 31.2 (CH_2), 54.9 (CH_3), 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 $C_{10}H_{13}NO_3$, 195.08954; found, 195.08958.

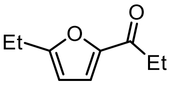
Preparation of dimethyl 5-methyl-1H-pyrrole-1,2-dicarboxylate (1l).



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 $MgSO_4$. 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 H_2O, and 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 **1l** (3.50 g, 17.8 mmol, 50%). ^{1}H NMR (392 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.4 (CH_3), 51.4 (CH_3), 54.6 (CH_3), 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 $C_9H_{11}O_4N$, 197.06881: found, 197.06882.

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

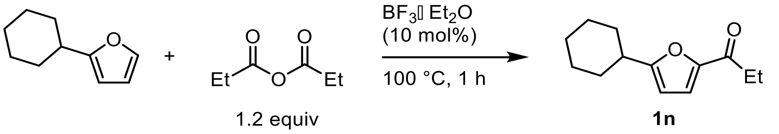


1m

1m (695 mg, 4.57 mmol, colorless oil) was prepared in 9% yield from 2-ethylfurane (5.00 g, 52.0 mmol) according to the reported procedure.[8] ^{1}H NMR (392 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz,

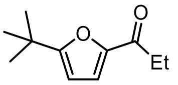
$CDCl_3$, δ): 8.1 (CH_3), 11.5 (CH_3), 21.4 (CH_2), 31.0 (CH_2), 106.9 (CH), 118.3 (CH), 150.8 (C), 162.6 (C), 189.3 (C). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_9H_{12}O_2Na$, 175.07295; found, 175.07310.

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. $BF_3\cdot Et_2O$ (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 H_2O (2.5 mL), and extracted with Et_2O three times. The combined organic layer was washed with saturated aqueous solution of Na_2CO_3, and dried over $MgSO_4$. 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, $CDCl_3$, 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 8.2 (CH_3), 25.5 (CH_2), 25.7 (CH_2), 31.0 (CH_2), 31.2 (CH_2), 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 $C_{13}H_{18}O_2Na$, 229.11990; found, 229.11993.

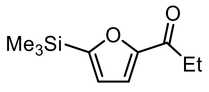
Preparation of 1-[5-(*tert*-butyl)furan-2-yl]propan-1-one (1o).



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, $CDCl_3$, δ): 1.20 (t, J = 7.3 Hz, 3H), 1.33 (s, 9H), 2.81 (q, J = 7.4 Hz, 2H), 6.13 (d, J = 3.6 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 8.1 (CH_3), 28.6 (CH_3), 31.2 (CH_2), 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 $C_{11}H_{16}O_2Na$, 203.10425; found, 203.10446.

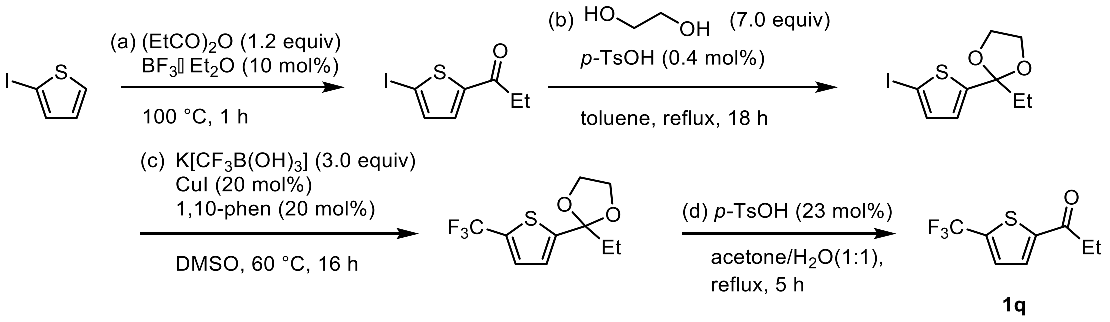
Preparation of 1-[5-(trimethylsilyl)furan-2-yl]propan-1-one (1p).



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, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$): -2.1 (CH_3), 7.9 (CH_3), 31.6 (CH_2), 116.2 (CH), 121.0 (CH), 156.2 (C), 165.7 (C), 190.1 (C). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{10}H_{16}O_2NaSi$, 219.08118; found, 219.08137.

Preparation of 1-[5-(trifluoromethyl)thiophen-2-yl]propan-1-one (1q).



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 an oven-dried flask, under nitrogen atmosphere, 1-(5-iodothiophen-2-yl)propan-1-one (3.51 g, 13.2 mmol), ethylene glycol (5.15 mL, 5.72 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 Na_2CO_3 (5%, w/w), 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 2-ethyl-2-(5-iodothiophen-2-yl)-1,3-dioxolane (2.62 g, 8.46 mmol, 64%) as a colorless oil.

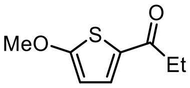
Step c: Preparation of 2-ethyl-2-[5-(trifluoromethyl)thiophen-2-yl]-1,3-dioxolane.

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 Et_2O (40 mL) and washed with 1 M HCl (100 mL). The aqueous layer was extracted with Et_2O (20 mL) twice and the combined organic layer was washed with conc. NH_3 (25% in H_2O, 100 mL). The aqueous layer was extracted with Et_2O (20 mL) twice and the combined organic layer was washed with brine (60 mL), dried over $MgSO_4$. 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 H_2O (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 $NaHCO_3$ and extracted with EtOAc three times. The combined organic layer was washed with H_2O, and dried over $MgSO_4$. 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. ^{1}H NMR (392 MHz, CDCl$_3$, 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). ^{13}C NMR (99 MHz, CDCl$_3$): 8.0 (CH$_3$), 32.5 (CH$_2$), 121.8 (q, $^1J_{C-F}$ = 269.7 Hz, CF$_3$), 128.9 (q, $^3J_{C-F}$ = 3.4 Hz, CH), 130.2 (CH), 137.5 (q, $^2J_{C-F}$ = 38.5 Hz, C), 146.9 (C), 193.5 (C). HRMS-ESI (m/z): [M–H]$^+$ calcd for $C_8H_6OF_3S$, 207.00969; found, 207.00962.

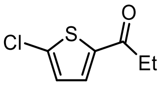
Preparation of 1-(5-methoxythiophen-2-yl)propan-1-one (1r).



1r

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**. ^{1}H NMR (392 MHz, CDCl$_3$, 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). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 8.8 (CH$_3$), 30.7 (CH$_2$), 60.1 (CH$_3$), 105.5 (CH), 130.1 (C), 131.9 (CH), 173.9 (C), 193.1 (C). HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_8H_{10}O_2NaS$, 193.02937; found, 193.02962.

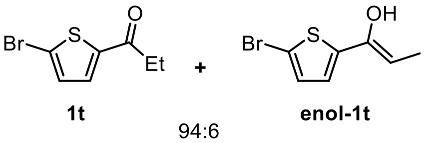
Preparation of 1-(5-chlorothiophen-2-yl)propan-1-one (1s).



1s

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**. ^{1}H NMR (396 MHz, CDCl$_3$, 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). ^{13}C NMR (100 MHz, CDCl$_3$, δ): 8.2 (CH$_3$), 31.6 (CH$_2$), 127.4 (CH), 130.9 (CH), 138.8 (C), 142.6 (C), 192.7 (C). HRMS-ESI (m/z): [M+H]$^+$ calcd for C_7H_8OClS, 174.99789; found, 174.99822.

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

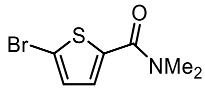


1t **enol-1t**

94:6

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**: ^{1}H NMR (392 MHz, CDCl$_3$, 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). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 8.3 (CH$_3$), 31.8 (CH$_2$), 122.0 (C), 131.1 (CH), 131.6 (CH), 145.5 (C), 192.7 (C). **enol-1t**: ^{1}H NMR (392 MHz, CDCl$_3$, 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). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 20.1 (CH$_3$), 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 $C_7H_8O^{79}BrS$, 218.94737; found, 218.94764.

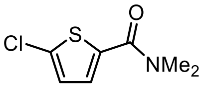
Preparation of 5-bromo-*N*,*N*-dimethylthiophene-2-carboxamide (1v).



1v

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_2NH (50%) according to the procedure for the synthesis of **1d**. ^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.18 (br s, 6H), 7.00–7.02 (m, 1H), 7.12 (d, *J* = 3.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 36.6 (br, *C*H_3), 39.1 (br, *C*H_3), 116.6 (*C*), 129.4 (*C*H), 129.5 (*C*H), 139.5 (*C*), 162.6 (*C*). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_7H_8ON^{79}BrNaS$, 255.94022; found, 255.94021.

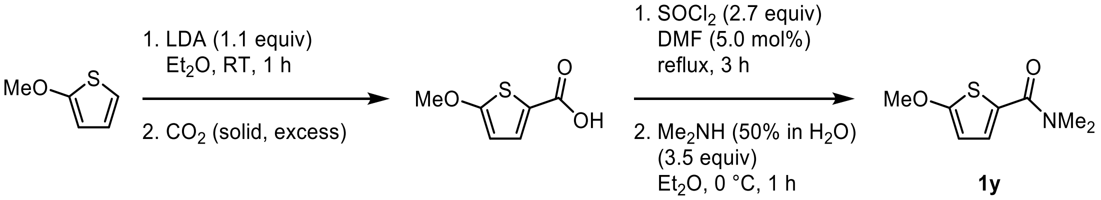
Preparation of 5-chloro-*N*,*N*-dimethylthiophene-2-carboxamide (1x).



1x

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_2NH (50%) according to the procedure described above. ^{1}H NMR (392 MHz, $CDCl_3$, δ): 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, $CDCl_3$, δ): 37.1 (br, *C*H_3), 38.9 (br, *C*H_3), 125.9 (*C*H), 128.7 (*C*H), 134.1 (*C*), 136.8 (*C*), 162.8 (*C*). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_7H_8ONClNaS$, 211.99073; found, 211.99089.

Preparation of 5-methoxy-*N*,*N*-dimethylthiophene-2-carboxamide (1y).

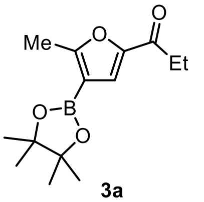


To an oven-dried flask, under nitrogen atmosphere at room temperature, (*i*-Pr)$_2$NH (2.0 mL, 14.4 mmol) in THF (66 ml). A hexane solution of *n*-BuLi (1.6 M, 9.0 mL, 14.4 mmol) was slowly added dropwise at –78 °C, and the mixture was warmed to room temperature and stirred for 15 min. The mixture was 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_2O. 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_2NH (50%) according to the procedure for the synthesis of **1d**. ^{1}H NMR (396 MHz, $CDCl_3$, δ): 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, $CDCl_3$, δ): 37.8 (br, *C*H_3), 59.8 (*C*H_3), 103.7 (*C*H), 124.0 (*C*), 128.5 (*C*H), 163.6 (*C*), 169.5 (*C*).

HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_8H_{11}O_2NNaS$, 208.04027; found, 208.04061.

Characterization of Borylation Products.

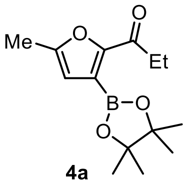
1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (3a).



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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 8.7 (CH_3), 14.5 (CH_3), 24.8 (CH_3), 31.3 (CH_2), 83.6 (*C*), 123.6 (*C*H), 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 $C_{14}H_{21}{}^{11}BO_4$, 264.15329; found, 264.15296.

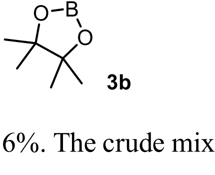
1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4a).



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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 7.8 (CH_3), 13.3 (CH_3), 24.5 (CH_3), 31.6 (CH_2), 83.9 (*C*), 112.9 (*C*H), 119.4 (br, B–*C*), 154.7 (*C*), 155.6 (*C*), 190.5 (*C*). HRMS–EI (*m/z*): $[M]^+$ calcd for $C_{14}H_{21}{}^{11}BO_4$, 264.15329; found, 264.15247.

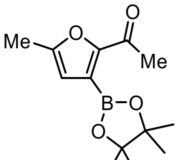
1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]ethan-1-one (3b).



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, $CDCl_3$, δ): 1.32 (s, 12H), 2.41 (s, 3H), 2.54 (s, 3H), 7.31 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 14.5 (CH_3), 24.8 (CH_3), 25.7 (CH_3), 83.6 (*C*), 124.5 (*C*H), 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 $C_{13}H_{19}O_4{}^{11}BNa$, 273.12686; found: 273.12686.

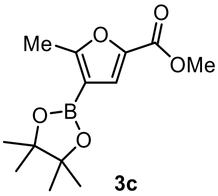
1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]ethan-1-one (4b).



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, $CDCl_3$, δ): 1.37 (s, 12H), 2.36 (d, $J = 0.8$ Hz, 3H), 2.52 (s, 3H), 6.27 (m, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.6 (CH_3), 24.7 (CH_3), 26.6 (CH_3), 84.3 (*C*), 113.4 (*C*H), 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 $C_{13}H_{19}O_4{}^{11}BNa$, 273.12686; found: 273.12667.

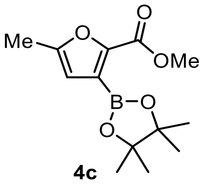
Methyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylate (3c).



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, $CDCl_3$, δ): 1.31 (s, 12H), 2.53 (s, 3H), 3.86 (s, 3H), 7.30 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 14.3 (CH_3), 24.7 (CH_3), 51.6 (CH_3), 83.4 (*C*), 108.9 (br, B–*C*), 123.6 (*C*H), 142.8 (*C*), 159.1 (*C*), 166.2 (*C*). HRMS–ESI(*m/z*): $[M+Na]^+$ calcd for $C_{13}H_{19}O_5{}^{10}BNa$, 288.12541; found: 288.12543.

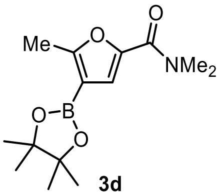
Methyl 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylate (4c).



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, $CDCl_3$, δ): 1.37 (s, 12H), 2.36 (s, 3H), 3.88 (s, 3H), 6.22 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.5 (CH_3), 24.7 (CH_3), 51.7 (CH_3), 84.2 (*C*), 112.4 (*C*H), 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 $C_{13}H_{19}O_5{}^{10}BNa$, 288.12541; found: 288.12543.

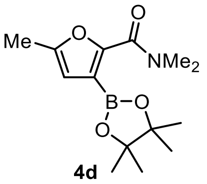
***N*,*N*-Dimethyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (3d).**



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 (*C*H_3), 24.6 (*C*H_3), 36.3 (br, *C*H_3), 38.5 (br, *C*H_3), 83.2 (*C*), 107.7 (br, B–*C*), 120.4 (*C*H), 145.5 (*C*), 160.2 (*C*), 163.8 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{14}H_{22}{}^{11}BNO_4$, 279.16419; found, 279.16506.

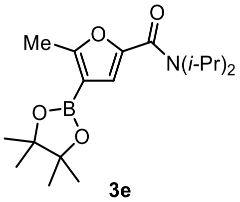
***N*,*N*-Dimethyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (4d).**



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 (*C*H_3), 24.7 (*C*H_3), 35.8 (br, *C*H_3), 38.4 (br, *C*H_3), 83.5 (*C*), 110.5 (*C*H), 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]$^+$ calcd for $C_{14}H_{22}O_4N^{10}BNa$, 301.15704; found, 301.15782.

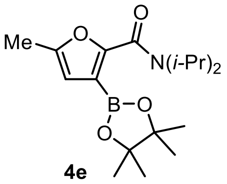
***N*,*N*-Diisopropyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (3e).**



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 (*C*H_3), 20.8 (*C*H_3), 24.7 (*C*H_3), 47.9 (br, *C*H), 83.2 (*C*), 107.4 (br, B–*C*), 117.5 (*C*H), 146.8 (*C*), 160.3 (*C*), 163.1 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{18}H_{30}{}^{11}BNO_4$, 335.22679; found, 335.22612.

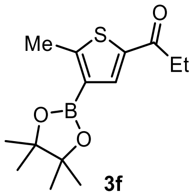
N,*N*-Diisopropyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (4e).



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 (*C*H$_3$), 20.1 (br, *C*H$_3$), 24.6 (*C*H$_3$), 45.5 (br, *C*H), 50.6 (br, *C*H), 83.1 (*C*), 109.3 (*C*H), 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 $C_{18}H_{30}O_4N^{10}BNa$, 357.21964; found, 357.22066.

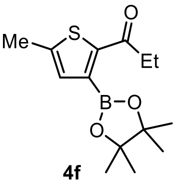
1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]propan-1-one (3f).



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 (*C*H$_3$), 16.6 (*C*H$_3$), 24.8 (*C*H$_3$), 31.9 (*C*H$_2$), 83.6 (*C*), 138.5 (*C*H), 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 $C_{14}H_{21}{}^{11}BO_3S$, 280.13045; found, 280.13022.

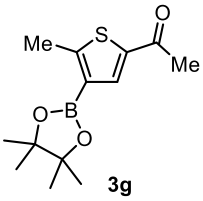
1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]propan-1-one (4f).



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 (*C*H$_3$), 15.3 (*C*H$_3$), 24.7 (*C*H$_3$), 33.5 (*C*H$_2$), 84.2 (*C*), 131.5 (*C*H), 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 $C_{14}H_{21}{}^{11}BO_3S$, 280.1304; found, 280.1304.

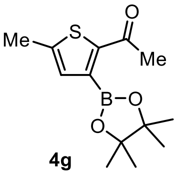
1-[5-Methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]ethan-1-one (3g).



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 (*C*H$_3$), 24.8 (*C*H$_3$), 26.4 (*C*H$_3$), 83.6 (*C*), 139.6 (*C*H), 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 $C_{13}H_{19}O_3{}^{11}BNaS$, 289.10402; found: 289.10380.

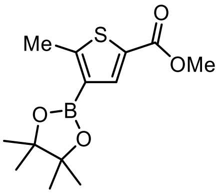
1-[5-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]ethan-1-one (4g).



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 (*C*H$_3$), 24.7 (*C*H$_3$), 28.0 (*C*H$_3$), 84.2 (*C*), 131.9 (*C*H), 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 $C_{13}H_{19}O_3{}^{11}BNaS$, 289.10402; found: 289.10386.

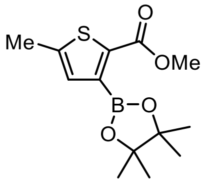
Methyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (3h).



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 (*C*H$_3$), 24.8 (*C*H$_3$), 51.8 (*C*H$_3$), 83.4 (*C*), 129.9 (*C*), 140.3 (*C*H), 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 $C_{13}H_{19}O_4{}^{11}BNaS$, 305.09893; found: 305.09874.

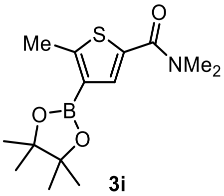
Methyl 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (4h).



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). ^{1}H NMR (392 MHz, CDCl$_3$, δ): 1.39 (s, 12H), 2.49 (d, J = 0.7 Hz, 3H), 3.85 (s, 3H), 6.85 (m, 1H). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 15.1 (CH$_3$), 24.6 (CH$_3$), 51.8 (CH$_3$), 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 C$_{13}$H$_{19}$O$_4$^{11}BNaS, 305.09893; found: 305.09875.

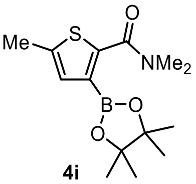
***N,N*-Dimethyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3i).**



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). ^{1}H NMR (401 MHz, CDCl$_3$, δ): 1.31 (s, 12H), 2.67 (s, 3H), 3.18 (br s, 6H), 7.43 (s, 1H). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 15.6 (CH$_3$), 24.6 (CH$_3$), 36.5 (br, CH$_3$), 39.1 (br, CH$_3$), 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 C$_{14}$H$_{22}$O$_3$N^{11}BNaS, 318.13057; found, 318.13120.

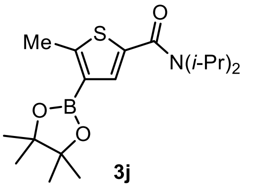
***N,N*-Dimethyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4i).**



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). ^{1}H NMR (396 MHz, CDCl$_3$, δ): 1.29 (s, 12H), 2.46 (d, J = 1.3 Hz, 3H), 3.02 (br s, 6H), 6.91–6.92 (m, 1H). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 14.6 (CH$_3$), 24.8 (CH$_3$), 35.2 (br, CH$_3$), 38.7 (br, CH$_3$), 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 C$_{14}$H$_{22}$O$_3$N^{10}BNaS, 317.13420; found, 317.13431.

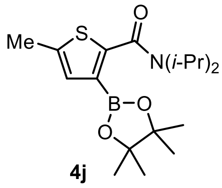
***N,N*-Diisopropyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3j).**



3j

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). ^{1}H NMR (401 MHz, CDCl$_3$, 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). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 15.6 (*C*H$_3$), 20.8 (*C*H$_3$), 24.8 (*C*H$_3$), 48.8 (br, *C*H), 83.2 (*C*), 127.5 (br, B–*C*), 132.6 (*C*H), 136.6 (*C*), 154.4 (*C*), 163.8 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{18}H_{30}{}^{10}BNO_3S$, 350.20758; found, 350.20720.

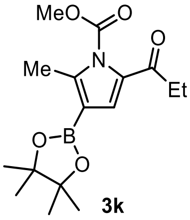
***N,N*-Diisopropyl-5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4j).**



4j

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). ^{1}H NMR (401 MHz, CDCl$_3$, 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). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 14.4 (*C*H$_3$), 20.0 (*C*H$_3$), 24.6 (*C*H$_3$), 45.8 (br, *C*H), 51.0 (br, *C*H), 83.1 (*C*), 129.7 (*C*H), 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 $C_{18}H_{30}{}^{11}BNO_3S$, 351.20394; found, 351.20396.

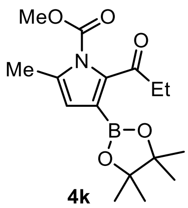
Methyl 2-methyl-5-propionyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1- carboxylate (3k).



3k

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). ^{1}H NMR (396 MHz, CDCl$_3$, 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). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 8.7 (*C*H$_3$), 12.4 (*C*H$_3$), 24.7 (*C*H$_3$), 31.2 (*C*H$_2$), 55.2 (*C*H$_3$), 83.1 (*C*), 109.7 (br, B–*C*), 125.0 (*C*H), 132.9 (*C*), 146.2 (*C*), 152.8 (*C*), 190.1 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{16}H_{24}{}^{10}BNO_5$, 320.17838; found, 320.17721.

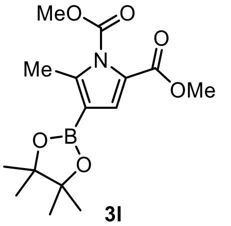
Methyl 5-methyl-2-propionyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1- carboxylate (4k).



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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 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 (*C*H), 134.5 (*C*), 139.3 (*C*), 152.2 (*C*), 196.8 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{16}H_{24}{}^{10}BNO_5$, 320.17838; found, 320.17705.

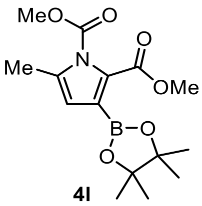
Dimethyl 5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2-dicarboxylate (3l).



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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 13.2 (CH_3), 24.8 (CH_3), 51.6 (CH_3), 55.0 (CH_3), 83.2 (*C*), 124.4 (*C*), 125.6 (*C*H), 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 $C_{15}H_{22}{}^{10}BNO_6$, 322.15765; found, 322.15768.

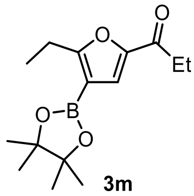
Dimethyl 5-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole-1,2-dicarboxylate (4l).



4l

The NMR yield of **4l** in the crude mixture was 43%. Colorless oil; ^{1}H NMR (396 MHz, $CDCl_3$, δ): 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, $CDCl_3$, δ): 13.9 (CH_3), 24.7 (CH_3), 51.9 (CH_3), 54.6 (CH_3), 83.6 (*C*), 115.1 (*C*H), 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 $C_{15}H_{22}{}^{10}BNO_6$, 322.15765; found, 322.15669.

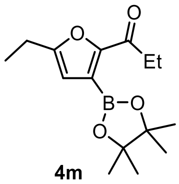
1-[5-Ethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (3m).



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). ^{1}H NMR (392 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 8.6 (CH_3), 13.0 (CH_3), 22.0 (CH_2), 24.7 (CH_3), 31.3 (CH_2), 83.5 (*C*), 123.5 (*C*H), 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 $C_{15}H_{23}O_4{}^{10}BNa$, 300.16179; found, 300.16162.

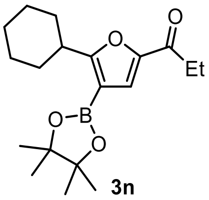
1-[5-Ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4m).



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). ^{1}H NMR (392 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 8.1 (CH_3), 11.8 (CH_3), 21.3 (CH_2), 24.7 (CH_3), 31.9 (CH_2), 84.2 (*C*), 111.5 (*C*H), 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 $C_{15}H_{23}O_4{}^{10}BNa$, 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).

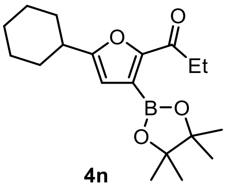


3n

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). ^{1}H NMR (396 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 8.6 (CH_3), 24.8 (CH_3), 25.7 (CH_2), 26.1 (CH_2), 31.3 (CH_2), 31.5 (CH_2), 38.2 (*C*H), 83.5 (*C*), 123.5 (*C*H), 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.

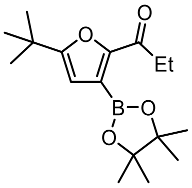
1-[5-Cyclohexyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4n).



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), 1.69–1.84 (m, 3H), 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): 7.9 (*C*H$_3$), 24.6 (*C*H$_3$), 25.6 (*C*H$_2$), 25.8 (*C*H$_2$), 31.1 (*C*H$_2$), 31.8 (*C*H$_2$), 37.0 (*C*H), 84.1 (*C*), 110.2 (*C*H), 118.9 (br, B–*C*), 154.4 (*C*), 164.2 (*C*), 190.8 (*C*). HRMS-EI (m/z): [M]$^+$ calcd for $C_{19}H_{29}{}^{11}BO_4$, 332.21589; found, 332.21729.

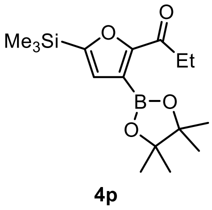
1-[5-(*tert*-Butyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-yl]propan-1-one (4o).



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 (*C*H$_3$), 24.6 (*C*H$_3$), 28.7 (*C*H$_3$), 31.8 (*C*H$_2$), 32.8 (*C*), 84.1 (*C*), 109.3 (*C*H), 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 $C_{17}H_{28}O_4{}^{10}B$, 306.21115; found, 306.21131.

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

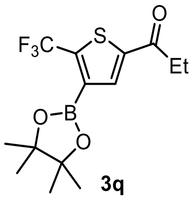


4p

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 (*C*H$_3$), 7.7 (*C*H$_3$), 24.7 (*C*H$_3$), 32.2 (*C*H$_2$), 84.1

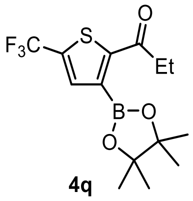
(*C*), 125.5 (*C*H), 160.0 (*C*), 164.3 (*C*), 191.5 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_{16}H_{27}O_4{}^{10}BNaSi$, 344.17002; found, 344.17025.

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


3q

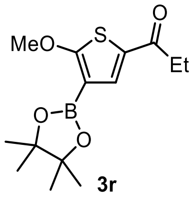
The total NMR yield in the crude mixture was 80% (**3q**:**4q** = 56:44). The crude mixture was purified by Kugelrohr distillation (50 Pa, 100 °C) to obtain **3q** (15.6 mg, 0.047 mmol, 9%) as a white solid from **1q** (104.5 mg, 0.502 mmol). This product contains small amount of impurities. ^{1}H NMR (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). ^{13}C 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 (*C*H), 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 $C_{14}H_{18}{}^{11}BF_3O_3S$, 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).


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. ^{1}H 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 8.2 (*C*H_3), 24.7 (*C*H_3), 34.0 (*C*H_2), 84.8 (*C*), 121.8 (q, $^1J_{C–F}$ = 269.9 Hz, *C*F_3), 134.0 (m, *C*H), 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 $C_{14}H_{18}O_3{}^{10}BF_3NaS$, 356.09503; found, 356.09538.

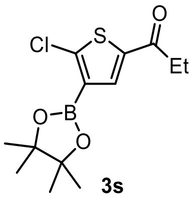
1-[5-Methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]propan-1-one (3r).


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). ^{1}H NMR (392

MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 8.8 (CH_3), 24.6 (CH_3), 30.6 (CH_2), 61.8 (CH_3), 83.4 (*C*), 110.5 (br, B–*C*), 130.3 (*C*), 138.4 (*C*H), 182.2 (*C*), 193.3 (*C*). HRMS-ESI (m/z): $[M+H]^+$ calcd for $C_{14}H_{22}O_4{}^{10}BS$, 296.13627; found, 296.13645.

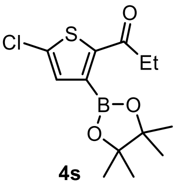
1-[5-Chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-yl]propan-1-one (3s).



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). ^{1}H NMR (396 MHz, $CDCl_3$, 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 8.3 (CH_3), 24.7 (CH_3), 31.5 (CH_2), 84.1 (*C*), 130.3 (br, B–*C*), 137.0 (*C*H), 142.3 (*C*), 148.4 (*C*), 193.2 (*C*). HRMS-EI (m/z): $[M]^+$ calcd for $C_{13}H_{18}{}^{11}BClO_3S$, 300.07582; found, 300.07679.

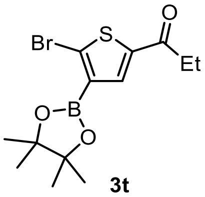
1-[5-Chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-yl]propan-1-one (4s).



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 (SiO_2 containing 5 wt% $B(OH)_3$,[13] hexane 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. ^{1}H NMR (396 MHz, $CDCl_3$, 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 8.2 (CH_3), 24.6 (CH_3), 33.4 (CH_2), 84.4 (*C*), 132.2 (*C*H), 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 $C_{13}H_{19}O_3{}^{10}BClS$, 300.08673; found, 300.08763.

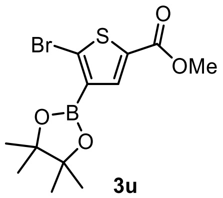
1-[5-Bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-2-yl]propan-1-one (3t).



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). ^{1}H NMR (396 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 8.3 (CH_3), 24.8 (CH_3), 31.7 (CH_2), 84.2 (*C*), 131.9 (*C*), 137.6 (*C*H), 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 $C_{13}H_{18}O_3{}^{10}B^{79}BrNaS$, 366.01816; found, 366.01825.

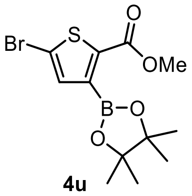
Methyl 5-bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (3u).



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). ^{1}H NMR (396 MHz, $CDCl_3$, δ): 1.34 (s, 12H), 3.86 (s, 3 H), 7.84 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (*C*H_3), 52.2 (*C*H_3), 84.2 (*C*), 129.7 (*C*), 134.0 (*C*), 139.7 (*C*H), 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 $C_{12}H_{17}O_4{}^{10}B^{79}BrS$, 346.01548; found, 346.01635.

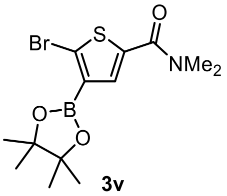
Methyl 5-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxylate (4u).



4u

The NMR yield of **4u** in the crude mixture was 20%. 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 (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. ^{1}H NMR (396 MHz, $CDCl_3$, δ): 1.39 (s, 12H), 3.86 (s, 3 H), 7.14 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.7 (*C*H_3), 52.3 (*C*H_3), 84.6 (*C*), 119.6 (*C*), 134.9 (*C*H), 138.7 (*C*), 161.9 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): $[M]^+$ calcd for $C_{12}H_{16}{}^{11}B^{81}BrO_4S$, 348.00253; found, 348.00172.

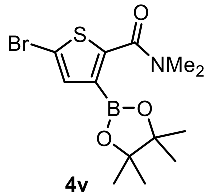
5-Bromo-*N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3v).



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). ^{1}H NMR (396 MHz, $CDCl_3$, δ): 1.34 (s, 12H), 3.18 (br s, 6H), 7.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.7 (*C*H_3), 36.6 (br, *C*H_3), 39.4 (br, *C*H_3), 84.0 (*C*), 126.9 (*C*), 134.9 (*C*H), 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 $C_{13}H_{19}O_3N^{10}B^{79}BrNaS$, 381.02906; found, 381.02931.

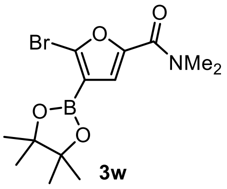
5-Bromo-*N*,*N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4v).



4v

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, $CDCl_3$, δ): 1.29 (s, 12H), 3.02 (br s, 6H), 7.22 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.3 (*C*H_3), 34.7 (br, *C*H_3), 38.6 (br, *C*H_3), 83.2 (*C*), 112.5 (*C*), 132.2 (br, B–*C*), 133.8 (*C*H), 146.5 (*C*), 163.8 (*C*). HRMS-APCI (m/z): [M+H]$^+$ calcd for $C_{13}H_{20}O_3N^{10}B^{79}BrS$, 359.04712; found, 359.04742.

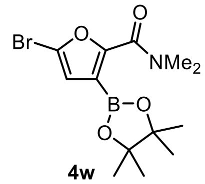
5-Bromo-*N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (3w).



3w

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, $CDCl_3$, δ): 1.33 (s, 12H), 3.09 (br s, 3H), 3.24 (br s, 3H), 7.09 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.5 (*C*H_3), 36.1 (br, *C*H_3), 38.1 (br, *C*H_3), 83.8 (*C*), 113.4 (br, B–*C*), 121.8 (*C*H), 132.6 (*C*), 149.2 (*C*), 158.8 (*C*). HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_{13}H_{19}O_4N^{10}B^{79}BrNa$, 365.05190; found, 365.05200.

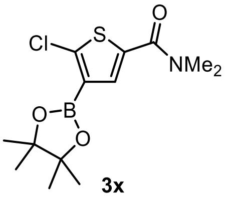
5-Bromo-*N*,*N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxamide (4w).



4w

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, $CDCl_3$, δ): 1.32 (s, 12H), 3.10 (br s, 6H), 6.50 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (*C*H_3), 35.8 (br, *C*H_3), 38.4 (br, *C*H_3), 84.0 (*C*), 116.1 (*C*H), 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 $C_{13}H_{19}O_4N^{10}B^{79}BrNa$, 365.05190; found, 365.05197.

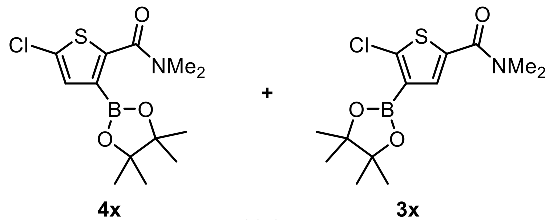
5-Chloro-*N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3x).



3x

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, $CDCl_3$, δ): 1.34 (s, 12H), 3.18 (br s, 6H), 7.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.7 (*C*H$_3$), 36.6 (br, *C*H$_3$), 39.3 (br, *C*H$_3$), 83.9 (*C*), 129.0 (br, B–*C*), 134.1 (*C*H), 136.5 (*C*) 143.7 (*C*), 162.8 (*C*). HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_{13}H_{19}O_3N^{10}BClNaS$, 337.07958; found, 337.07972.

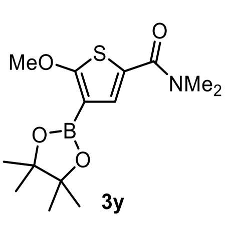
5-Chloro-*N*,*N*-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (4x).



4x 63:37 **3x**

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_2 containing 5 wt% $B(OH)_3$,[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, $CDCl_3$, δ): 1.29 (s, 12H), 3.03 (br s, 6H), 7.07 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (*C*H$_3$), 35.8 (br, *C*H$_3$), 39.3 (br, *C*H$_3$), 83.8 (*C*), 130.6 (*C*H), 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.

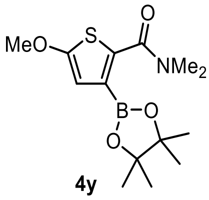
5-Methoxy-*N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiophene-2-carboxamide (3y).



3y

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, $CDCl_3$, δ): 1.32 (s, 12H), 3.20 (br s, 6H), 4.02 (s, 3H), 7.33 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.7 (*C*H$_3$), 38.1 (br, *C*H$_3$), 61.8 (*C*H$_3$), 83.2 (*C*), 124.5 (*C*), 134.5 (*C*H), 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 $C_{14}H_{22}O_4N^{10}BNaS$, 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).



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 (*C*H_3), 37.5 (br, *C*H_3), 60.2 (*C*H_3), 82.7 (*C*), 106.9 (*C*H), 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 $C_{14}H_{22}O_4N^{10}BNaS$, 333.12911; found, 333.12930.

Regiodivergent Synthesis of Biologically Active Furan Derivatives from 1w.

The Procedure for One-pot Synthesis of 6.

$[Ir(OMe)(cod)]_2$ (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, $PdCl_2(dppf)\cdot CH_2Cl_2$ (81.0 mg, 0.10 mmol), K_3PO_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, *C*H_3), 38.2 (br, *C*H_3), 115.6 (d, $^2J_{C\text{–}F}$ = 21.6 Hz, *C*H), 119.4 (*C*H), 121.8 (*C*), 125.9 (d, $^4J_{C\text{–}F}$ = 3.8 Hz, *C*), 126.6 (*C*H), 127.7 (*C*H), 128.4 (d, $^3J_{C\text{–}F}$ = 4.7 Hz, *C*H), 128.5 (*C*H), 130.0 (*C*H), 134.5 (*C*), 134.7 (*C*), 146.7 (*C*), 149.0 (*C*), 159.7 (*C*), 162.6 (d, $^1J_{C\text{–}F}$ = 249.0 Hz, *C*). HRMS-EI (m/z): $[M]^+$ calcd for $C_{19}H_{15}ClFNO_2$, 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 $AsPh_3$ (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, $PdCl_2(dppf)\cdot CH_2Cl_2$ (88.0 mg, 0.11 mmol), K_3PO_4 (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 H_2O (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 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 **8** (102.5 mg, 0.300 mmol, 30%) as a syrup. ^{1}H NMR (392 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 34.8 (*C*H$_3$), 37.6 (*C*H$_3$), 107.1 (*C*H), 121.8 (*C*H), 123.6 (*C*H), 127.2 (*C*H), 127.5 (*C*H), 127.6 (*C*H), 128.3 (*C*H), 128.8 (*C*), 129.7 (*C*H), 130.9 (*C*), 131.2 (*C*), 134.2 (*C*), 141.2 (*C*), 151.9 (*C*), 161.5 (*C*). HRMS-EI (m/z): $[M]^+$ calcd for $C_{19}H_{16}ClNO_2$, 325.08696; found, 325.08639.

References

1) a) Bosc, D.; Lethu, S.; Mouray, E.; Grellier, P.; Dubois, J.; *Med. Chem. Commun.* **2012**, *3*, 1512; b) Kai, T.; Susanne, G.; Steffen, W.; Daniela, P. (AICURIS GmbH & Co. KG), WO2010075957A1, **2010**; c) Yang, H.; Hendricks, R. T.; Arora, N.; Nitzan, D.; Yee, C.; Lucas, M. C.; Yang, Y.; Fung, A.; Rajyaguru, S.; Harris, S. F. Bioorg. *Med. Chem. Lett.* **2010**, *20*, 4614; d) McGrath, N. A.; Brichacek, M.; Njardarson, J. T. J. *Chem. Educ.* **2010**, *87*, 1348; e) Yasui, E.; Wada, M.; Takamura, N. *Tetrahedron Lett.* **2009**, *50*, 4762; f) Lee, S.; Kim, T.; Lee, B. H.; Yoo, S.; Lee, K.; Yi, K. Y. Bioorg. Med. *Chem. Lett.* **2007**, *17*, 1291; g) Fujita, M.; Hirayama, T.; Ikeda, N. *Bioorg. Med. Chem.* **2002**, *10*, 3113.
2) C–H borylation of five-membered heteroarenes, see: a) Green, A. G.; Liu, P.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 4575; b) Mkhalid, I. A.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890; c) Kallepalli, V. A.; Shi, F.; Paul, S.; Onyeozili, E. N.; Maleczka, Jr. R. E.; Smith III, M. R. *J. Org. Chem.* **2009**, *74*, 9199 – 9201; d) Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A.; Perutz, R. N.; Marder, T. B. *Angew. Chem.*, *Int. Ed.* **2006**, 45, 489; e) Ishiyama, T.; Takagi, J.; Yonekawa, Y.; Hartwig, J. F.; Miyaura, N. *Adv. Synth. Catal.* **2003**, *345*, 1103; f) Konishi, S.; Kawamorita, S.; Iwai, T.; Steel, P. G.; Marder, T. B.; Sawamura, M. *Chem. Asian J.* **2014**, *9*, 434.
3) Chotana, G. A.; Rak, M. A.; Smith III, M. R. *J. Am. Chem. Soc.* **2005**, *127*, 10539.
4) Kawamorita, S.; Ohmiya, H.; Sawamura, M. *J. Org. Chem.* **2010**, *75*, 3855.
5) Sasaki, I.; Taguchi, J.; Hiraki, S.; Ito, H.; Ishiyama, T. *Chem. Eur. J.* **2015**, *21*, 9236.
6) a) Leroux, F. *ChemBioChem* **2004**, *5*, 644; b) Nagai, T.; Nishioka, G.; Koyama, M.; Ando, A.; Miki, T.; Kumadaki, I. *J. Fluorine Chem.* **1992**, *57*, 229.
7) Kawamorita, S.; Ohmiya, H.; Hara, K.; Fukuoka, A.; Sawamura, M. *J. Am. Chem. Soc.* **2009**, *131*, 5058.
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).
9) a) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287; b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263; c) Tamura, H.; Yamazaki, H.; Sato, H.; Sakaki, S. *J. Am. Chem. Soc.* **2003**, *125*, 16114.

Chapter 2.

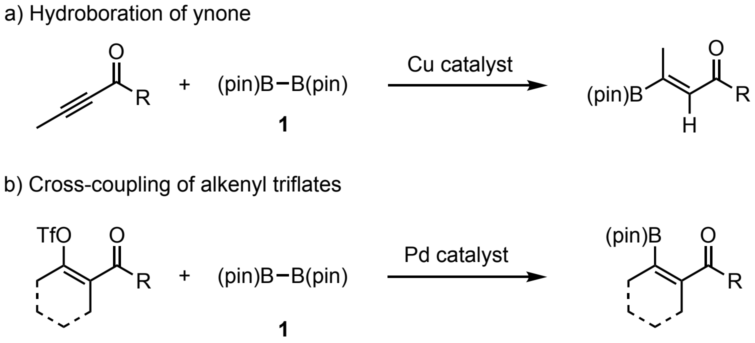
Iridium(I)-catalyzed Vinylic C–H Borylation of Acyclic α,β-Unsaturated Esters

Abstract

We developed a method for the iridium catalyzed vinyl C–H borylation of α,β-unsaturated esters using bis(pinacolato)diboron (B_2pin_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.

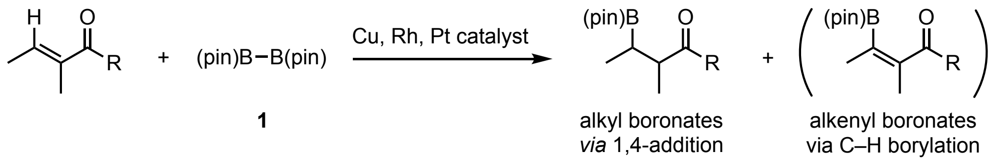
Introduction

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.



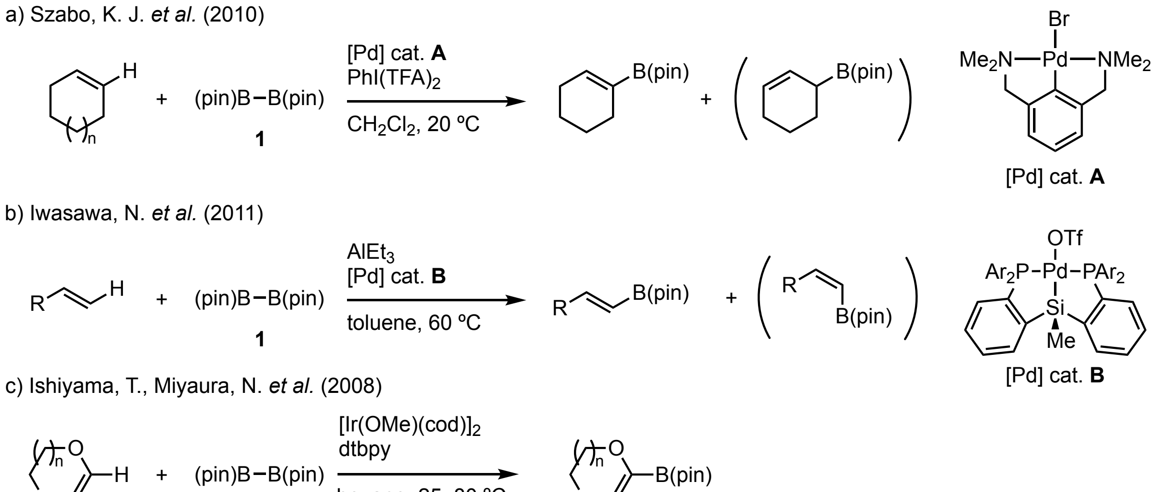
Scheme 2-1. Conventional synthesis method for β-boryl α,β-unsaturated carbonyl compounds. a) Hydroboration of ynone. b) Cross-coupling of alkenyl triflates.

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.



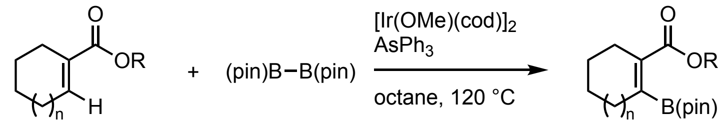
Scheme 2-2. Transition metal-catalyzed borylation reaction of α,β-unsaturated carbonyl compounds.

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.[9a] 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.[9b] 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.[10] 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.



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

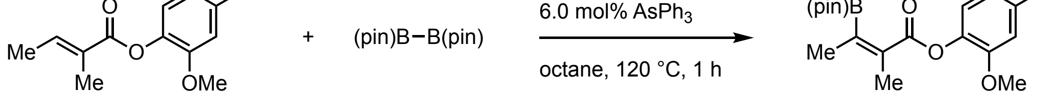
In addition, we recently reported the vinylic C–H borylation of α,β-unsaturated esters with an iridium catalyst.[11] Borylation of 1-cyclohexene-1-carboxylic acid esters with **1** and Ir/2 AsPh$_3$ catalyst affords alkenyl boronic acid. Although, this particular reaction is easily accessible to a wide range of tetra-substituted alkenylboronates in high yields with good regioselectivities, it was only amenable to cyclic vinyl ether substrates.



1

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 $[IrCl(cod)]_2$ and $AsPh_3$ as a catalyst, and in octane solvent at 80 or 120°C.[12] 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.



2
E/*Z* = >98:2

1
2.0 equiv

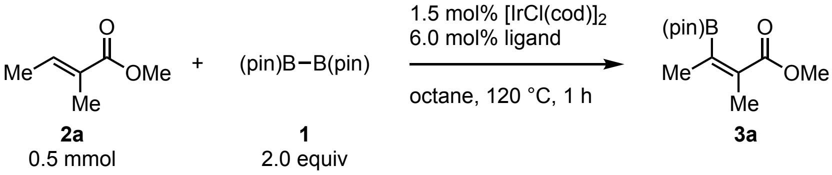
3
E/*Z* = >98:2
82% GC yield

Scheme 2-5. This work

Results and Discussion

The reaction of unsaturated methyl ester **2a** with $B_2(pin)_2$ **1** (1.1 equiv) in the presence of 1.5 mol% $[Ir(Cl)(cod)]_2$ and 6.0 mol% $AsPh_3$ in octane at 120ºC 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 $P[3,5\text{-}(CF)_2C_6H_3]_3$, $P(C_6F_5)_3$, PPh_3, and $P(4\text{-}MeO\text{-}C_6H_4)_3$ 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 $AsPh_3$ is the best ligand for this catalytic system as well as the borylation of cyclic substrate.

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

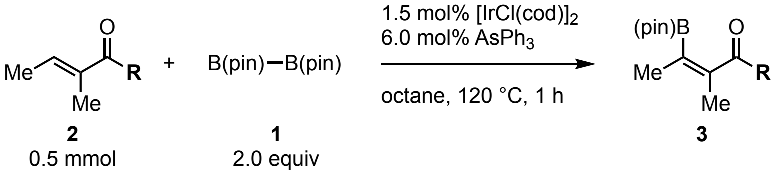


entry	ligand	yield (%)	entry	ligand	yield (%)
1	$AsPh_3$	43	6	dtbpy	21
2	PPh_3	7	7	phen	trace
3	PCy_3	6	8	Me_4phen	14
4	$P(OPh)_3$	0	9	dppe	0
5	$P(C_6F_5)_3$	6	10	-	0
4	$P[3,5\text{-}(CF_3)_2\text{-}C_6H_3]_3$	trace			
5	$P(2\text{-furyl})_3$	0			

[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) Futhermore, 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.[a]

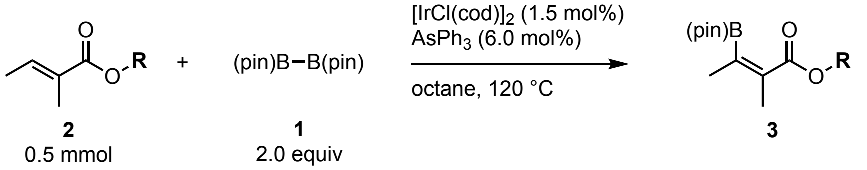


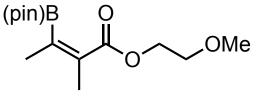
entry	R	time (h)	conv. of **2** (%)	conv. of **1** (%)	yield (%)
1	OMe (**2a**)	16	100	50	43
2	OPh (**2b**)	16	100	54	62
3	Ph	24	98	72	trace
4	NMe_2	24	0	30	0
5	$N(^{i}Pr)_2$	48	28	47	0
6	NMe(OMe)	2	100	81	0

[a] Yields were determined by GC analysis.

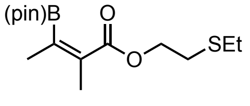
With the optimized conditions in hand, we proceeded to examine the scope of this C−H borylation reaction using a variety of acyclic α,β-unsaturated esters (Table 2-3). The reaction of methyl (*E*)-2-methylbut-2-enoate **2a** with 2.0 equivalents of **1** proceeded at 120 °C in the presence of $[Ir(Cl)(cod)]_2$ (1.5 mol %) as the catalyst precursor and $AsPh_3$ (6.0 mol %) as the ligand to afford the (*E*)-alkenylboronate **3a** in moderate yield with excellent stereoselectivity. Several other alkyl (*E*)-2-methylbut-2-enoates, including the methoxy **3c** and ethyl thioether **3d** substrates showed moderate-to-low reactivity, with both reactions providing the *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 (*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-(*E*)-2-methylpent-2-enoates **2k** and 4-methoxyphenyl-(*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.

Table 2-3. Investigation of aryl moiety in conjugated ester.[a]

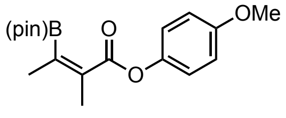




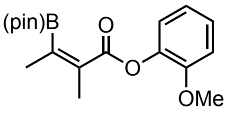
3c
48% (29%)[b], (6 h)



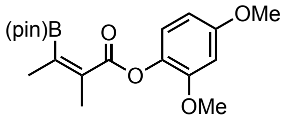
3d
21%, (31 h)



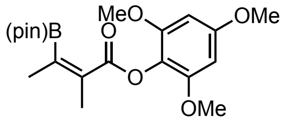
3e
76%, (1 h)



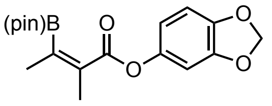
3f
74% (56%)[b], (4.5 h)



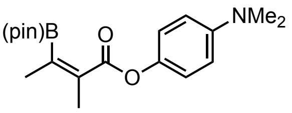
3g
82% (55%)[b], (1h)



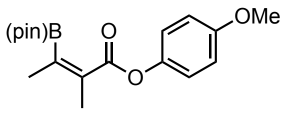
3h
64% (49%)[b], (4 h)



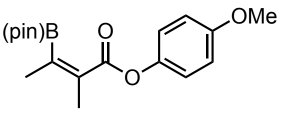
3i
65%, (1 h)



3j
77% (51%)[b], (1 h)



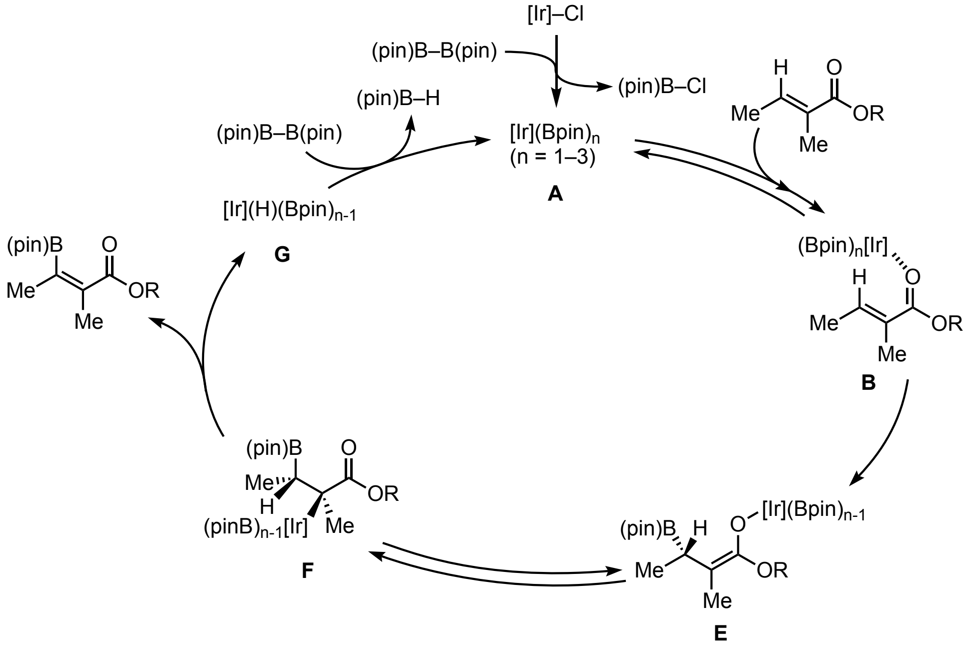
3k
41%, (2 h)



3l
19%, (72 h)

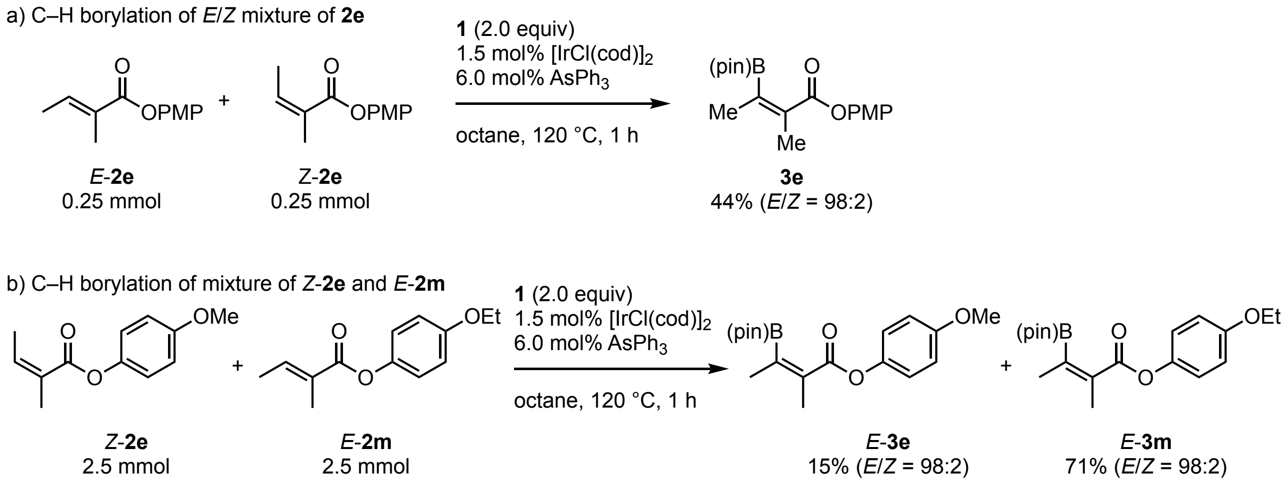
[a] Yields were determined by GC analysis. [b] Isolated yield.

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 B_2pin_2 to **D**, followed by the reductive elimination of 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 *syn*-configuration between the Ir center and the β-H atom. Finally, the β-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.



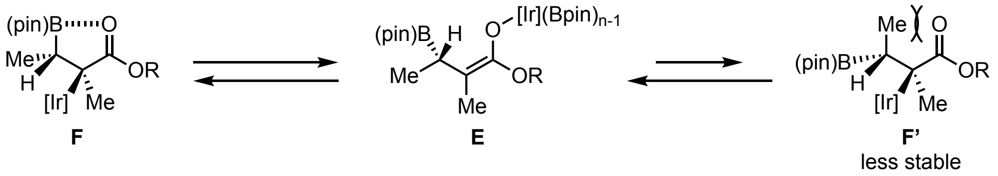
Scheme 2-6. Proposed mechanism (Pathway 2)

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.



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

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 *O*-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 2-8. Difference between the conformational stability of Ir C-enolate **F** and **F'**

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_2 bubbling, and further dried over molecular sieves (MS 4 Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 400 MHz and ^{13}C: 100 MHz). Tetramethylsilane (^{1}H) and $CDCl_3$ (^{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. $[Ir(Cl)(cod)]_2$ and $[Ir(OMe)(cod)]_2$ were synthesized according to the reported procedure.[11] 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.

$[Ir(Cl)(cod)]_2$ (5.0 mg, 7.3 μmol), bis(pinacolato)diboron (**1**) (254 mg, 1.0 mmol) and $AsPh_3$ (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.

$[Ir(Cl)(cod)]_2$ (5.2 mg, 7.7 μmol), **1** (254 mg, 1.0 mmol) and $AsPh_3$ (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_2, EtOAc/hexane, 1:99–5:95) to give the corresponding alkenylboronate **3e** (*E*/*Z* = 98:2).

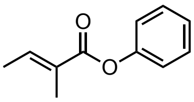
A Representative Procedure for the Competition Experiment with 2e and 2m.

$[Ir(Cl)(cod)]_2$ (5.1 mg, 7.6 μmol), **1** (253.3 mg, 1.00 mmol) and $AsPh_3$ (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.

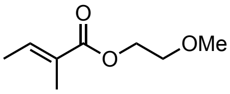
Preparation of phenyl (*E*)-2-methylbut-2-enoate (2b).



2b

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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 12.2 (*C*H$_3$), 14.6 (*C*H$_3$), 121.7 (*C*H), 125.5 (*C*H), 128.2 (*C*), 129.3 (*C*H), 139.3 (*C*H), 151.1 (*C*), 166.6 (*C*). HRMS–ESI (*m/z*): [M+Na]$^+$ calcd for $C_{11}H_{12}O_2Na$, 199.07295; found, 199.07301.

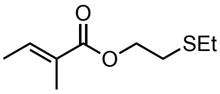
Preparation of 2-methoxyethyl (*E*)-2-methylbut-2-enoate (2c).



2c

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_2Cl_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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 11.7 (*C*H$_3$), 14.0 (*C*H$_3$), 58.6 (*C*H$_3$), 63.2 (*C*H$_2$), 70.3 (*C*H$_2$), 128.1 (C), 137.2 (*C*H), 167.6 (*C*). HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_8H_{14}O_3Na$, 181.08352; found, 181.08400.

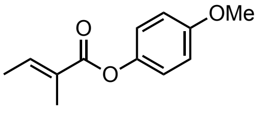
Preparation of 2-(ethylthio)ethyl (*E*)-2-methylbut-2-enoate (2d).



2d

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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 11.7 (*C*H$_3$), 14.1 (*C*H$_3$), 14.6 (*C*H$_3$) , 25.9 (*C*H$_2$), 29.8 (*C*H$_2$), 63.4 (*C*H$_2$), 128.2 (*C*), 137.3 (*C*H), 167.5 (*C*). HRMS–ESI (*m/z*): [M+Na]$^+$ calcd for $C_9H_{16}O_2NaS$, 211.07632; found, 211.07670.

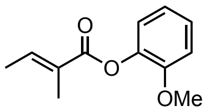
Preparation of 4-methoxyphenyl (*E*)-2-methylbut-2-enoate (3e).



2e

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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 12.0 (CH_3), 14.4 (CH_3), 55.4 (CH_3), 114.2 (*C*H), 122.3 (*C*H), 128.0 (*C*), 139.0 (*C*H), 144.4 (*C*), 156.9 (*C*), 166.7 (*C*). HRMS–ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.08352; found, 229.08405.

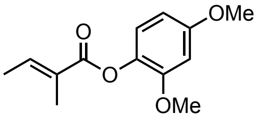
Preparation of 2-methoxyphenyl (*E*)-2-methylbut-2-enoate (2f).



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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 11.9 (CH_3), 14.2 (CH_3), 55.5 (CH_3), 112.1 (*C*H), 120.4 (*C*H), 122.7 (*C*H), 126.3 (*C*H), 127.6 (*C*), 138.9 (*C*H), 139.9 (*C*), 151.1 (*C*), 165.7 (*C*). HRMS–ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.08352; found, 229.08391.

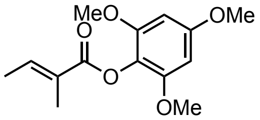
Preparation of 2,4-dimethoxyphenyl (*E*)-2-methylbut-2-enoate (2g).



2g

2,4-Dimethoxyphenol (3.62 g, 23.5 mmol) was prepared in 78% yield from 2,4-dimethoxy- benzaldehyde (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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 12.2 (CH_3), 14.5 (CH_3), 55.5 (CH_3), 55.8 (CH_3), 100.1 (*C*H), 103.7 (*C*H), 122.8 (*C*H), 127.9 (*C*), 133.8 (*C*), 139.1 (*C*H), 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.

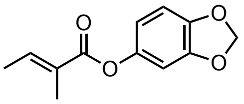
Preparation of 2,4,6-trimethoxyphenyl (*E*)-2-methylbut-2-enoate (2h).



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**. ^{1}H NMR (396 MHz, CDCl$_3$, 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). ^{13}C NMR (100 MHz, CDCl$_3$, δ): 12.1 (*C*H$_3$), 14.4 (*C*H$_3$), 55.3 (*C*H$_3$), 55.9 (*C*H$_3$), 91.2 (*C*H), 122.7 (*C*), 127.6 (*C*), 138.9 (*C*H), 152.6 (*C*), 157.9 (*C*), 166.0 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{14}H_{18}O_5$, 266.11542; found, 266.11521.

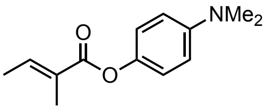
Preparation of benzo[d][1,3]dioxol-5-yl (*E*)-2-methylbut-2-enoate (2i).



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**. ^{1}H NMR (392 MHz, CDCl$_3$, 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). ^{13}C NMR (100 MHz, CDCl$_3$, δ): 12.0 (*C*H$_3$), 14.5 (*C*H$_3$), 101.5 (*C*H$_2$), 103.8 (*C*H), 107.8 (*C*H), 113.9 (*C*H), 127.9 (*C*), 139.3 (*C*H), 145.0 (*C*), 145.3 (*C*), 147.8 (*C*), 166.7 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{12}H_{12}O_4$, 220.07356; found, 220.07339.

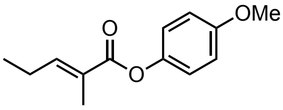
Preparation of 4-(dimethylamino)phenyl (*E*)-2-methylbut-2-enoate (2j).



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.[4] **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**. ^{1}H NMR (396 MHz, CDCl$_3$, 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). ^{13}C NMR (100 MHz, CDCl$_3$, δ): 12.1 (*C*H$_3$), 14.5 (*C*H$_3$), 40.9 (*C*H$_3$), 113.1 (*C*H), 121.8 (*C*H), 128.3 (*C*), 138.6 (*C*H), 141.9 (*C*), 148.4 (*C*), 167.1 (*C*). HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{13}H_{17}NO_2$, 219.12593; found, 219.12525.

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



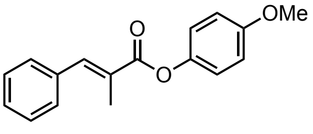
2k

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_4Cl, and extracted with Et_2O 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_2Cl_2 (6.0 ml) at –30 °C. The reaction mixture was extracted with CH_2Cl_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_2Cl_2 (6.0 ml) at 0 °C, and stirred at the same temperature for 1 h. The reaction mixture was extracted with CH_2Cl_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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 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 $C_{13}H_{16}O_3$, 220.10994; found, 220.10937.

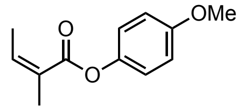
Preparation of 4-methoxyphenyl (*E*)-2-methyl-3-phenylacrylate (2l).



2l

2l (2.14 g, 7.97 mmol, white solid) was prepared in 80% from α-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, $CDCl_3$, δ): 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, $CDCl_3$, δ): 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.

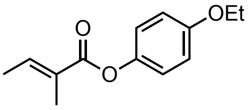
Preparation of 4-methoxyphenyl (*Z*)-2-methylbut-2-enoate ((*Z*)-2e).



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_2Cl_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 (*C*H), 122.4 (*C*H), 127.2 (*C*), 140.3 (*C*H), 144.1 (*C*), 157.1 (*C*), 166.6 (*C*). HRMS–ESI (*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{14}O_3Na$, 229.08352; found, 229.08385.

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

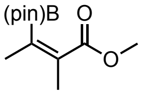


2m

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 (*C*H), 122.0 (*C*H), 127.8 (*C*), 138.6 (*C*H), 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.

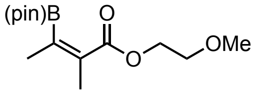
Methyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3a).



3d

^{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 (*C*H$_3$), 16.5 (*C*H$_3$), 24.6 (*C*H$_3$), 52.1 (*C*H$_3$), 82.9 (*C*), 131.6 (*C*), 149.1 (br, B–*C*), 170.7 (*C*). HRMS–ESI(*m/z*): $[M+Na]^+$ calcd for $C_{12}H_{21}O_4{}^{10}BNa$, 262.14614; found: 262.14619.

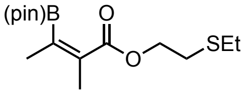
2-Methoxyethyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3c).



3c

^{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 (*C*H$_3$), 16.7 (*C*H$_3$), 24.7 (*C*H$_3$), 58.9 (*C*H$_3$), 64.4 (*C*H$_2$), 70.3 (*C*H$_2$), 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): $[M+Na]^+$ calcd for $C_{14}H_{25}O_5{}^{10}BNa$, 306.17236; found, 306.17305.

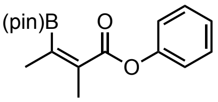
2-(Ethylthio)ethyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3d).



3d

^{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 (*C*H$_3$), 14.7 (*C*H$_3$), 16.7 (*C*H$_3$), 24.7 (*C*H$_3$), 26.1 (*C*H$_2$), 29.6 (*C*H$_2$), 64.6 (*C*H$_2$), 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*): $[M+Na]^+$ calcd for $C_{15}H_{27}O_4{}^{10}BNaS$, 336.16516; found, 336.16608.

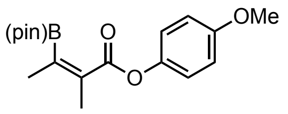
Phenyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3b).



3b

^{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 (*C*H$_3$), 17.3 (*C*H$_3$), 24.7 (*C*H$_3$), 83.5 (*C*), 121.8 (*C*H), 125.6 (*C*H), 129.2 (*C*H), 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*): $[M+Na]^+$ calcd for $C_{17}H_{23}O_4{}^{10}BNa$, 324.16179; found, 324.16187.

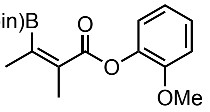
4-Methoxyphenyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3e).



3e

^{1}H NMR (396 MHz, $CDCl_3$, δ): 1.25 (s, 12H), 1.91 (q, J = 1.1 Hz, 3H), 1.97 (q, J = 1.1 Hz, 3H), 3.80 (s, 3H), 6.85–6.89 (m, 2H), 7.01–7.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 12.8 ($\mathit{C}H_3$), 17.3 ($\mathit{C}H_3$), 24.8 ($\mathit{C}H_3$), 55.4 ($\mathit{C}H_3$), 83.5 (*C*), 114.2 (*C*H), 122.5 (*C*H), 132.2 (*C*), 144.3 (*C*), 157.1 (*C*), 167.8 (*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 $C_{18}H_{25}O_5{}^{10}BNa$, 354.17236; found, 354.17236.

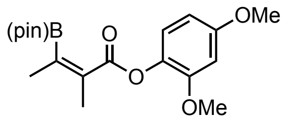
2-Methoxyphenyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3f).



3f

^{1}H NMR (396 MHz, $CDCl_3$, δ): 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 12.9 ($\mathit{C}H_3$), 17.3 ($\mathit{C}H_3$), 24.7 ($\mathit{C}H_3$), 55.8 ($\mathit{C}H_3$), 83.4 (*C*), 112.5 (*C*H), 120.5 (*C*H), 123.0 (*C*H), 126.6 (*C*H), 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 $C_{18}H_{25}O_5{}^{10}BNa$, 354.17236; found: 354.17334.

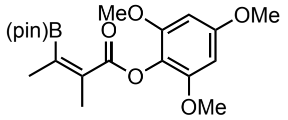
2,4-Dimethoxyphenyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3g).



3g

^{1}H NMR (392 MHz, $CDCl_3$, δ): 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 12.8 ($\mathit{C}H_3$), 17.2 ($\mathit{C}H_3$), 24.6 ($\mathit{C}H_3$), 55.3 ($\mathit{C}H_3$), 55.6 ($\mathit{C}H_3$), 83.2 (*C*), 100.0 (*C*H), 103.5 (*C*H), 122.8 (*C*H), 132.0 (*C*), 133.5 (*C*), 147.5 (br, B–*C*), 151.8 (*C*), 158.0 (*C*), 167.0 (*C*). HRMS–EI (*m/z*): $[M]^+$ calcd for $C_{19}H_{27}{}^{10}BO_6$, 361.19370; found, 361.19285.

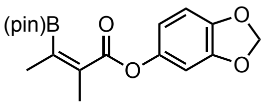
2,4,6-trimethoxyphenyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3h).



3h

^{1}H NMR (396 MHz, $CDCl_3$, δ): 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 13.0 ($\mathit{C}H_3$), 17.2 ($\mathit{C}H_3$), 24.7 ($\mathit{C}H_3$), 55.4 ($\mathit{C}H_3$), 56.0 ($\mathit{C}H_3$), 83.2 (*C*), 91.5 (*C*H), 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 $C_{20}H_{29}{}^{10}BO_7$, 391.20426; found: 391.20307.

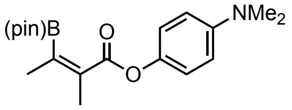
Benzo[*d*][1,3]dioxol-5-yl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3i).



3i

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.26 (s, 12H), 1.91 (q, J = 1.1 Hz, 3H), 1.96 (q, J = 1.1 Hz, 3H), 5.98 (s, 2H), 6.56 (dd, J = 2.4, 8.4 Hz, 1H), 6.65 (d, J = 2.2 Hz, 1H), 6.76 (d, J = 8.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 12.8 (CH$_3$), 17.3 (CH$_3$), 24.7 (CH$_3$), 83.4 (C), 101.5 (CH$_2$), 103.8 (CH), 107.7 (CH), 114.1 (CH), 132.0 (C), 145.0 (C), 145.1 (C), 147.7 (C), 148.1 (br, B–C), 167.6 (C). HRMS-EI (m/z): [M]$^+$ calcd for $C_{18}H_{23}{}^{10}BO_6$, 345.16240; found, 345.16130.

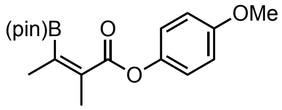
4-(Dimethylamino)phenyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enoate (3j).



3j

^{1}H NMR (392 MHz, $CDCl_3$, δ): 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 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 $C_{19}H_{28}{}^{10}BNO_4$, 344.21477; found: 344.21401.

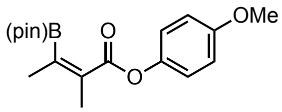
4-Methoxyphenyl (*E*)-2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate (3k).



3k

^{1}H NMR (401 MHz, $CDCl_3$, δ): 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 12.2 (CH$_3$), 12.5 (CH$_3$), 24.9 (CH$_3$), 25.0 (CH$_2$), 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 quadropolar relaxation. HRMS–EI (*m/z*): [M]$^+$ calcd for $C_{19}H_{27}{}^{10}BO_5$, 345.19879; found, 345.19775.

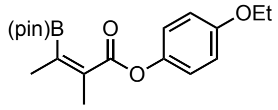
4-Methoxyphenyl (*E*)-2-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate (3l).



3l

^{1}H NMR (396 MHz, $CDCl_3$, δ): 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 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 $C_{23}H_{27}{}^{10}BO_5$, 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).



3m

^{1}H NMR (392 MHz, CDCl$_3$, 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). ^{13}C NMR (100 MHz, CDCl$_3$, δ): 12.8 (CH$_3$), 14.8 (CH$_3$), 17.3 (CH$_3$), 24.8 (CH$_3$), 63.6 (CH$_2$), 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 $C_{19}H_{27}{}^{10}BO_5$, 345.19879; found, 345.19777.

References

1. a) Ueda, M.; Saitoh, A.; Miyaura, N. *J. Organomet. Chem.* **2002**, *642*, 145; b) Moran, W. J.; Morken, J. P. *Org. Lett.* **2006**, *8*, 2413; c) Paptchikhine, A.; Cheruku, P.; Engman, M.; Andersson, P. G. *Chem. Commun.* **2009**, 5996; d) Jung, H.-Y.; Feng, X.; Kim, H.; Yun, J. *Tetrahedron* **2012** *68*, 3444; e) Pulis, A. P.; Fackler, P.; Aggarwal V. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 4382.
2. a) Fresneda, P. M.; Vauliter, M. *Tetrahedron Lett.* **1989**, *30*, 2929; b) Davies, C. D.; Marsden S. P.; Stokes, E. S. E. *Tetrahedron Lett.* **2000**, *41*, 4229.
3. Guennouni, N.; Lhermitte, F.; Cochard S.; Carboni, B. *Tetrahedron* **1995**, *51*, 6999.
4. Ishiyama, T.; Takagi, J.; Kamon A.; Miyaura, N.; *J. Organomet. Chem.* **2003**, *687*, 284.
5. Lee, J.-E.; Kwon, J.; Yun, J. *Chem. Commun.* **2008**, 733.
6. Ishiyama, T.; Takagi, J.; Kamon, A.; Miyaura, N. *J. Organomet. Chem.* **2003**, *687*, 284.
7. a) Nagao, K.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2014**, *136*, 10605.; b) Mannathan, S.; Jeganmohan, M.; Cheng C.-H. *Angew. Chem., Int. Ed.* **2009**, *48*, 2192.
8. a) Ito, H.; Yamanaka, H.; Tateiwa, H.; Hosomi, A. *Tetrahedron Lett.* **2000**, *41*, 6821; b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, *29*, 982; c) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedoron Lett.* **2002**, *43*, 2323; d) Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* **1997**, 2051.
9. a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890; b) Takaya, J.; Kirai, N.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 12980; c) Selander, N.; Willy, B.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4051; d) Kondoh, A.; Jamison, T. F. *Chem. Commun.* **2010**, *46*, 907; e) Ohmura, T.; Takasaki, Y.; Furukawa, H.; Suginome, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2372; f) Olsson, V. J.; Szabó, K. J. *J. Org. Chem.* **2009**, *74*, 7715; g) Garon, C. N.; McIsaac, D. I.; Vogels, C. M.; Decken, A.; Williams, I. D.; Kleeberg, C.; Marder, T. B.; Westcott, S. A. *Dalton Trans.* **2009**, 1624; (h) Olsson, V. J.; Szabó, K. J. *Org. Lett.* **2008**, *10*, 3129; i) Mkhalid, I. A. I.; Coapes, R. B.; Edes, S. N.; Coventry, D. N.; Souza, F. E. S.; Thomas, R. L.; Hall, J. J.; Bi, S. W.; Lin, Z. Y.; Marder, T. B. *Dalton Trans.* **2008**, 1055; j) Caballero, A.; Etienne, S. S. *Organometallics* **2007**, *26*, 1191; (k) Olsson, V. J.; Szabó, K. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6891; l) Coapes, R. B.; Souza, F. E. S.; Thomas, R. L.; Hall, J. J.; Marder, T. B. *Chem. Commun.* **2003**, 614.
10. a) Kikuchi, T.; Takagi, J.; Isou, H.; Ishiyama, T.; Miyaura, N.; *Chem. Asian J.* **2008**, *3*, 2082; b) Kikuchi, T.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2008**, *37*, 664.
11. Sasaki, I.; Doi, H.; Hashimoto, T.; Kikuchi, T.; Ito, H.; Ishiyama, T.; *Chem. Commun.* **2013**, *49*, 7546.
12. Sasaki, I.; Taguchi, J.; Doi, H.; Ito, H.; Ishiyama, T. *Chem. Asian J.* **2016**, *11*, 1400.
13. a) J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864; b) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263.
14. Denes, F.; Perez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366.
15. Herde, J. L.; Lambert, J. C.; Senoff, C. V. *Inorg. Synth.* **1974**, *15,* 18.
16. Uson, R.; Oro, L. A.; Cabeza, J. A.; Bryndza, H. E.; Stepro, M. P. *Inorg. Synth.* **2007**, *23*, 126.

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.

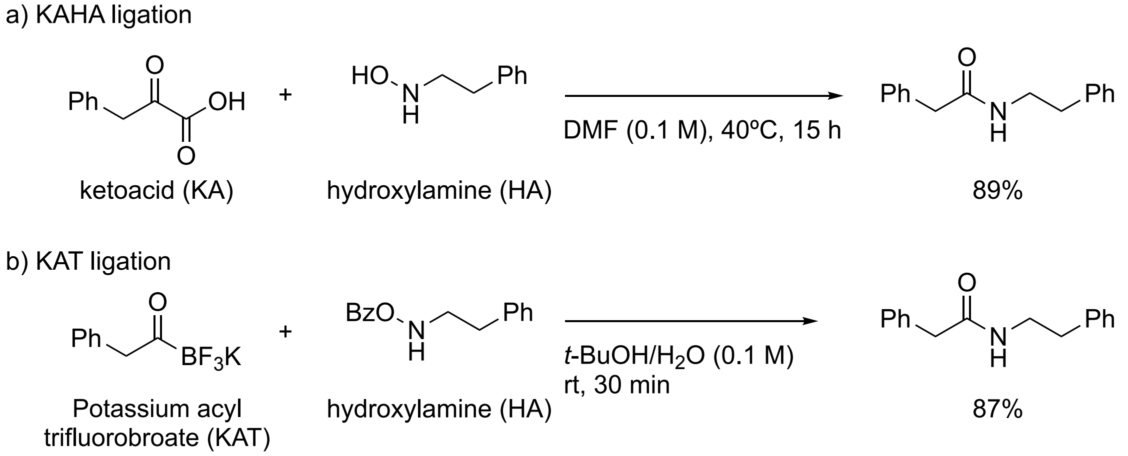
Introduction

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).[1] Chemical ligation, such as native chemical ligation (NCL) has been developed to synthesize longer peptide chains by connecting two peptide fragments.[2] 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.[2b] 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

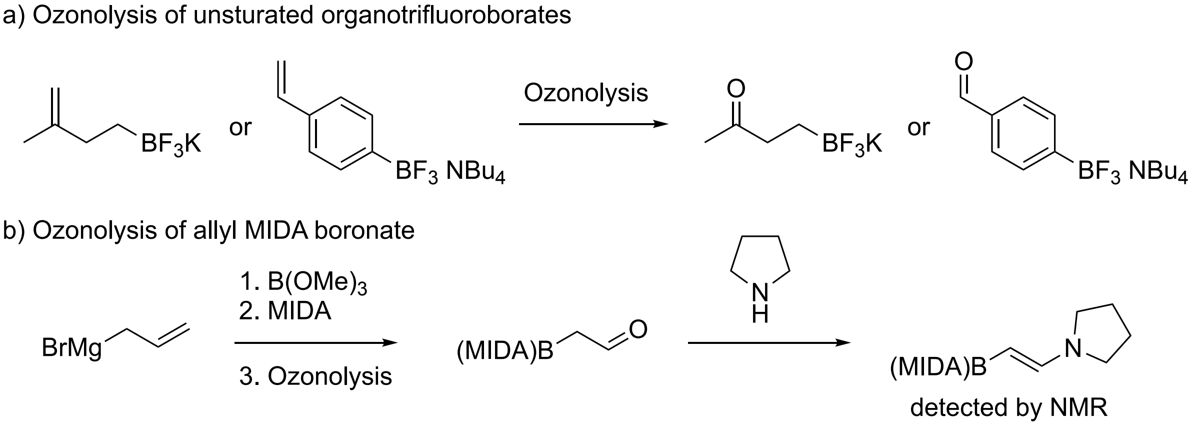
Method / Feature	SPPS (1950)	▶ NCL (1994)	▶ KAHA ligation (2006)	▶ **KAT ligation** (2012)
Reaction Rate	△	○	○	◎
Accessible Peptide (Residues of AAs)	50	200	200	>200?
Conjugation Site	–	only Cys	Applicable to any AAs	

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).[3] 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).[4] 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.[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.[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.[5] Thus, synthetic routes to KAT-containing α-amino-acid analogues (α-amino KATs), i.e., peptide-KATs models, have not yet been reported.



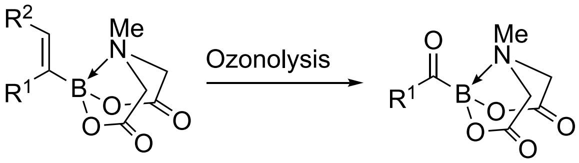
Scheme 3-1. KAHA ligation and KAT ligation

In 2007, Molander *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.[6a] In addition, Yudin reported the ozonolysis of allyl MIDA (*N*-methyliminodiacetic acid) boronates to afford α-boryl substituted aldehyde (Scheme 3-2b).[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.



Scheme 3-2. Ozonolysis of unsaturated organoboron compounds. a) Ozonolysis of unsaturated organotrifluoroborates. b) Ozonolysis of allyl MIDA boronate.

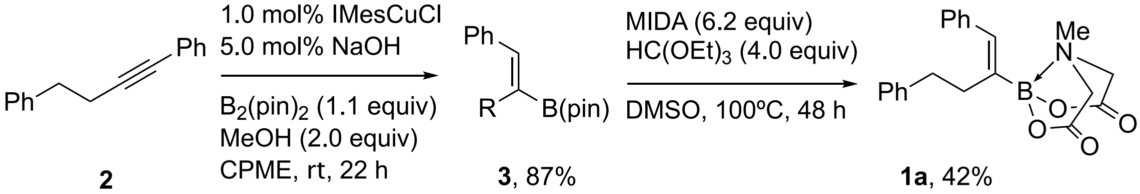
Herein, we report a concise acylboron synthesis by the ozonolysis of alkenyl MIDA boronates (Scheme 3-3).[7] This new method has the following two important features; (a) synthesis of alkenyl boronates are well-studied, they can be readily available by hydroboration of alkynes, cross-coupling of alkenyl halides or C–H borylation of alkene,[8] and they are transformed to MIDA boronates easily by Burke's method;[9] 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.[6a] 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 **1a** based on the known tolerance of MIDA boronates to ozonolysis.[6b] **1a** can be easily prepared by Cu(I)-catalyzed protoboration of alkyne **2**, followed by conversion of pinacol boronate **3** to MIDA boronate **1a**, according to a modified procedure based on the Burke's method (Scheme 3-4).[8,9]

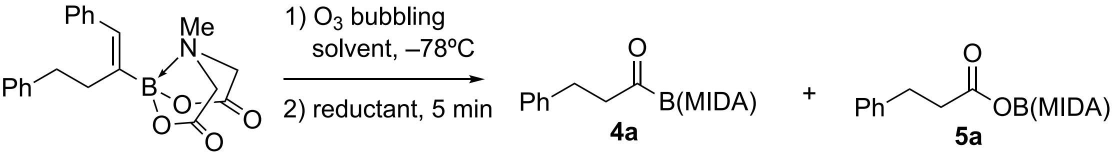


Scheme 3-4. Synthesis of substrate for ozonolysis and initial investigation.

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 ^{11}B NMR spectrum in addition to **4a**. Based on the ^{11}B 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 ^{11}B 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.[10] Even though the mechanism of this over-oxidation is not clear, a similar reaction is known in the ozonolysis of alkenylsilanes.[11]

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 PPh_3 or Zn instead of Me_2S 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).[12] 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%).

Table 3-2. Optimization of reaction conditions of ozonolysis of alkenyl MIDA boronate.



1a
E/*Z* = >20:<1

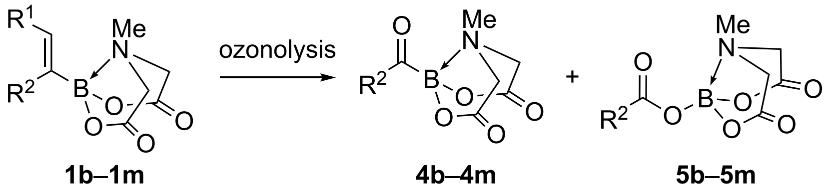
entry	Solvent	Reductant	Yield (%)[b]	**4a**/**5a**[c]
1	acetone	Me_2S	85	87:13
2	CH_3CN	Me_2S	88	70:30
3	EtOAc	Me_2S	–	56:44
4	MeOH	Me_2S	–	–
5[d]	acetone	PPh_3	85	80:20
6[e]	acetone	Zn/AcOH	–	–
7[f]	acetone	pyridine	94	>95:<5

[a] Reaction conditions: a) O_3, acetone, –78°C. b) Me_2S (excess), acetone, –78°C, 5 min. [b] Combined isolated yields of products (**4a**+**5a**) are reported. [c] Product ratio (**4a**:**5a**) in the crude reaction mixture were determined by ^{11}B NMR spectroscopy analysis. [d] PPh_3 (3.0 equiv) was used as reductant. [e] Zn (1.5 equiv) and AcOH (0.3 M H_2O) were used as reductant. [f] Reaction conditions: O_3, pyridine (3.0 equiv), acetone, –78°C.

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 3-3, 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 Me_2S 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 R^1 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 R^1 moiety can also be employed for this reaction.

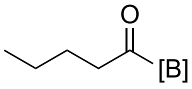
Next, synthesis of α-amino alkenyl boronates were investigated. Alkenyl boronates bearing amines at allylic position can easily be prepared in high yield and high regioselectivity by Cu(I)-catalyzed hydroboration of propargyl amine reported by Hoveyda.[8f] As a result, *N*-Phth, *N*-Cbz, *N*-Boc and *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]

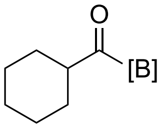


Conditions **A**;
Ozone bubbling
then SMe_2 (excess)

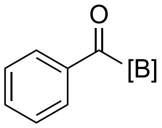
Conditions **B**;
Ozone bubbling
Pyridine (3.0 equiv)



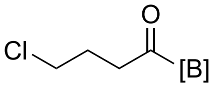
4b, R^1 = Ph (**A**)
87%, 94:6



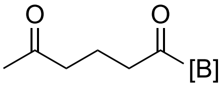
4c, R^1 = Ph (**A**)
84%, >95:<5



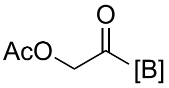
4d, R^1 = Ph (**B**)
90%, >95:<5



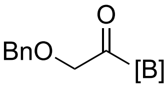
4e, R^1 = Ph (**A**)
94%, 84:16



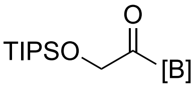
4f, R^1 = Ph (**A**)
88%, >95:<5



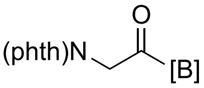
4g, R^1 = Ph (**A**)
81%, 95:5



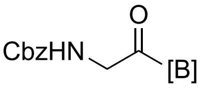
4h, R^1 = Ph (**A**)
80%, 85:15



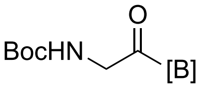
4i, R^1 = Ph (**A**)
66%, 74:26



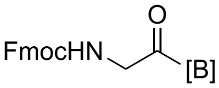
4j, R^1 = TMS (**A**)
90%, >95:<5



4k, R^1 = H (**A**)
88%, 90:10



4l, R^1 = H (**A**)
91%, 95:5



4m, R^1 = H (**A**)
65%, 93:7

[a] Reaction condition A: a) **1** (0.3 mmol), O_3, acetone, –78°C. b) Me_2S (excess), acetone, –78°C, 5 min. Reaction condition B: 1 (0.3 mmol), O_3, pyridine (3.0 equiv), acetone, –78°C. [b] Combined isolated yields of products (**4**+**5**) are reported. [c] Product ratio (**4**:**5**) in the crude reaction mixture were determined by ^{11}B NMR spectroscopy analysis. [d] 0.03 mol% of Sudan III was added as an indicator.

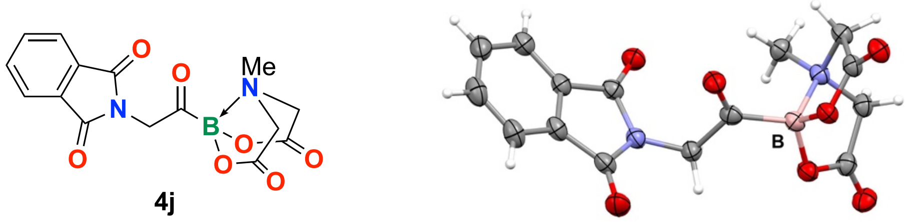
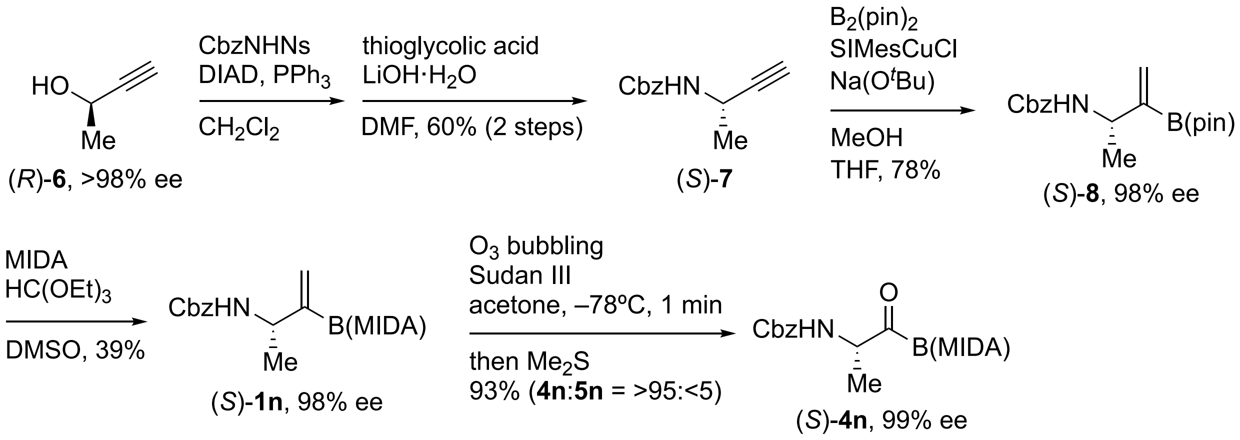


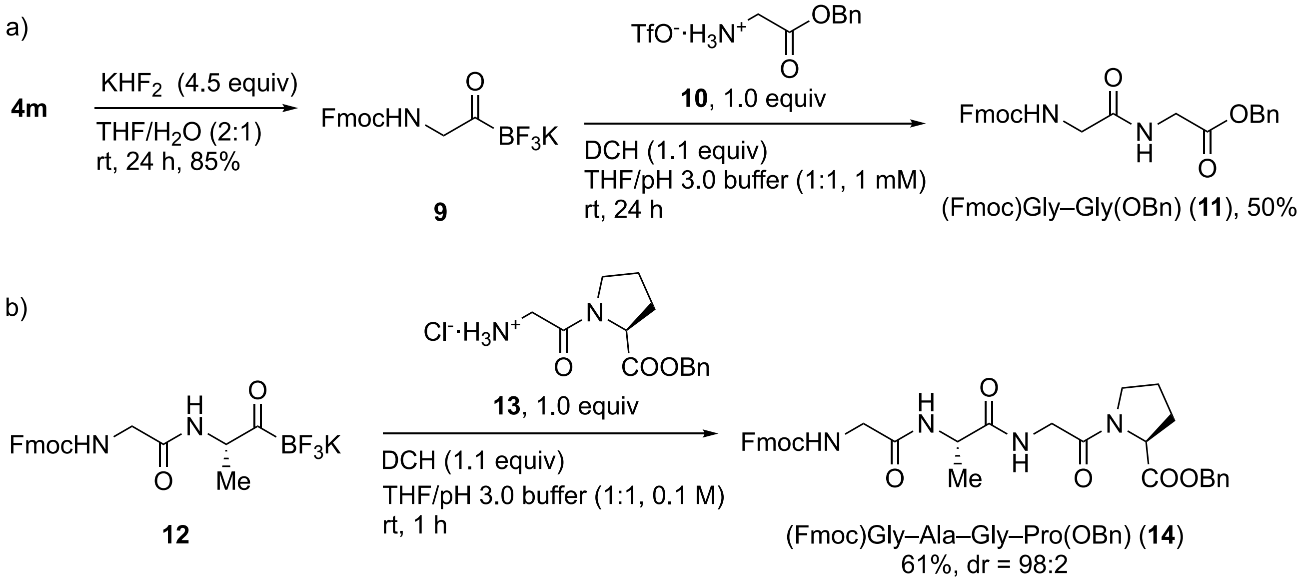
Figure 3-1. Crystal Structure of **4j**·CH_3CN. CH_3CN was omitted for clarification.

Next, we tried to synthesize other optically active *α*-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 （Ns = 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 ºC 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 α-position.



Scheme 3-5. Synthesis of L-Alanine type acyl MIDA boronates

α-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 **4m** 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 α-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_3CN: 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_3CN: 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 ($BF_3 \cdot Et_2O$: 0.0 ppm). Chemoselectivities 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.[16]

General Experimental Procedures.

A General Procedure for the Ozonolysis of Alkenyl MIDA Boronates 1a with Me_2S 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 –78ºC, 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_2S (0.30 mL) and stirred at –78ºC 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_2O to yield a white solid.

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

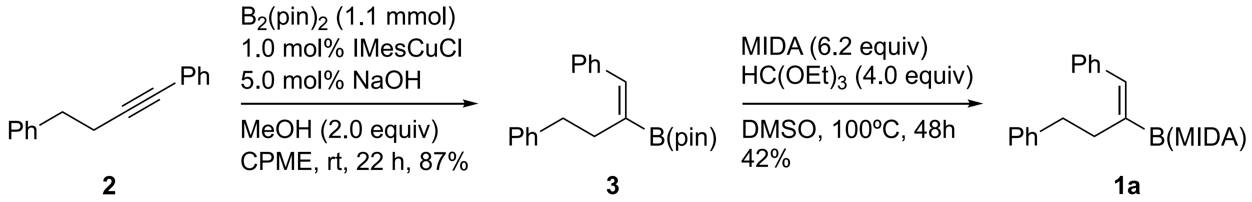
Alkenyl MIDA boronate **1a** (108.9 mg, 0.30 mmol) were placed in an oven-dried reaction vial. The vial was filled with nitrogen gas and then sealed with a screw cap containing a Teflon-coated rubber septum. Dry acetone (2.00 mL) and pyridine (72.5 μL, 0.90 mmol) were added in the vial through the rubber septum using syringes. The solution was cooled to –78ºC, 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 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_2O 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, CH_3CN and acetone, but Et_2O 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).

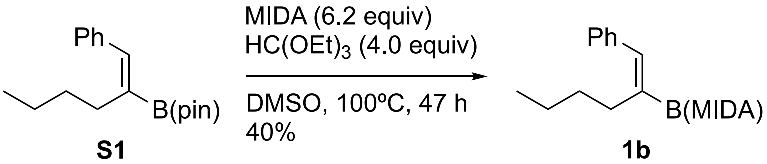


$B_2(pin)_2$ (2.51 g, 9.9 mmol), (IMes)CuCl (36.4 mg, 0.09 mmol), NaOH (18.0 mg, 0.45 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. 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.[8e] ^{1}H NMR (396 MHz, $CDCl_3$, 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (CH_3), 31.3 (CH_2), 36.0 (CH_2), 83.4 (*C*), 125.6 (*C*H), 127.1 (*C*H), 128.1 (*C*H), 128.2 (*C*H), 128.5 (*C*H), 128.8 (*C*H), 137.7 (*C*), 142.3 (*C*), 142.6 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): $[M]^+$ calcd for $C_{22}H_{27}{}^{10}BO_2$, 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 H_2O. 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 H_2O and brine, and then dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was washed with Et_2O three times to obtain **1a** (1.08 g, 2.97 mmol, 42%) as a white solid.[8c]

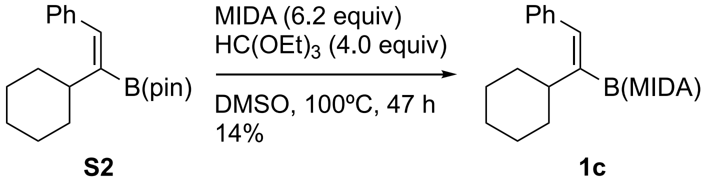
^{1}H NMR (396 MHz, CD_3CN, δ): 2.43–2.48 (m, 2H), 2.70–2.74 (m, 2H), 2.83 (s, 3H), 3.91 (d, *J* = 17.4 Hz, 2H), 4.03 (d, *J* = 17.0 Hz, 2H), 6.86 (s, 1H), 7.12–7.17 (m, 3H), 7.23–7.29 (m, 3H), 7.38 (d, *J* = 4.4 Hz, 4H). ^{13}C NMR (100 MHz, CD_3CN, δ): 33.8 (CH_2), 36.8 (CH_2), 47.9 (CH_3), 63.0 (CH_2), 126.7 (*C*H), 127.8 (*C*H), 129.1 (*C*H), 129.2 (*C*H), 129.3 (*C*H), 129.5 (*C*H), 138.8 (*C*H), 139.4 (*C*), 143.6 (*C*), 169.6 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): $[M]^+$ calcd for $C_{21}H_{22}{}^{10}BNO_4$, 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).



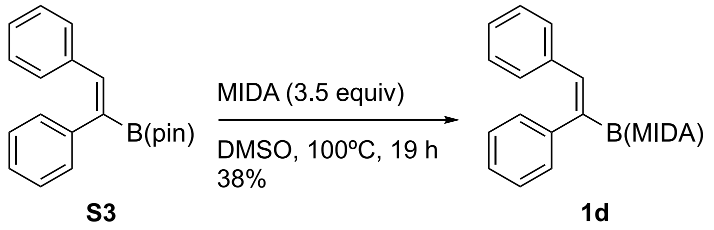
S1 (2.19 g, 7.64 mmol) was prepared in 85% yield from hex-1-yn-1-ylbenzene (1.42 g, 9.0 mmol) according to the procedure for the synthesis of **3**. The spectral data was consistent with those reported in the literature.[17] **1b** (891 mg, 2.83 mmol, white solid) was prepared in 40% yield from **S1** (2.00 g, 7.0 mmol) according to the procedure for the synthesis of **1a**. ^{1}H NMR (396 MHz, CD_3CN, δ): 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_3CN, δ): 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 (*C*H), 129.2 (*C*H), 129.6 (*C*H), 137.9 (*C*H), 139.5 (*C*), 169.6 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): $[M]^+$ calcd for $C_{17}H_{22}{}^{10}BNO_4$, 314.16782; found, 314.16791.

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



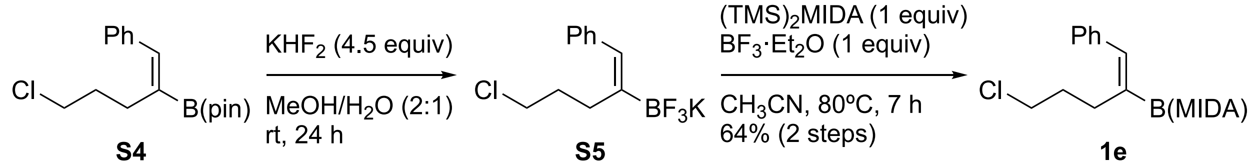
S2 (2.32 g, 7.43 mmol) was prepared in 83% yield from (cyclohexylethynyl)benzene (1.66 g, 9.0 mmol) according to the procedure for the synthesis of **3**. The spectral data was consistent with those reported in the literature.[17] **1c** (322.0 mg, 0.94 mmol, white solid) was prepared in 14% yield from **S2** (2.19 g, 7.0 mmol) according to the procedure for the synthesis of **1a**. ^{1}H NMR (396 MHz, CD_3CN, δ): 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_3CN, δ): 26.9 (CH_2), 27.4 (CH_2), 32.8 (CH_2), 42.1 (*C*H), 49.0 (CH_3), 63.4 (CH_2), 127.5 (*C*H), 129.0 (*C*H), 129.6 (*C*H), 138.4 (*C*H), 140.1 (*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 $C_{19}H_{24}{}^{10}BNO_4$, 340.18347; found, 340.18250.

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_3CN, δ): 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_3CN, δ): 47.6 (CH_3), 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 $C_{19}H_{18}{}^{10}BNO_4$, 334.13652; found, 334.13602.

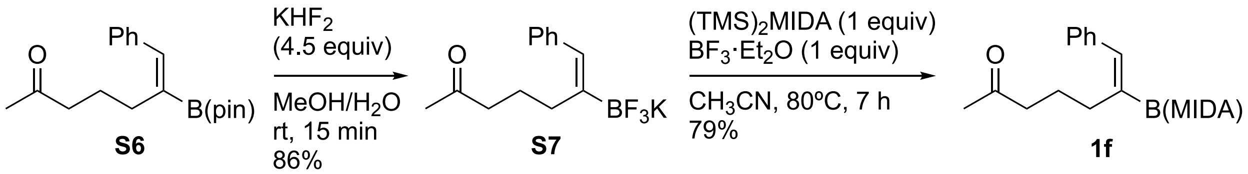
Preparation of (*Z*)-2-(5-chloro-1-phenylpent-1-en-2-yl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1e).



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_2O (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_2O, 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_3CN (6.5 mL), $(TMS)_2$MIDA (188 mg, 0.65 mmol), and $BF_3{\cdot}Et_2O$ (81.2 μL, 0.65 mmol), and then the resultant solution was stirred at 80°C 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_3CN, δ): 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_3CN, δ): 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 $C_{16}H_{19}{}^{10}BClNO_4$, 334.11320; found, 334.11211.

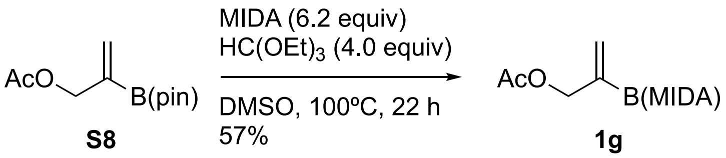
Preparation of (*Z*)-6-methyl-2-(6-oxo-1-phenylhept-1-en-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (1f).



S6 (630 mg, 2.0 mmol) was prepared in 80% yield from 7-phenylhept-6-yn-2-one (465 mg, 2.5 mmol) according to the procedure for the synthesis of **3**. ^{1}H NMR (392 MHz, CDCl$_3$, δ): 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$_3$, δ): 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 $C_{19}H_{27}{}^{10}BO_3$, 313.20896; found, 313.20944.

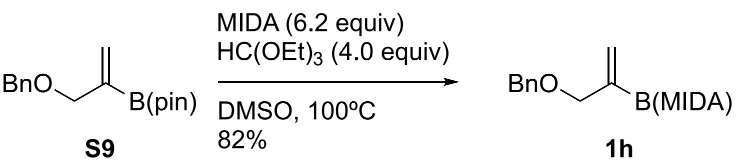
S7 (756 mg, 2.57 mmol, white solid) was prepared in 86% yield from **S6** (693 mg, 3.0 mmol) according to the procedure for the synthesis of **S5**. **1f** (404 mg, 1.18 mmol, white solid) was prepared in 79% yield from **S7** (441 mg, 1.50 mmol) according to the procedure for the synthesis of **1e**. ^{1}H NMR (392 MHz, CD$_3$CN, δ): 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, CD$_3$CN, δ): 24.8 (CH$_2$), 29.9 (CH$_3$), 30.2 (CH$_2$), 44.1 (CH$_2$), 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 $C_{18}H_{22}{}^{10}BNO_5$, 342.16273; found, 342.16225

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



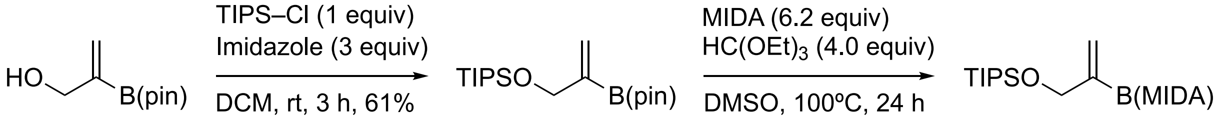
S8 was prepared from prop-2-yn-1-yl acetate according to the reported procedure.[19] **1g** (435 mg, 1.70 mmol, white solid) was prepared in 57% yield from **S8** (678 mg, 3.0 mmol) according to the procedure for the synthesis of **1a**. ^{1}H NMR (396 MHz, CD$_3$CN, δ): 2.02 (s, 3H), 2.83 (s, 3H), 3.84 (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$_3$CN, δ): 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 $C_{10}H_{14}{}^{10}BNO_6$, 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).



S9 was prepared in from [(prop-2-yn-1-yloxy)methyl]benzene according to the reported procedure.[8f] **1h** (742 mg, 2.45 mmol, white solid) was prepared in 82% yield from **S9** (823 g, 3.0 mmol) according to the procedure for the synthesis of **1a**. ^{1}H NMR (396 MHz, CD_3CN, δ): 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}C NMR (100 MHz, CD_3CN, δ): 48.3 (CH_3), 63.3 (CH_2), 73.8 (CH_2), 76.1 (CH_2), 126.1 (CH_2), 128.7 (*C*H), 129.1 (*C*H), 129.4 (*C*H), 139.0 (*C*), 169.7 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): [M]$^+$ calcd for $C_{15}H_{18}{}^{10}BNO_5$, 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 (1i).

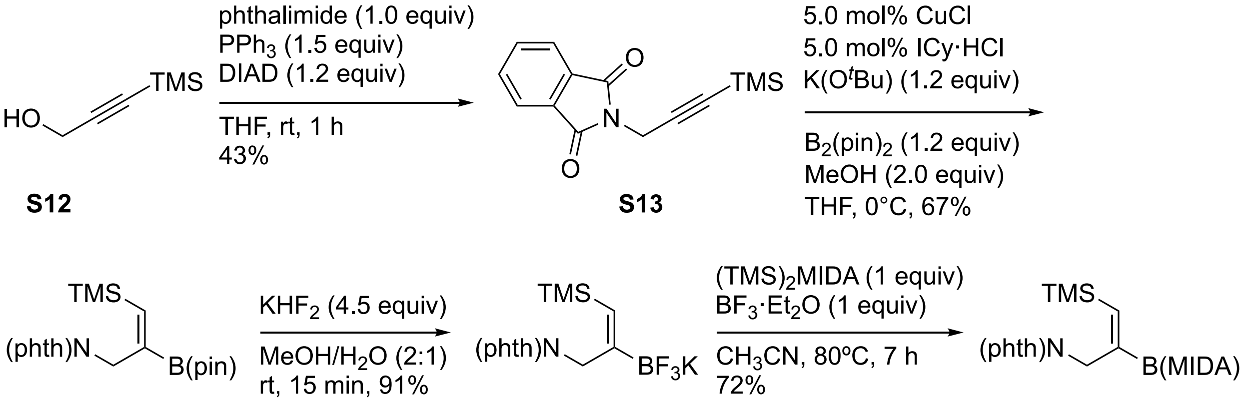


S10 **S11** **1i**

S10 was prepared from propargylalcohol according to the reported procedure.[8f] **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_2Cl_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 **S11** (885 mg, 2.46 mmol, 61%) as a colorless oil.

1i (124 mg, 0.336 mmol, white solid) was prepared in 56% yield from **S11** (204 mg, 0.60 mmol) according to the procedure for the synthesis of **1a**. ^{1}H NMR (392 MHz, $CDCl_3$, δ): 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}C NMR (99 MHz, $CDCl_3$, δ): 11.9 (*C*H), 18.0 (CH_3), 47.1 (CH_3), 61.9 (CH_2), 68.2 (CH_2), 126.3 (CH_2), 168.2 (*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 $C_{17}H_{32}O_5N^{10}BNaSi$, 391.20713; found, 391.20766.

Preparation of (*Z*)-2-[3-(1,3-dioxoisoindolin-2-yl)-1-phenylprop-1-en-2-yl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (1j).

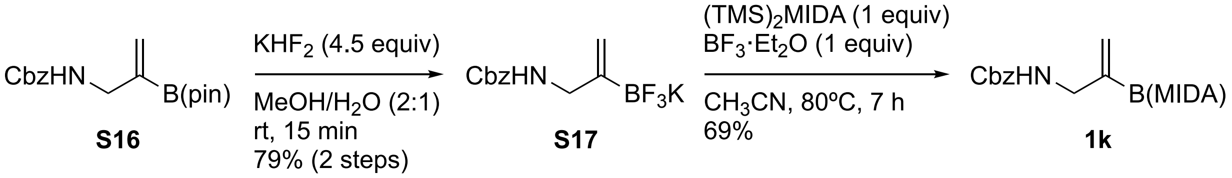


S14 **S15** **1j**

Phthalimide (2.94 g, 20 mmol) and PPh_3 (6.30 g, 24 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 (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 0ºC. After stirring for 1 h, the solution was dituted with water and extracted with Et_2O three times, and then 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 **S13** (2.21 g, 8.60 mmol) in 43%.

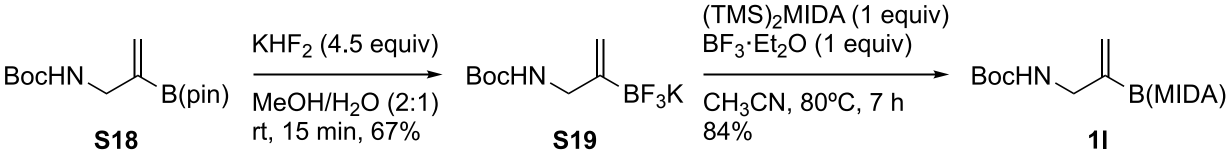
$B_2(pin)_2$ (1.52 g, 6.00 mmol), CuCl (24.8 mg, 0.25 mmol), ICy·HCl (67.2 mg, 0.25 mmol) were placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. KO^{t}Bu (1 M in THF, 6.0 mL, 6.0 mmol) was then added in the flask and stirred for 30 min at room temperature. Then, the solution was cooled to –78ºC, **S13** (1.286 g, 5.0 mmol, in 6.6 mL THF) and MeOH (410 μL, 10.0 mmol) were then added in the flask through the rubber septum using syringes. The resultant solution was allowed to warm to 0ºC, 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**. ^{1}H NMR (392 MHz, Acetone-d$_6$, 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). ^{13}C NMR (100 MHz, Acetone-d$_6$, δ): 0.42 (CH_3), 43.7 (CH_2), 47.6 (CH_3), 62.5 (CH_2), 123.7 (*C*H), 133.5 (*C*), 134.8 (*C*H), 145.7 (*C*H), 168.9 (*C*), 169.4 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): [M]$^+$ calcd for $C_{19}H_{23}{}^{10}BN_2O_6Si$, 413.14547; found, 413.14413.

Preparation of benzyl [2-(6-methyl-4,8-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**. ^{1}H NMR (396 MHz, CD_3CN, 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). ^{13}C NMR (100 MHz, CD_3CN, δ): 45.1 (CH_2), 47.6 (CH_3), 62.6 (CH_2), 66.9 (CH_2), 123.3 (CH_2), 128.7 (*C*H), 128.8 (*C*H), 129.4 (*C*H), 138.4 (*C*), 157.4 (*C*), 169.4 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. HRMS-EI (m/z): [M]$^+$ calcd for $C_{16}H_{19}{}^{10}BN_2O_6$, 345.13725; found, 345.13631.

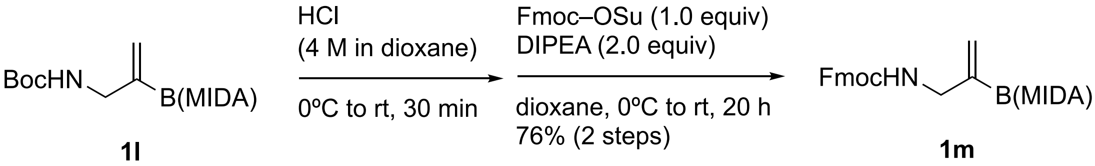
Preparation of *tert*-butyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)allyl]carbamate (1l).



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**. ^{1}H NMR (392 MHz, CD_3CN, δ): 1.40 (s, 9H), 3.60 (d, *J* = 5.4 Hz, 2H), 4.93 (s, 1H), 4.98 (s, 1H), 5.26 (brs, 1H). ^{13}C NMR (99 MHz, CD_3CN, δ): 28.7 (CH_3), 45.5 (CH_2), 79.1 (*C*), 113.5 (CH_2), 153.4 (br, B–*C*), 157.4 (*C*). ^{11}B NMR (127 MHz, CD_3CN, δ): 3.63 (s). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_8H_{14}O_2N^{10}BF_3$, 223.11115; found, 223.11140.

1l (17.1 g, 65.0 mmol) was prepared in 84% from **S19** (17.1 g, 65 mmol) according to the procedure for the synthesis of **1e**. ^{1}H NMR (396 MHz, CD_3CN, δ): 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). ^{13}C NMR (99 MHz, CD_3CN, δ): 28.7 (CH_3), 44.6 (CH_2), 47.6 (CH_3), 62.7 (CH_2), 79.3 (*C*), 123.1 (CH_2), 145.2 (br, B–*C*), 157.0 (*C*), 169.4 (*C*). ^{11}B NMR (127 MHz, CD_3CN, δ): 11.19 (s). HRMS-ESI (m/z: $[M+Na]^+$ calcd for $C_{13}H_{21}O_6N_2{}^{10}BNa$, 334.14212; found, 334.14221.

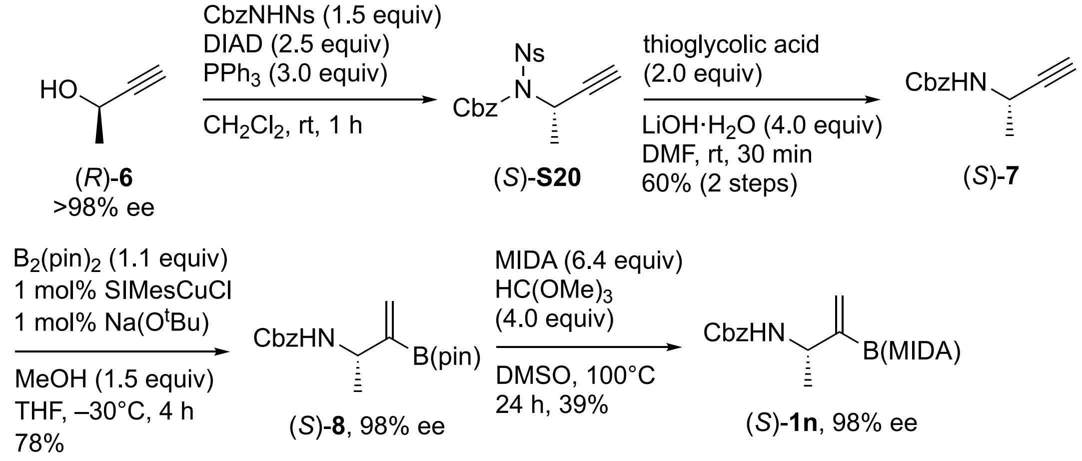
Preparation of (9H-Fluoren-9-yl)methyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)allyl] carbamate (1m).



1l (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 Et_2O and the precipitated solid was collected by decantation, and dried in vacuo. The resultant solid (1.24 g) and Fmoc–OSc (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 NH_4Cl_4 solution. The obtained organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to obtain **1m** (1.65 g, 3.80 mmol, 76%) as a white solid. ^{1}H NMR (392 MHz, CD_3CN, δ): 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* =

6.7 Hz, 1H), 4.34 (d, *J* = 7.2 Hz, 2H), 5.38 (s, 1H), 5.51 (s, 1H), 5.85 (brs, 1H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.2 Hz, 2H) 7.84 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (99 MHz, CD_3CN, δ): 45.0 (CH_2), 47.6 (CH_3), 48.2 (CH), 62.7 (CH_2), 66.9 (CH_2), 121.0 (CH), 123.2 (CH_2), 126.2 (CH), 128.1 (CH), 128.7 (CH), 142.2 (C), 145.3 (C), 157.4 (C), 169.4 (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 $C_{23}H_{33}O_6N_2{}^{10}BNa$, 456.15777; found, 456.15848.

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



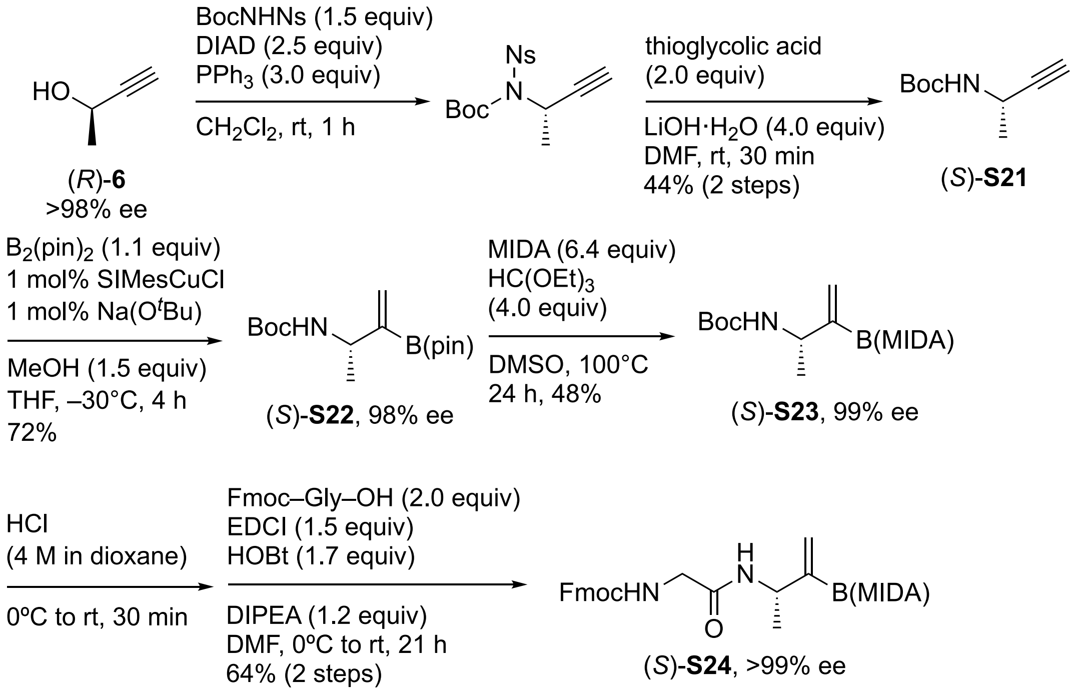
NsNHCbz (6.34 g, 21.0 mmol) and PPh_3 (4.41 g, 16.8 mmol) was placed in an oven-dried two-neck equipped with a stir bar. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. THF (42 mL) and (*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 0ºC. 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 $LiOH{\cdot}H_2O$ (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. After stirring for 30 min, the solution was dituted with saturated $NaHCO_3$ solution and extracted with Et_2O four times, and then 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 **7** (1.70 g, 8.36 mmol) in 60% (2 steps). ^{1}H NMR (392 MHz, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.3 (CH_3), 38.7 (CH), 66.8 (CH_2), 70.5 (C), 84.0 (CH), 128.1 (CH), 128.4 (CH), 136.1 (C), 155.1 (C). HRMS-EI (m/z): $[M]^+$ calcd for $C_{12}H_{13}NO_2$, 203.09463; found, 203.09526. $[\alpha]_D^{27.8}$ –38.0 (*c* 1.0 in $CHCl_3$).

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**. ^{1}H NMR (392 MHz, CD_3CN, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.2 (CH_3), 24.5 (CH_3), 24.7 (CH_3), 52.2 (CH), 66.2 (CH_2), 83.5 (C), 127.8 (CH), 127.9 (CH), 128.3 (CH), 129.0 (CH_2), 136.7 (*C*), 142.2 (br, B–*C*), 155.4 (*C*). HRMS-EI (m/z): [M]$^+$ calcd for $C_{18}H_{26}{}^{10}BNO_6$, 330.19912; found, 330.19877. [α]$_D^{24.1}$ +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 min., (*S*)-isomer: t_R = 44.00 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_3CN, δ): 1.21 (d, *J* = 7.2 Hz, 3H), 2.81 (s, 3H), 3.75 (d, *J* = 17.0 Hz, 1H), 3.86–3.99 (m, 3H), 4.11 (quint, *J* = 7.1 Hz, 1H), 5.02 (s, 2H), 5.38 (s, 1H), 5.67 (s, 1H), 5.81 (brd, *J* = 6.3 Hz, 1H), 7.29–7.39 (m, 5H). ^{13}C NMR (99 MHz, CD_3CN, δ): 22.4 (*C*H_3), 47.7 (*C*H_3), 50.8 (*C*H), 62.6 (*C*H_2), 62.8 (*C*H_2), 66.8 (*C*H_2), 122.7 (*C*H_2), 128.6 (*C*H), 128.9 (*C*H), 129.5 (*C*H), 138.5 (*C*), 151.7 (br, B–*C*), 156.7 (*C*), 169.4 (*C*), 169.6 (*C*). HRMS-EI (m/z): [M]$^+$ calcd for $C_{17}H_{21}{}^{10}BN_2O_6$, 359.15290; found, 359.15409. [α]$_D^{27.7}$ –10.8 (*c* 1.0 in CH_3CN, 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 min., (*S*)-isomer: t_R = 52.59 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).



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, $CDCl_3$, δ): 1.40 (d, *J* = 7.2 Hz, 3H), 1.45 (s, 9H), 2.26 (d, *J* = 2.4 Hz, 1H), 4.50 (brs, 1H), 4.71 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 22.4 (*C*H_3), 28.3 (*C*H_3), 38.1 (*C*H), 70.1 (*C*), 79.8 (*C*), 84.5 (*C*H), 154.6 (*C*). HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_9H_{15}O_2N$ Na, 192.09950; found, 192.10017. [α]$_D^{25.1}$ –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, $CDCl_3$, δ): 1.22 (d, *J* = 6.4 Hz, 3H), 1.27 (s, 12H), 1.44 (s, 9H), 4.32 (m, 1H), 5.02 (brd, *J* = 7.2 Hz, 1H), 5.72 (s, 1H), 5.79 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 22.2 (*C*H_3), 24.6 (*C*H_3), 28.3 (*C*H_3), 51.4 (*C*H), 78.6 (*C*), 83.4 (*C*), 128.4 (*C*H_2), 143.0 (br, B–*C*), 155.0 (*C*). HRMS-EI (m/z): [M–CH_3]$^+$ calcd for

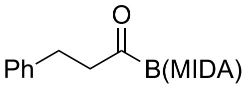
$C_{14}H_{25}{}^{10}BNO_4$, 281.19129; found, 281.19103. $[\alpha]_D^{27.2}$ –12.0 (*c* 1.1 in $CHCl_3$, 99% ee). The ee value was determined by HPLC analysis. Daicel CHIRALPAK® OD-3, 2-PrOH/Hexane = 0.5/99.5, 0.5 mL/min, 40 °C, (*R*)-isomer: t_R = 12.27 min., (*S*)-isomer: t_R = 16.56 min.

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%. ^{1}H NMR (401 MHz, CD_3CN, δ): 1.16 (d, *J* = 6.8 Hz, 3H), 1.37 (s, 9H), 2.83 (s, 3H), 3.79 (d, *J* = 17.2 Hz, 1H), 3.89–4.08 (m, 4H), 5.38 (s, 1H), 5.60 (brs, 1H), 5.65 (s, 1H). ^{13}C NMR (99 MHz, acetone-d$_6$, δ): 22.6 (CH_3), 28.7 (CH_3), 47.3 (CH_3), 50.0 (*C*H), 62.4 (CH_2), 62.7 (CH_2), 78.7 (*C*), 121.8 (CH_2), 152.9 (br, B–*C*), 156.2 (*C*), 169.0 (*C*), 169.5 (*C*). ^{11}B NMR (127 MHz, acetone-d$_6$, δ): 11.36 (s). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{23}O_6N_2{}^{10}BNa$, 348.15777; found, 348.15828. $[\alpha]_D^{24.0}$ +3.0 (*c* 0.7 in CH_3CN, 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_2O 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 0ºC, and then the solution was allowed to warm to room temperature and stirred for 17 h. Then aq. NH_4Cl 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. ^{1}H NMR (392 MHz, CD_3CN, 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 (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). ^{13}C NMR (99 MHz, CD_3CN, δ): 22.2 (CH_3), 44.8 (CH_2), 47.7 (CH_3), 47.9 (*C*H), 48.9 (*C*H), 62.5 (CH_2), 62.8 (CH_2), 67.3 (CH_2), 121.0 (*C*H), 122.9 (CH_2), 126.2 (*C*H), 128.1 (*C*H), 128.7 (*C*H), 142.1 (*C*), 145.1 (*C*), 157.6 (*C*), 169.3 (*C*), 169.4 (*C*), 169.7 (*C*). ^{11}B NMR (127 MHz, CD_3CN): 11.03 (s). HRMS-ESI: $[M+Na]^+$ calculated for $C_{26}H_{28}O_7N_3{}^{10}BNa$, 527.19488; found, 527.19522. $[\alpha]_D^{24.0}$ +25.3 (*c* 1.0 in CH_3CN, 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.

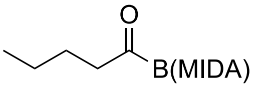
6-Methyl-2-(3-phenylpropanoyl)-1,3,6,2-dioxazaborocane-4,8-dione (4a).



4a

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.[9] ^{1}H NMR (396 MHz, CD_3CN, 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). ^{13}C NMR (100 MHz, CD_3CN, δ): 28.7 (CH_2), 47.4 (CH_3), 48.9 (CH_2), 63.1 (CH_2), 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 quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): 4.80 (s). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{16}O_5N^{10}BNa$, 311.10501; found, 311.10499.

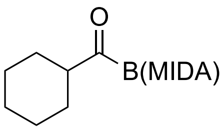
6-Methyl-2-pentanoyl-1,3,6,2-dioxazaborocane-4,8-dione (4b).



4b

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.10 ^{1}H NMR (396 MHz, CD_3CN, 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). ^{13}C NMR (100 MHz, CD_3CN, δ): 14.3 (CH_3), 23.1 (CH_2), 24.9 (CH_2), 47.2 (CH_2), 47.3 (CH_3), 63.0 (CH_2), 169.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): 4.77 (s). HRMS-EI (m/z): $[M]^+$ calcd for $C_{10}H_{16}{}^{10}BNO_5$, 240.11578; found, 240.11555.

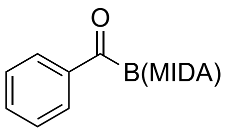
2-(Cyclohexanecarbonyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4c).



4c

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.10 ^{1}H NMR (396 MHz, CD_3CN, 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). ^{13}C NMR (100 MHz, CD_3CN, δ): 26.4 (CH_2), 26.8 (CH_2), 27.3 (CH_2), 47.4 (CH_3), 53.7 (CH), 62.9 (CH_2), 169.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): 4.98 (s). HRMS-EI (m/z): $[M]^+$ calcd for $C_{12}H_{18}{}^{10}BNO_5$, 266.13143; found, 266.13137.

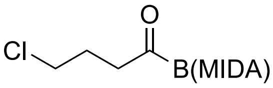
2-Benzoyl-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4d).



4d

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] ^{1}H NMR (396 MHz, CD_3CN, δ): 2.94 (s, 3H), 3.99 (d, *J* = 17.2 Hz, 2H), 4.10 (d, *J* = 16.7 Hz, 2H), 7.50–7.54 (m, 2H), 7.61 (tt, *J* = 1.7, 7.2 Hz, 2H), 8.04–8.07 (m, 2H). ^{13}C NMR (100 MHz, CD_3CN, δ): 47.5 (CH_3), 63.0 (CH_2), 129.2 (CH), 129.7 (CH), 134.2 (CH), 141.7 (C), 169.0 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): 5.96 (s). HRMS-EI (m/z): [M]$^+$ calcd for $C_{12}H_{12}{}^{10}BNO_5$, 260.08448; found, 260.08411.

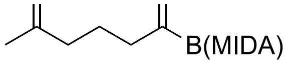
2-(4-Chlorobutanoyl)-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4e).



4e

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}H NMR (396 MHz, CD_3CN, δ): 1.95–1.99 (m, 2H), 2.80 (t, *J* = 7.1 Hz, 2H), 2.82 (s, 3H), 3.58 (t, *J* = 6.7 Hz, 2H), 3.89 (d, *J* = 17.0 Hz, 2H), 4.03 (d, *J* = 17.4 Hz, 2H). ^{13}C NMR (100 MHz, CD_3CN, δ): 25.9 (CH_2), 44.4 (CH_2), 45.8 (CH_2), 47.4 (CH_3), 63.0 (CH_2), 169.1 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 4.76 (s). HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_9H_{13}O_5N{}^{10}BClNa$, 283.05038; found, 283.05010.

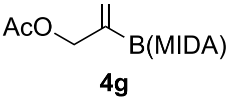
6-Methyl-2-(5-oxohexanoyl)-1,3,6,2-dioxazaborocane-4,8-dione (4f).



4f

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}H NMR (396 MHz, CD_3CN, δ): 1.69 (quint, *J* = 7.3 Hz, 2H), 2.05 (s, 3H), 2.40 (t, *J* = 7.3 Hz, 2H), 2.64 (t, *J* = 7.2 Hz, 2H), 2.81 (s, 3H), 3.88 (d, *J* = 16.7 Hz, 2H), 4.02 (d, *J* = 17.2 Hz, 2H). ^{13}C NMR (100 MHz, CD_3CN, δ): 17.0 (CH_2), 30.0 (CH_3), 43.2 (CH_2), 46.6 (CH_2), 47.5 (CH_3), 63.1 (CH_2), 169.2 (C), 209.6 (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): 5.14 (s). HRMS-EI (m/z): [M]$^+$ calcd for $C_{11}H_{16}{}^{10}BNO_6$, 268.11070; found, 268.10983.

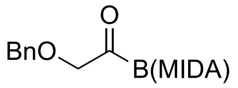
2-(6-Methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl acetate (4g).



4g

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_3CN, δ): 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). ^{13}C NMR (100 MHz, CD_3CN, δ): 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. ^{11}B NMR (127 MHz, CD_3CN, δ): 4.90 (s, 1B). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_9H_{12}O_7N^{10}BNa$, 279.06353; found, 279.06353.

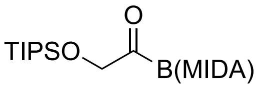
2-[2-(Benzyloxy)acetyl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4h).



4h

4h (76.9 mg, 0.25 mmol, white solid) was prepared in 84% yield (**4h**:**5h** =82:18) from **1h** (90.9 mg, 0.30 mmol). ^{1}H NMR (396 MHz, CD_3CN, δ): 2.84 (s, 3H), 3.88 (d, J = 17.0 Hz, 2H), 4.03 (d, J = 17.0 Hz, 2H), 4.31 (s, 2H), 4.53 (s, 2H), 7.31–7.38 (m, 5H). ^{13}C NMR (100 MHz, CD_3CN, δ): 47.9 (CH_3), 63.4 (CH_2), 73.9 (CH_2), 80.3 (CH_2), 128.8 (*C*H), 129.1 (*C*H), 129.4 (*C*H), 138.9 (*C*), 169.2 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): 5.12 (s). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{16}O_6N^{10}BNa$, 327.09992; found, 327.09967.

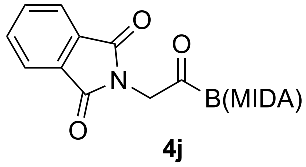
6-Methyl-2-{2-[(triisopropylsilyl)oxy]acetyl}-1,3,6,2-dioxazaborocane-4,8-dione (4i).



4i

4i (73.8 mg, 0.20 mmol, white solid) was prepared in 66% yield (**4i**:**5i** = 74:26) from **1i** (110.8 mg, 0.30 mmol). ^{1}H NMR (392 MHz, CD_3CN, δ): 1.04–1.18 (m, 21H), 2.85 (s, 3H), 3.90 (d, J = 17.0 Hz, 2H), 4.04 (d, J = 16.6 Hz, 2H), 4.65 (s, 2H). ^{13}C NMR (99 MHz, CD_3CN, δ): 12.8 (*C*H), 18.3 (CH_3), 47.7 (CH_3), 63.1 (CH_2), 74.6 (CH_2), 169.1 (*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): 5.04 (s). HRMS-EI (m/z): $[M]^+$ calcd for $C_{16}H_{30}{}^{10}BNO_6Si$, 370.19718; found, 370.19750.

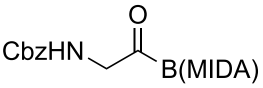
2-[2-(1,3-Dioxoisoindolin-2-yl)acetyl]-6-methyl-1,3,6,2-dioxazaborocane-4,8-dione (4j).



4j

4j (30.8 mg, 1.38 mmol, white solid) was prepared in 90% yield (**4j**:**5j** = >95:<5) from **1j** (41.4 mg, 0.10 mmol). ^{1}H NMR (392 MHz, CD_3CN, δ): 2.91 (s, 3H), 3.94 (d, J = 17.2 Hz, 2H), 4.09 (d, J = 16.8 Hz, 2H), 4.71 (s, 2H), 7.80–7.87 (m, 4H). ^{13}C NMR (100 MHz, CD_3CN, δ): 47.9 (CH_3), 52.1 (CH_2), 63.2 (CH_2), 124.1 (*C*H), 133.1 (*C*), 135.4 (*C*H), 168.8 (*C*), 168.9 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): 5.10 (s). HRMS-EI (m/z): $[M]^+$ calcd for $C_{15}H_{13}{}^{10}BN_2O_7$, 343.08521; found, 343.08387.

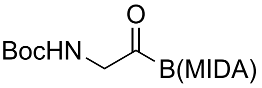
Benzyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl]carbamate (4k).



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). ^{1}H NMR (396 MHz, CD_3CN, δ): 2.84 (s, 3H), 3.91 (d, *J* = 17.0 Hz, 2H), 4.05 (d, *J* = 16.6 Hz, 2H), 4.19 (d, *J* = 5.5 Hz, 2H), 5.06 (s, 2H), 5.77 (brs, 1H), 7.32–7.38 (m, 5H). ^{13}C NMR (100 MHz, CD_3CN, δ): 47.7 (CH_3), 55.4 (CH_2), 63.1 (CH_2), 67.1 (CH_2), 128.7 (CH), 128.9 (CH), 129.4 (CH), 138.3 (C), 157.4 (C) 168.9 (C). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): 5.01 (s). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{17}O_7N_2{}^{10}BNa$, 370.10573; found, 370.10557.

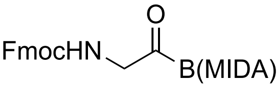
***tert*-Butyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl]carbamate (4l).**



4l

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). ^{1}H NMR (396 MHz, acetone-d_6, δ): 1.40 (s, 9H), 3.09 (s, 3H), 4.16 (d, *J* = 17.2 Hz, 2H), 4.17 (d, *J* = 4.9 Hz, 2H), 4.38 (d, *J* = 17.2 Hz, 2H), 5.89 (brs, 1H). ^{13}C NMR (99 MHz, acetone-d_6, δ): 28.9 (CH_3), 47.8 (CH_3), 55.5 (CH_2), 63.4 (CH_2), 79.3 (C), 156.9 (C), 169.1 (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): 5.38 (s). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{12}H_{19}O_7N_2{}^{10}BNa$, 336.12138; found, 336.12209.

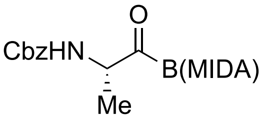
(9H-Fluoren-9-yl)methyl [2-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-2-oxoethyl]carbamate (4m).



4m

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). ^{1}H NMR (396 MHz, acetone-d_6, δ): 3.10 (s, 3H), 4.17 (d, *J* = 17.2 Hz, 2H), 4.23–4.35 (m, 5H), 4.39 (d, *J* = 16.7 Hz, 2H), 6.51 (brt, *J* = 4.8 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.74 (d, *J* = 7.7 Hz, 2H), 7.87 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (99 MHz, acetone-d_6, δ): 47.5 (CH_3), 47.9 (CH), 55.4 (CH_2), 63.1 (CH_2), 67.2 (CH_2), 120.8 (CH), 126.2 (CH), 128.0 (CH), 128.5 (CH), 142.1 (C), 145.1 (C), 157.3 (C), 168.9 (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, δ): 5.35 (s). HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{21}O_7N_2{}^{10}BNa$, 458.13703; found, 458.13718.

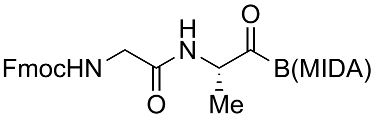
Benzyl (*S*)-[1-(6-methyl-4,8-dioxo-1,3,6,2-dioxazaborocan-2-yl)-1-oxopropan-2-yl]carbamate (4n).



4n

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$_6$, δ): 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$_6$, δ): 15.6 (CH$_3$), 47.9 (CH$_3$), 59.3 (CH), 63.3 (CH$_2$), 63.4 (CH$_2$), 67.0 (CH$_2$), 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$_6$, δ): 5.52 (s). HRMS-ESI (m/z): [M+Na]$^+$ calcd for $C_{16}H_{19}O_7N_2{}^{10}BNa$, 384.12138; found, 384.12228. $[\alpha]_D^{27.6}$ +81.3 (*c* 1.0 in CH$_3$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).

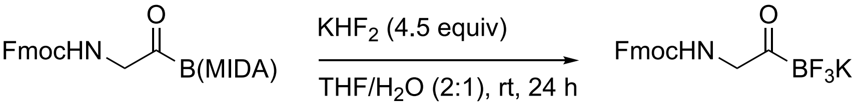


S25

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$_6$, δ): 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$_6$, δ): 14.5 (CH$_3$), 43.1 (CH$_2$), 46.7 (CH), 47.0 (CH$_3$), 56.1 (CH), 62.1 (CH$_2$), 65.8 (CH$_2$), 120.2 (CH), 125.3 (CH), 127.2 (CH), 127.7 (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$_6$, δ): 4.77 (s). HRMS-ESI: [M+Na]$^+$ calculated for $C_{25}H_{26}O_8N_3{}^{10}BNa$, 529.17415; found, 529.17476. $[\alpha]_D^{23.9}$ +28.3 (*c* 1.0 in CH$_3$CN).

Oligopeptide Synthesis by Ligation between KAT and Amino Acid

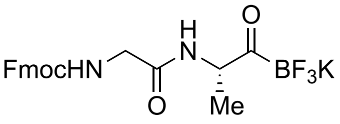
Preparation of potassium ({[(9H-fluoren-9-yl)methoxy]carbonyl}glycyl)trifluoroborate (9)



4m **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$_6$, δ): 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$_6$, δ): 46.7 (*C*H), 52.5 (*C*H$_2$), 65.6 (*C*H$_2$), 120.1 (*C*H), 125.4 (*C*H), 127.1 (*C*H), 127.7 (*C*H), 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^{10}BF$_3$, 347.10606; found, 347.10653.

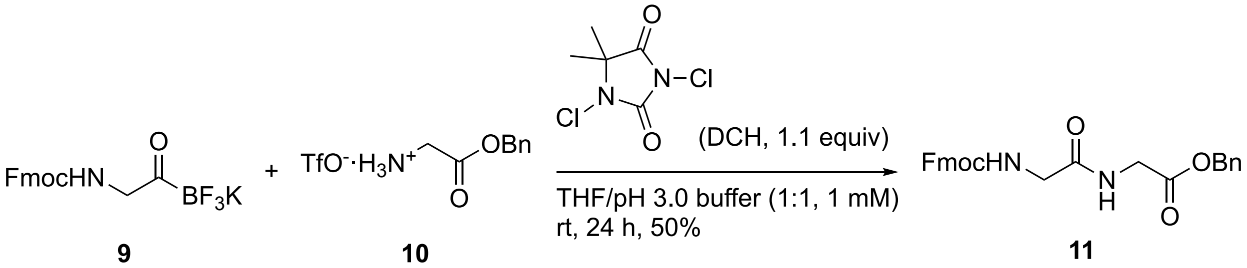
Potassium ({[(9H-fluoren-9-yl)methoxy]carbonyl}glycyl-*L*-alanyl)trifluoroborate (12)



12

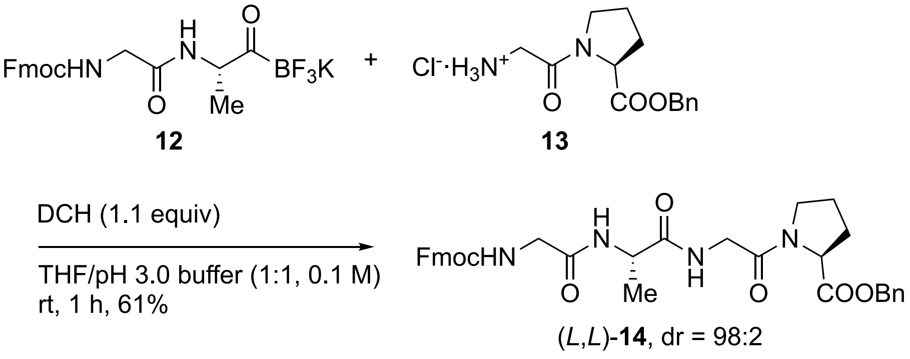
12 (346.5 mg, 0.76 mmol) was prepared in 64% from **S25** (600.4 mg, 1.18 mmol) according to the procedure for the synthesis of **9**. ^{1}H NMR (396 MHz, acetone-d$_6$, δ): 1.23 (d, *J* = 7.1 Hz, 3H), 3.82–3.88 (m, 2H), 4.23–4.34 (m, 3H), 4.59 (quint, *J* = 6.8 Hz, 1H), 6.89 (brt, *J* = 4.8 Hz, 1H), 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, δ): 16.3 (*C*H$_3$), 44.8 (*C*H$_2$), 47.8 (*C*H), 56.5 (*C*H), 67.4 (*C*H$_2$), 120.9 (*C*H), 126.1 (*C*H), 128.0 (*C*H), 128.6 (*C*H), 142.0 (*C*), 144.97 (*C*), 145.00 (*C*), 157.6 (*C*), 169.4 (*C*). ^{11}B NMR (127 MHz, acetone-d$_6$): 0.00 (s). HRMS-ESI: [M□K]$^-$ calculated for C$_{20}$H$_{19}$O$_4$N$_2$^{10}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.[14]



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_2SO_3, concentrated in vacuo, and poured into brine and extracted with EtOAc (3 x 3 mL). The organic layers were dried over $MgSO_4$, 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%). ^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.93 (d, *J* = 5.0 Hz, 2H), 4.10 (d, *J* = 5.0 Hz, 2H), 4.23 (t, *J* = 6.8 Hz, 1H), 4.45 (d, *J* = 6.8 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 Hz, 2H), 7.76 (d, *J* = 7.3 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 41.2 (CH_2), 44.2 (CH_2), 47.0 (*C*H), 67.1 (CH_2), 67.2 (CH_2), 119.9 (*C*H), 125.0 (*C*H), 127.0 (*C*H), 127.7 (*C*H), 128.3 (*C*H), 128.5 (*C*H), 128.6 (*C*H), 134.9 (*C*), 141.2 (*C*), 143.6 (*C*), 156.6 (*C*), 169.4 (*C*), 169.6 (*C*). HRMS-ESI: $[M+Na]^+$ calculated for $C_{26}H_{24}O_5N_2Na$, 467.15774; found, 467.15823.

Tetrapeptide 14 synthesis between 12 and 13 in water.[14]



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_2SO_3, poured into brine and extracted with EtOAc (3 x 3 mL). The organic layers were dried over $MgSO_4$, 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). ^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.41 (d, *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, *J* = 7.2 Hz, 1H), 4.41 (d, *J* = 7.2 Hz, 2H), 4.56–4.61 (m, 2H), 5.13 (d, *J* = 12.1 Hz, 1H), 5.18 (d, *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 (*C*H_3), 24.4 (*C*H_2), 28.8 (*C*H_2), 41.8 (*C*H_2), 44.1 (*C*H_2), 45.9 (*C*H_2), 46.9 (*C*H), 48.7 (*C*H), 58.9 (*C*H), 66.8 (*C*H_2), 67.0 (*C*H_2), 119.7 (*C*H), 125.1 (*C*H), 126.9 (*C*H), 127.5 (*C*H), 127.9 (*C*H), 128.2 (*C*H), 128.4 (*C*H), 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 $C_{34}H_{36}O_7N_4Na$, 635.24762; found, 635.24799. $[\alpha]_D^{24.0}$ –45.0 (*c* 1.0 in CH_3CN).

14 was separated from chlorinated product by reverse-phase HPLC. HPLC conditions were as follows: Simadzu 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_2O (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**.

compound	**4j** by pricking
CCDC Number	1559429
Empirical Formula	$C_{17}H_{16}BN_3O_7$
Formula Weight	385.14
Crystal System	monoclinic
Crystal Size / mm	0.511×0.300×0.125
a / Å	14.643(3)
b / Å	9.9748(16)
c / Å	12.737(2)
α / °	90
β / °	109.390(4)
γ / °	90
V / Å^3	1754.9(5)
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc} / g cm^{-3}	1.458
Temperature / K	123
$2\theta_{\text{max}}$ / °	55.0
μ(Mo K$_\alpha$) / cm^{-1}	1.134
No. of Reflections	Total: 16286 Unique: 4008 R_{int} = 0.1052
R_1[a]	0.0691
wR_2[b]	0.1971
GOF[c]	1.092
Max./Mini. peak I[d] / Å^3	0.36 e$^-$/–0.38 e$^-$

[a]:$I > 2.00\sigma(I)$. [b]:All reflections. [c]:Goodness of Fit Indicator. [d]: in Final Diff. Map.

The References

1) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.
2) a) Dawson, P. E.; Muir, T. W.; Clark-Lewis, I.; Kent, S. B. H. *Science* **1994**, *266*, 776; b) Torbeev, V. Y.; Kent, S. B. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 1667.
3) a) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1248; b) He, C.; Kulkarni, S. S.; Thuaud, F.; Bode, J. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 12996.
4) a) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 5683; b) Saito, F.; Noda, H.; Bode, J. W. *ACS Chem. Biol.* **2015**, *10*, 1026; c) H. Noda, G. Erós, J. W. Bode, *J. Am. Chem. Soc.* **2014**, *136*, 5611; d) Noda, H.; Bode, J. W. *Org. Biomol. Chem.* **2016**, *14*, 16.
5) For a review on the preparation of acylboron compounds, see: Scharnagl, F. K.; Bose, S. K.; Marder, T. B. *Org. Biomol. Chem.* **2017**, *15*, 1738.
6) a) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2007**, *72*, 3558; b) St. Denis, J. D.; Zajdlik, A.; Tan, J.; Trinchera, P.; Lee, C. F.; He, Z.; Adachi, S.; Yudin, A. K.; *J. Am. Chem. Soc.* **2014**, *136*, 17669; c) Brauer, D. J.; Pawelke, G.; *J. Organomet. Chem.* **2000**, *604*, 43.
7) Taguchi, J.; Ikeda, T.; Takahashi, R.; Sasaki, I.; Ogasawara, Y.; Dairi, T.; Kato, N.; Yamamoto, Y.; Bode, J. W.; Ito, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 13847.
8) a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457; b) Neeve, E. C.; Geier, S. J.; Mkhalid, I. A. I.; Westcott, S. A.; Marder, T. B. *Chem. Rev.* **2016**, *116*, 9091; c) Yun, J. *Asian J. Org. Chem*. **2013**, *2*, 1016; d) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890; e) Bidal, Y. D.; Lazreg, F.; Cazin, C. S. J. *ACS Catal.* **2014**, *4*, 1564; f) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859.
9) a) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc*. **2007**, *129*, 6716; b) Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130; c) Woerly, E. M.; Cherney, A. H.; Davis, E. K.; Burke, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 6941; d) Woerly, E. M.; Miller, J. E.; Burke, M. D. *Tetrahedron* **2013**, *69*, 7732.
10) Trinchera, P.; Adachi, S.; St Denis, J. D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11092.
11) a) Büchi, G.; Wüest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294; b) Igawa, K.; Kawasaki, Y.; Tomooka, K. *Chem. Lett.* **2011**, *40*, 233.
12) Willand-Charnley, R.; Fisher, T. J.; Johnson, B. M.; Dussault, P. H. *Org. Lett.* **2012**, *14*, 2242.
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**.
14) Gµlvez, A. O.; Schaack, C. P.; Noda, H.; Bode, J. W. *J. Am. Chem. Soc.* **2017**, *139*, 1826.
15) Noda, H.; Bode, J. W. *Chem. Sci.* **2014**, *5*, 4328.
16) Santoro, O.; Collado, A.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. *Chem. Commun.* **2013**, *49*, 10483.
17) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y. *Chem. Eur. J.* **2012**, *18*, 4179.
18) Kim, H. R.; Yun, J. *Chem. Commun.* **2011**, *47*, 2943.
19) Moure, A. L.; Mauleòn, P.; Arrayàs, R. G.; Carretero, J. C. *Org. Lett*. **2013**, *15*, 2054.

Chapter 4.

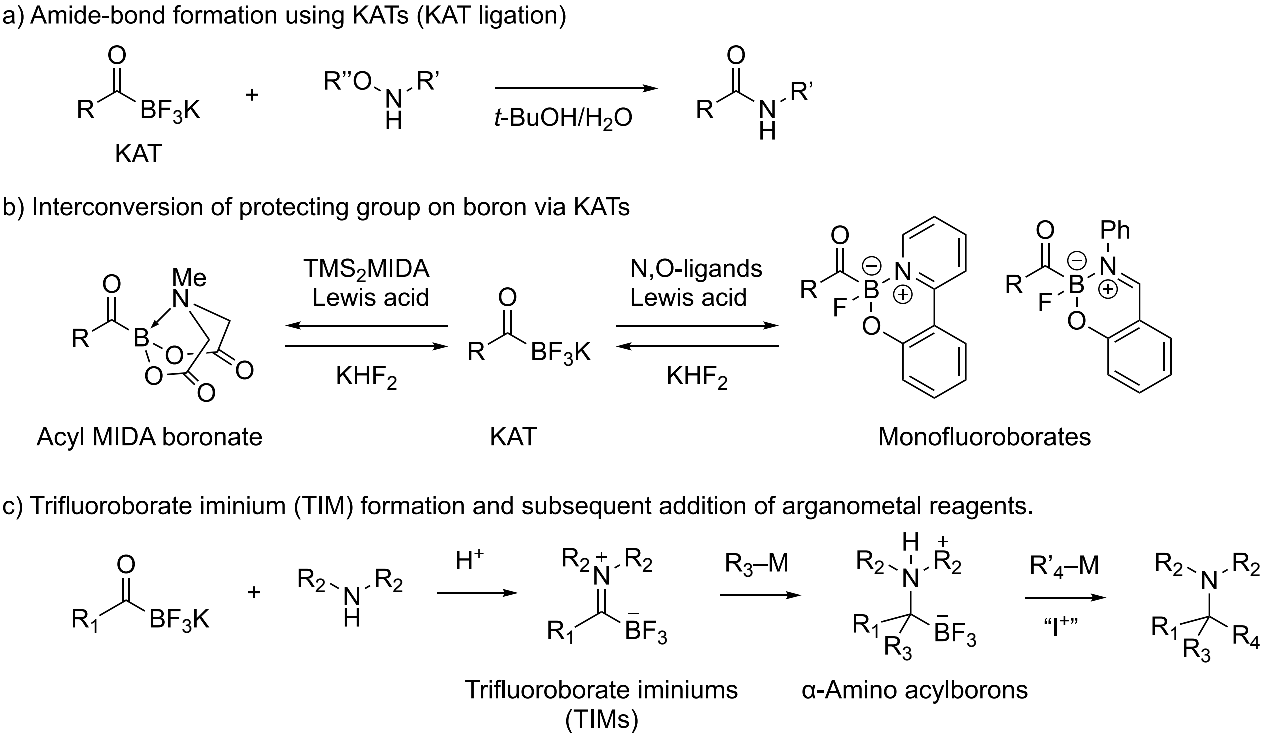
Synthesis of Potassium Acyltrifluoroborates from Aldehydes by a Cu(I)-catalyzed Borylation/Oxidation Protocol

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.[1] Among these acylboron species, potassium acyltrifluoroborates (KATs) are of particular interest due to their unique reactivities and remarkable stabilities toward air and moisture.[2] In 2012, Dumas, Bode, and Molander reported KAT ligation.[3] 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.[3b,c] 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.[4]

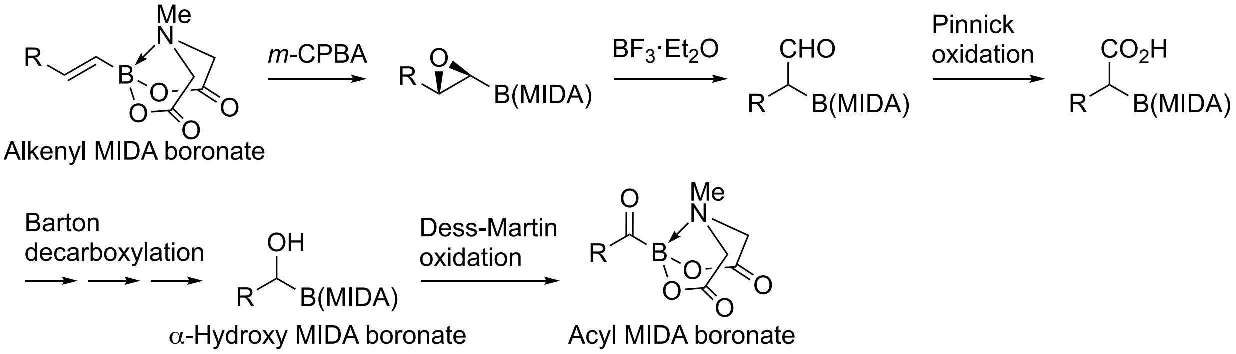


Scheme 4-1. Transformation reaction of KATs. a) KAT ligation. b) Interconversion of KATs and acyl MIDA boronates and acyl monofluoroborates. c) TIM formation and subsequent addition of organometal reagents.

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.[5a] Just after our publication, Perrin also reported the dihydroxylation/oxidative cleavage of alkenyl MIDA boronates to afford acyl MIDA boronates.[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.

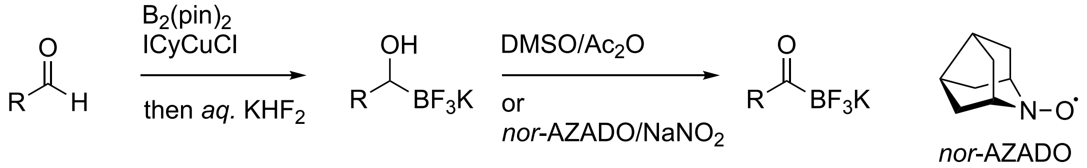
Yudin and co-workers reported Dess-Martin oxidation of α-hydroxy MIDA boronates, which affords acyl MIDA boronates in 2012. Although this reaction is attractive because of the mild conditions, , functional group tolerance was not examined in this study (Scheme 4-2).[6] This is because preparation of 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

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/Ac_2O under optimized conditions (Scheme 4-3).[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_2 in a one-pot fashion.[8] This MIDA-free approach drastically reduces the number of preparation steps and enables the shortest and scalable approach to

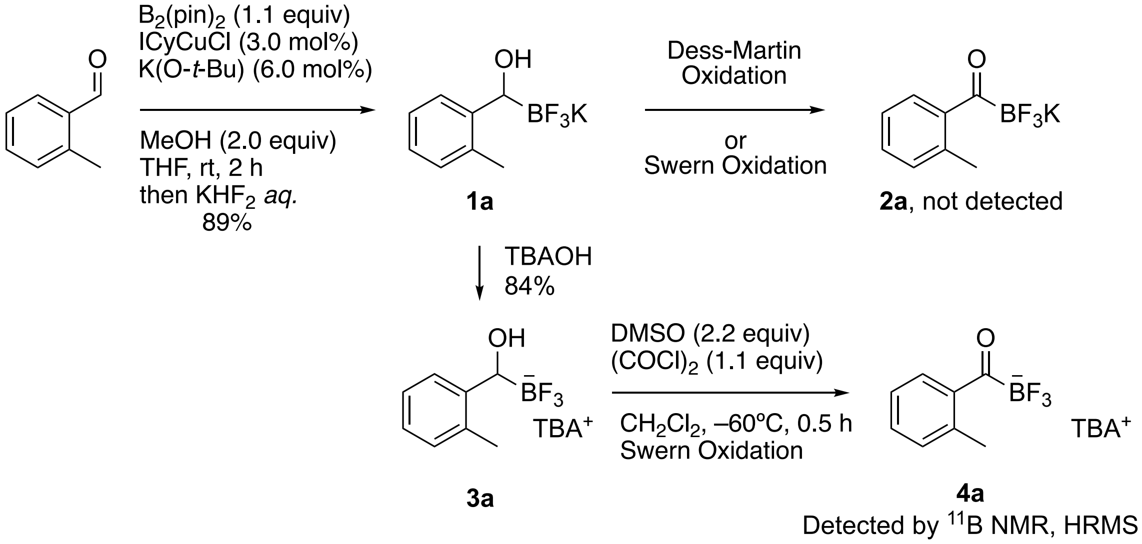
KATs with keeping high functional compatibility. The important features of this approach are the commercial availability of a wide variety of aldehydes, its step-economy, and a wide product scope including KATs derived from biologically-related molecules including carbohydrate, steroid, and α-amino acids. 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 a-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

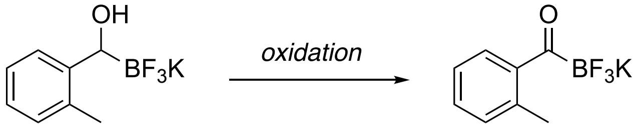
Aryl substituted α-hydroxy trifluoroborate **1a** was prepared from *o*-tolualdehyde according to the procedure reported by Molander (Scheme 4-4).[8b] Our initial attempt to synthesize α-hydroxy MIDA boronates via the reaction between **1a** and $(TMS)_2MIDA/BF_3\cdot Et_2O$ was unsuccessful.[3b] Therefore, 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 and HRMS.



Scheme 4-4. Initial investigation of oxidation of α-hydroxy trifluoroborate.

Encouraged by these results, we next investigated Albright-Goldman oxidation of potassium salt **1a** using $DMSO/Ac_2O$ 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).

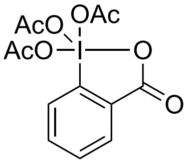
Table 4-1. Optimization of oxidation conditions



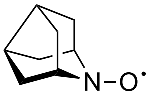
1a **2a**

entry	Oxidation Conditions	Yield (%)[a]
1[b]	DMSO, Ac_2O, rt, 4 h	85
2[c]	*nor*-AZADO, $NaNO_2$, AcOH, rt, 30 min	92
3[d]	AZADOL, $NaNO_2$, AcOH, rt, 17 h	66
4[e]	AZADOL, NaClO, rt, 0.5 h	<5
5[f]	AZADOL, $PhI(OAc)_2$, rt, 1 h	<5
6[g]	TPAP, NMO, MS 3A, rt, 2 h	38

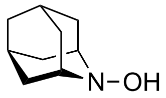
[a] Isolated product yield are reported. [b] **1a** (0.5 mmol), Ac_2O (20 equiv), DMSO, rt, 4 h. [c] **1a** (0.5 mmol), *nor*-AZADO (10 mol%), $NaNO_2$ (1.5 equiv), AcOH (2.0 equiv), CH_3CN, rt, 18 h. [d] **1a** (0.3 mmol), AZADOL (10 mol%), $NaNO_2$ (1.5 equiv), AcOH (2.0 equiv), [e] **1a** (0.5 mmol), AZADOL (5 mol%), NaClO (1.5 equiv), CH_3CN, rt, 0.5 h. [f] **1a** (0.3 mmol), *nor*-AZADO (10 mol%), $PhI(OAc)_2$ (1.5 equiv), CH_3CN, rt, 1 h. CH_3CN, rt, 17 h. [g] **1a** (0.5 mmol), TPAP (10 mol%), NMO (6.0 equiv), MS 3A, CH_3CN, rt, 2 h.



Dess-Martin
preiodinane



nor-AZADO

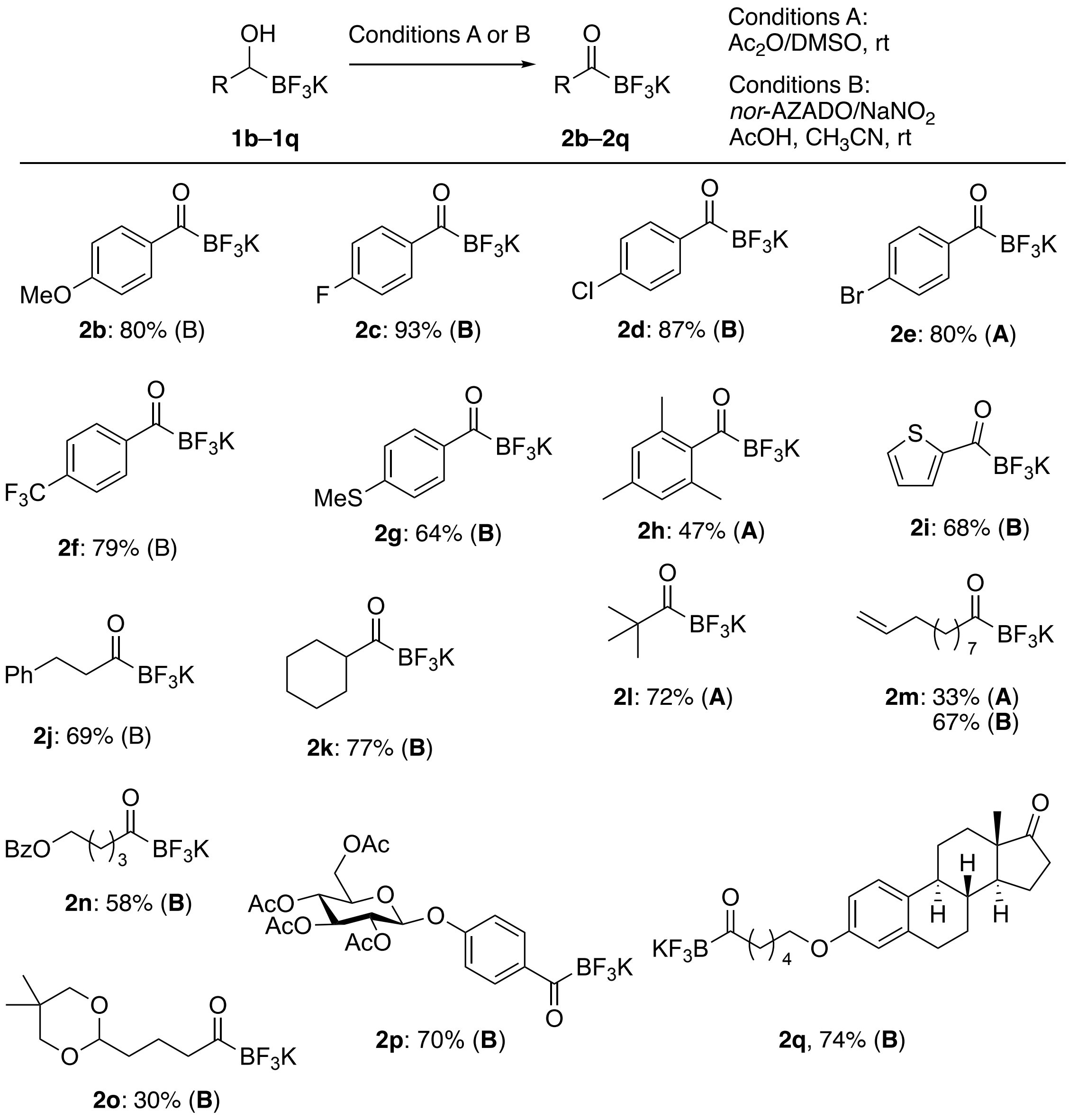


AZADOL

$n\text{-}Pr_4N^+ \cdot RuO_4^-$

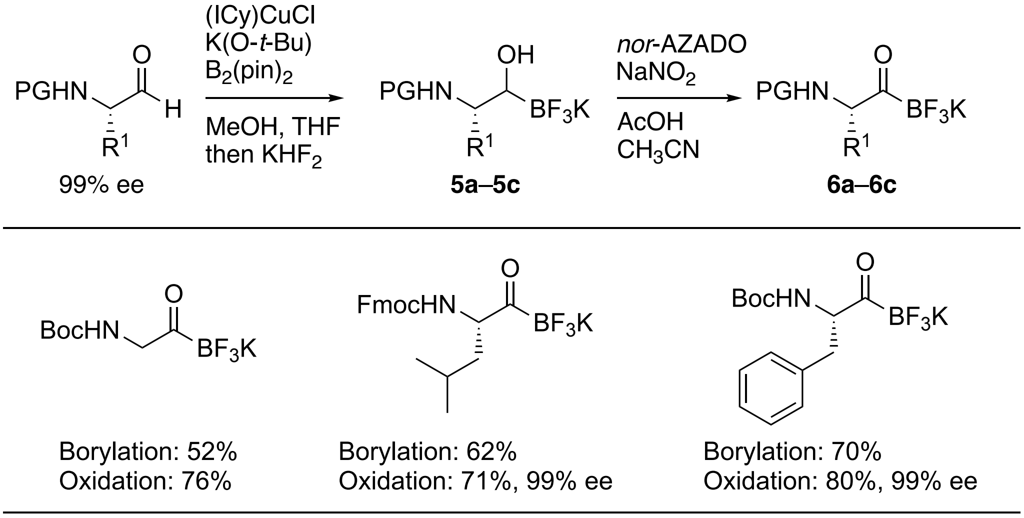
TPAP

Then, we investigated the scope of this reaction using two favorable procedures: oxidation with reaction conditions A) DMSO/Ac_2O 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.



Scheme 4-5. Substrate Scope. Reaction conditions A: **1** (0.3 mmol), Ac_2O (20 equiv), DMSO, r. Reaction conditions B: **1** (0.3 mmol), *nor*-AZADO (10 mol%), $NaNO_2$ (1.5 equiv), AcOH (2.0 equiv), CH_3CN, rt. Isolated product yields are reported.

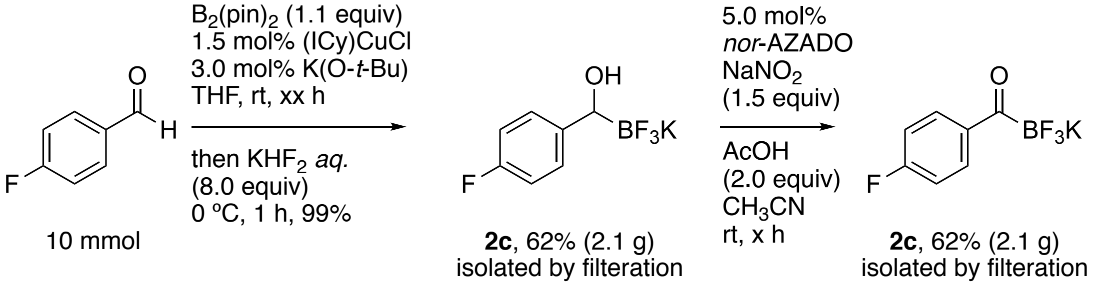
Subsequently, we investigated the synthesis of α-amino acid-derived KATs (Scheme 4-6). This class of compounds is very attractive due to its potential use as a building block in peptide conjugation using KAT ligation.[1b,3a] *N*-Boc glycinal can be synthesized by the oxidation of *N*-Boc-protected 1,2-amino 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.[5a,b]



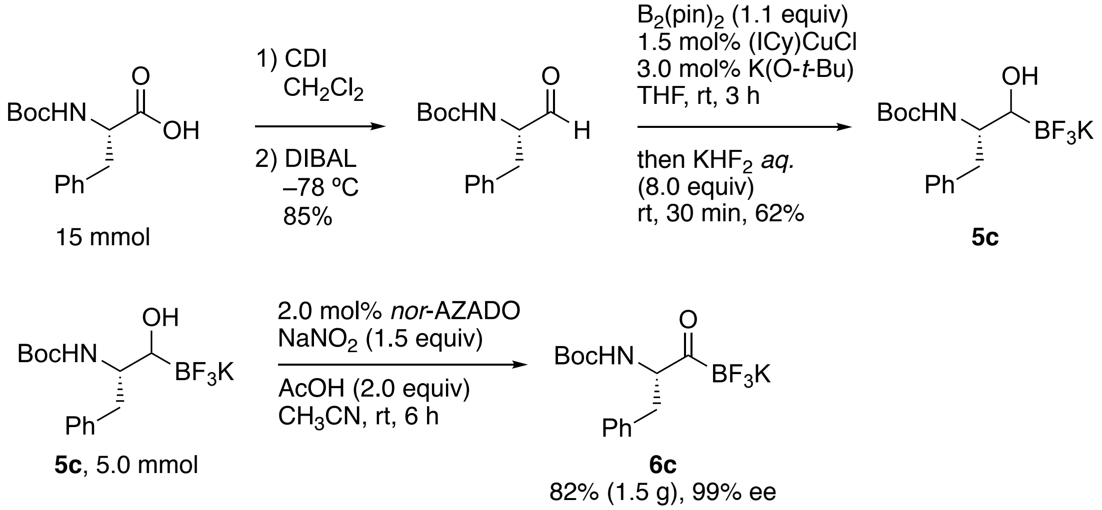
Scheme 4-6. Preparation of α-amino KATs. [a] Borylation conditions: aldehydes, B_2pin_2 (1.1 equiv), (ICy)CuCl. Oxidation conditions: **1** (0.3 mmol), *nor*-AZADO (10 mol%), $NaNO_2$ (1.5 equiv), AcOH (2.0 equiv), CH_3CN, rt, 6–7 h. Isolated product yields are reported.

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.

a) Gram-scale synthesis of **2c**



b) Gram-scale synthesis of **6c**



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/Ac$_2$O 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.

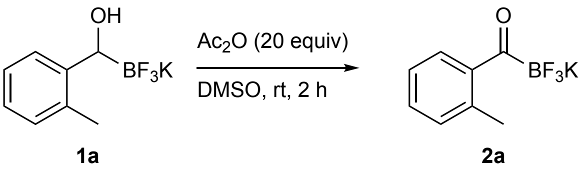
Experimental

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_3CN 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_3CN: 1.94 ppm; DMSO-d_6: 2.50 ppm; CD_3OD: 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_3CN: 1.39 ppm; DMSO-d_6: 39.52 ppm; CD_3OD: 49.00 ppm). ^{11}B NMR spectra were recorded on JEOL JNM-ECX400P (128 MHz) spectrometer and spectra are referenced to an external sample ($BF_3 \cdot Et_2O$: 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]

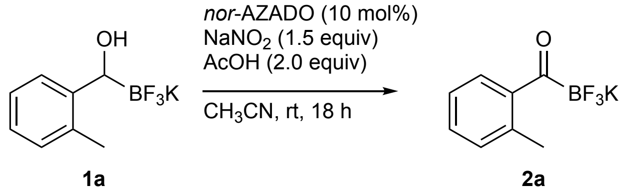
General Experimental Procedures.

A General Procedure of Oxidation of Potassium α-Hydroxytrifluoroborate 1a with DMSO/Ac_2O. (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_2O (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_2O (360 μL) and concentrated *in vacuo*. The resultant solid was washed with Et_2O to give KAT **2a** as a white solid.

A General Procedure of Oxidation of Potassium α-Hydroxyrifluoroborate 1a with *nor*-AZADO/NaNO$_2$. (Reaction Condition B)

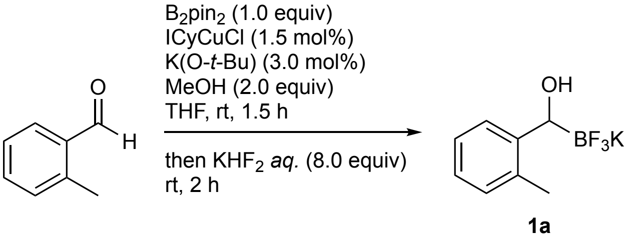


Potassium α-hydroxyrifluoroborate **1a** (114.2 mg, 0.5 mmol), *nor*-AZADO (6.8 mg, 0.05 mmol) and NaNO$_2$ (57.1 mg, 0.75 mmol) were placed in an oven-dried screw neck reaction vial. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, CH$_3$CN (0.5 mL) and AcOH (57 µL, 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 Et$_2$O 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.

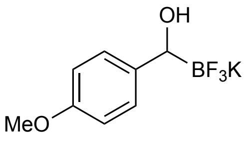
Preparation of potassium trifluoro[hydroxy(*o*-tolyl)methyl]borate (1a).[2]



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 0ºC, 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 KHF$_2$ 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 Et$_2$O to give **1a** (1.97 g, 86%) as a white solid. ^{1}H 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). ^{13}C NMR (100 MHz, acetone-d6, δ): 20.1 (CH$_3$), 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. ^{11}B 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): [M–K]$^-$ calcd for $C_8H_9O^{10}BF_3$, 188.07403; found, 188.07393.

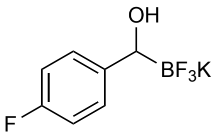
Preparation of potassium trifluoro[hydroxy(4-methoxyphenyl)methyl]borate (1b).



1b

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 (CH_3), 113.3 (*C*H), 113.5 (*C*), 127.7 (*C*H), 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): [M–K]$^-$ calcd for $C_8H_9O_2{}^{10}BF_3$, 204.06895; found, 204.06876.

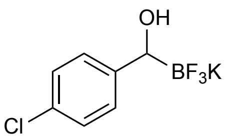
Preparation of potassium trifluoro[(4-fluorophenyl)(hydroxy)methyl]borate (1c).



1c

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, *C*H), 127.9 (d, $J_{C\text{–}F}$ = 6.7 Hz, *C*H), 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): [M–K]$^-$ calcd for $C_7H_6O^{10}BF_4$, 192.04896; found, 192.04897.

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

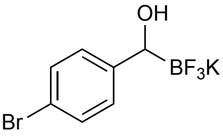


1d

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 (*C*H), 128.1 (*C*H), 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-d6, δ): 3.93 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.0 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_7H_6O^{10}BClF_3$, 208.01941; found, 208.01927.

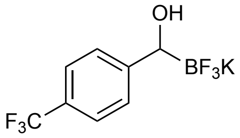
Preparation of potassium [(4-bromophenyl)(hydroxy)methyl]trifluoroborate (1e).



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-d6, δ): 4.00 (s, 1H), 7.25 (q, *J* = 7.9 Hz, 4H). ^{13}C NMR (100 MHz, acetone-d6, δ): 117.4 (*C*), 128.5 (*C*H), 130.6 (*C*H), 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-d6, δ): 3.89 (s). ^{19}F NMR (373 MHz, acetone-d6, δ): –148.8 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_7H_6O^{10}BBrF_3$, 251.96890; found, 251.96896.

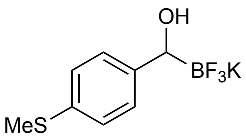
Preparation of potassium trifluoro{hydroxy[4-(trifluoromethyl)phenyl]methyl}borate (1f).



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-d6, δ): 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-d6, δ): 70.5 (br, B–*C*), 123.5 (q, J_{C-F} = 3.8 Hz, *C*H), 124.1 (q, J_{C-F} = 31.0 Hz, *C*), 125.1 (q, J_{C-F} = 271.2 Hz, *C*), 125.6 (*C*H), 155.6 (*C*). ^{11}B NMR (127 MHz, acetone-d6, δ): 3.66 (q, *J* = 53.4 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –61.0 (s, 3F), –149.2 (s, 3F). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_8H_6O^{10}BF_6$, 242.04577; found, 242.04582.

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

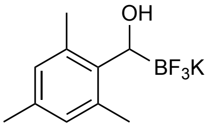


1g

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-d6, δ): 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-d6, δ): 17.0 (*C*H_3), 103.4 (*C*), 127.2 (*C*H), 127.5 (*C*H), 132.8 (*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): 3.79 (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 $C_8H_9O^{10}BF_3S$, 220.04611; found, 220.04601.

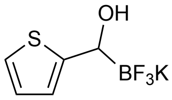
Preparation of potassium trifluoro[hydroxy(mesityl)methyl]borate (1h).



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 (CH_3), 21.9 (*C*H_3), 69.3 (br, B–*C*H), 129.7 (*C*H), 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 $C_{10}H_{13}O^{10}BF_3$, 216.10533; found, 216.10522.

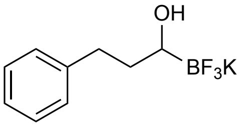
Preparation of potassium trifluoro[hydroxy(thiophen-2-yl)methyl]borate (1i).



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 (*C*H), 126.8 (*C*H), 153.7 (*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): 3.76 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.0 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_5H_5O^{10}BF_3S$, 180.01481; found, 180.01455.

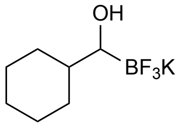
Preparation of potassium trifluoro(1-hydroxy-3-phenylpropyl)borate (1j).



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 (*C*H_2), 37.7 (*C*H_2), 125.9 (*C*H), 128.9 (*C*H), 129.4 (*C*H), 145.5 (*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): 4.64 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.1 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_9H_{11}O^{10}BF_3$, 202.08968; found, 202.08949.

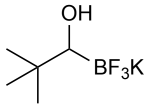
Preparation of potassium [cyclohexyl(hydroxy)methyl]trifluoroborate (1k).



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_3OD, δ): 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_3OD, δ): 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_3OD, δ): 4.11 (q, J = 47.0 Hz). ^{19}F NMR (373 MHz, CD_3OD, δ): –146.4 (s). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_7H_{13}O^{10}BF_3$, 180.10533; found, 180.10509.

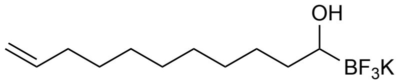
Preparation of potassium trifluoro(1-hydroxy-2,2-dimethylpropyl)borate (1l).



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-d6, δ): 0.89 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d6, δ): 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-d6, δ): 3.68 (q, J = 57.5 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –142.6 (q, J = 56.9 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_5H_{11}O^{10}BF_3$, 154.08968; found, 154.08950.

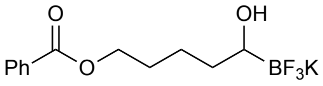
Preparation of potassium trifluoro(1-hydroxyundec-10-en-1-yl)borate (1m).



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-d6, δ): 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-d6, δ): 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-d6, δ): 4.48 (q, J = 58.3 Hz). ^{19}F NMR (372 MHz, acetone-d6, δ): –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.

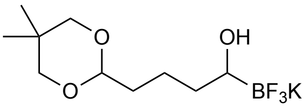
Preparation of potassium [5-(benzoyloxy)-1-hydroxypentyl]trifluoroborate (1n).



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-d6, δ): 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-d6, δ): 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 quadropolar relaxation. ^{11}B NMR (127 MHz, acetone-d6, δ): 5.05 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.2 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{12}H_{15}O_3{}^{10}BF_3$, 274.11081; found, 274.11112.

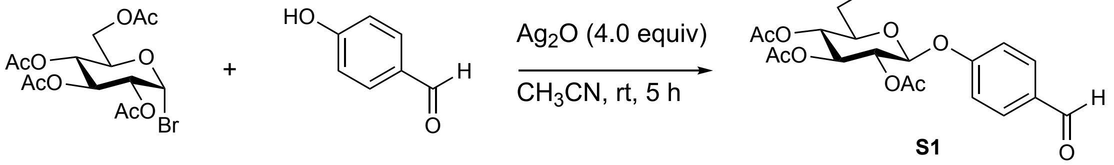
Preparation of potassium [4-(5,5-dimethyl-1,3-dioxan-2-yl)-1-hydroxybutyl]trifluoroborate (1o).



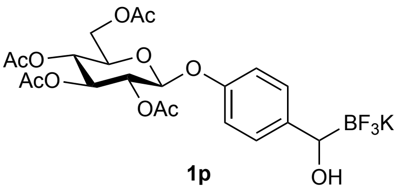
1o

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-d6, δ): 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-d6, δ): 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 quadropolar relaxation. ^{11}B NMR (127 MHz, acetone-d6, δ): 4.60 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.2 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{10}H_{19}O_3{}^{10}BF_3$, 254.14211; found, 254.14224.

Preparation of potassium trifluoro[hydroxy(4-{[(2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl) tetrahydro-2H-pyran-2-yl]oxy}phenyl)methyl]borate (1p).



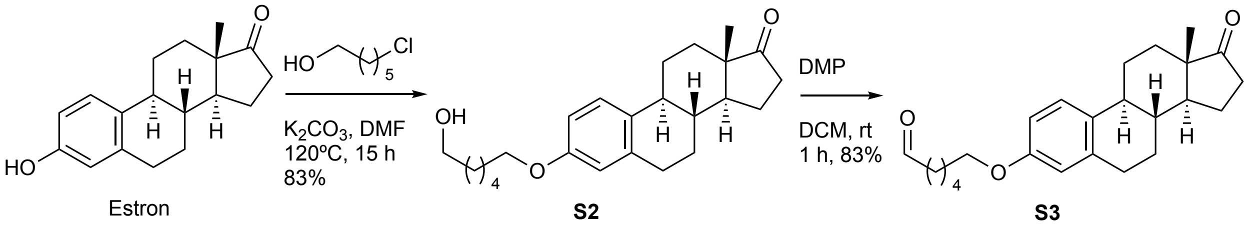
2,3,4,6-Tetra-O-acetyl-1-bromo-α-D-glucose (4.12 g, 10 mmol) was placed in an oven-dried two-neck flask. The flask was connected to a vacuum/nitrogen manifold through a rubber tube. It was evacuated and then backfilled with nitrogen. This cycle was repeated three times. CH_3CN (100.0 mL) was then added 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 concentrated *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

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**. ^{1}H NMR (396 MHz, acetone-d6, δ): 1.96 (s, 3H), 2.01 (s, 3 H), 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). ^{13}C NMR (100 MHz, acetone-d6, δ): 20.6 (*C*H$_3$), 20.7 (*C*H$_3$), 20.8 (*C*H$_3$), 25.3 (*C*H$_3$), 62.9 (*C*H$_2$), 69.5 (*C*H), 72.2 (*C*H), 72.5 (*C*H), 73.5 (*C*H), 100.4 (*C*H), 116.7 (*C*H), 127.5 (*C*H), 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. ^{11}B NMR (127 MHz, acetone-d6, δ): 3.89 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –148.9 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{21}H_{25}O_{11}{}^{10}BF_3$, 520.14838; found, 520.14884.

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[a]phenanthren-3-yl]oxy}hexyl)borate (1q).



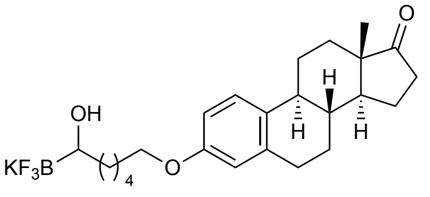
Estron

S2

S3

Estrone (1.09 g, 4.0 mmol) and K_2CO_3 (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℃ for 39 h. The resulting mixture was cool down to room temperature, and then extracted with DCM three times. The combined organic layer was dried over $MgSO_4$, 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. ^{1}H NMR (396 MHz, $CDCl_3$, 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). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 13.8 (*C*H$_3$), 21.5 (*C*H$_2$), 25.5 (*C*H$_2$), 25.9 (*C*H$_2$), 26.5 (*C*H$_2$), 29.2 (*C*H$_2$), 29.6 (*C*H$_2$), 31.5 (*C*H$_2$), 32.6 (*C*H$_2$) 35.8 (*C*H$_2$), 38.3 (*C*H), 43.9 (*C*H), 48.0 (*C*), 50.3 (*C*H), 62.8 (*C*H$_2$), 67.7 (*C*H$_2$), 112.0 (*C*H), 114.5 (*C*H), 126.3 (*C*H), 131.8 (*C*), 137.7 (*C*), 157.0 (*C*), 221.1 (*C*). HRMS-ESI (m/z): [M]$^+$ calcd for $C_{24}H_{34}O_3Na$, 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 $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution, and then extracted with DCM three times. The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution, dried over $MgSO_4$, 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, $CDCl_3$, 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). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.8 (CH_3), 21.5 (CH_2), 21.7 (CH_2), 25.6 (CH_2), 25.8 (CH_2), 26.5 (CH_2), 29.0 (CH_2), 29.6 (CH_2), 31.5 (CH_2), 35.8 (CH_2), 38.3 (CH), 43.7 (CH_2), 43.9 (CH), 47.9 (C), 50.3 (CH), 67.3 (CH_2), 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 $C_{24}H_{32}O_3Na$, 391.22437; found, 391.22507.

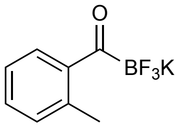


1q

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). ^{13}C NMR (100 MHz, acetone-d6, δ): 20.1 (CH_3), 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. ^{11}B NMR (127 MHz, acetone-d6, δ): 3.98 (q, *J* = 55.5 Hz). ^{19}F NMR (372 MHz, CD_3OD, δ): –150.3 (s). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{24}H_{33}O_3{}^{10}BF_3$, 189.07040; found, 189.07403.

Characterization of Acylboron Compounds.

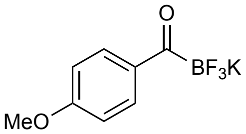
Potassium trifluoro(2-methylbenzoyl)borate (2a).



2a

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] ^{1}H NMR (401 MHz, acetone-d6, δ): 2.39 (s, 3H), 7.10 (dd, J = 1.2, 6.7 Hz, 1H), 7.20 (quintet of doublet, J = 1.7, 7.0 Hz, 2H), 8.05 (d, J = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, acetone-d6, δ): 21.3 (*C*H$_3$), 125.8 (*C*H), 130.0 (*C*H), 131.7 (*C*H), 132.1 (*C*H), 136.7 (*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): –0.45 (q, J = 52.3 Hz). ^{19}F NMR (372 MHz, acetone-d6, δ): –145.0 (q, J = 49.3 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_8H_7O^{10}BF_3$, 186.05838; found, 186.05865.

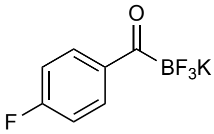
Potassium trifluoro(4-methoxybenzoyl)borate (2b).



2b

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] ^{1}H NMR (396 MHz, acetone-d6, δ): 3.84 (s, 3H), 6.92 (d, J = 9.1 Hz, 2H), 8.09 (d, J = 9.1 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d6, δ): 55.7 (*C*H$_3$), 113.8 (*C*H), 131.7 (*C*H), 135.4 (*C*), 163.4 (*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): –0.08 (q, J = 49.8 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –145.8 (q, J = 41.8 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_8H_7O_2{}^{10}BF_3$, 202.05330; found, 202.05319.

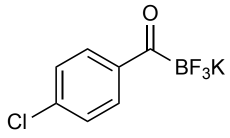
Potassium trifluoro(4-fluorobenzoyl)borate (2c).



2c

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] ^{1}H NMR (396 MHz, acetone-d6, δ): 7.14 (tt, J = 2.2, 9.2 Hz, 2H), 8.15 (dd, J = 5.9, 8.3 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d6, δ): 115.4 (d, $J_{C\text{–}F}$ = 22.0 Hz, *C*H), 132.0 (d, $J_{C\text{–}F}$ = 8.6 Hz, *C*H), 138.7 (*C*), 165.6 (d, $J_{C\text{–}F}$ = 248.9 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): –0.16 (q, J = 49.8 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –117.3 (s), –148.9 (q, J = 45.4 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_7H_4O^{10}BF_4$, 190.03331; found, 190.03320.

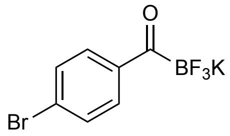
Potassium (4-chlorobenzoyl)trifluoroborate (2d).



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] ^{1}H NMR (396 MHz, acetone-d6, δ): 7.41 (dt, J = 2.1, 8.8 Hz, 2H), 8.06 (d, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d6, δ): 128.8 (*C*H), 131.0 (*C*H), 137.4, 140.7 (*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): –0.20 (q, J = 51.4 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –143.7 (q, J = 49.3 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_7H_4O^{10}BClF_3$, 206.00376; found, 206.00363.

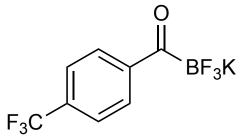
Potassium (4-bromobenzoyl)trifluoroborate (2e).



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] ^{1}H 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). ^{13}C NMR (100 MHz, acetone-d6, δ): 126.1 (*C*), 131.2 (*C*H), 131.8 (*C*H), 141.1 (*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): –0.17 (q, J = 51.4 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –143.9 (q, J = 45.5 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_7H_4O^{10}BBrF_3$, 249.95325; found, 249.95332.

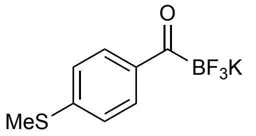
Potassium trifluoro[4-(trifluoromethyl)benzoyl]borate (2f).



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**. ^{1}H NMR (396 MHz, acetone-d6, δ): 7.73 (d, J = 7.1 Hz, 2H), 8.21 (d, J = 8.3 Hz, 2H). ^{13}C NMR (100 MHz, acetone-d6, δ): 125.7 (*C*H), 129.7 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.19 (q, J = 51.0 Hz). ^{19}F NMR (372 MHz, acetone-d6, δ): –62.0 (s), –143.97 (q, J = 49.2 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_8H_4O^{10}BF_6$, 240.03012; found, 240.03016.

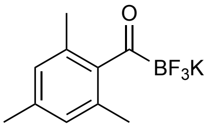
Potassium trifluoro[4-(methylthio)benzoyl]borate (2g).



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-d6, 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-d6, δ): 14.8 (*C*H$_3$), 125.4 (*C*H), 130.0 (*C*H), 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-d6, δ): –0.10 (q, *J* = 52.2 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –144.44 (q, *J* = 45.5 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_8H_7O^{10}BF_3S$, 218.03046; found, 218.03021.

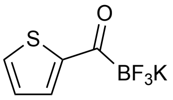
Potassium trifluoro(2,4,6-trimethylbenzoyl)borate (2h).



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-d6, δ): 1.98 (s, 6H), 2.17 (s, 3H), 6.65 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d6, δ): 18.5 (*C*H$_3$), 20.6 (*C*H$_3$), 127.3 (*C*H), 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-d6, δ): –0.92 (q, *J* = 49.8 Hz). ^{19}F NMR (373 MHz, acetone-d6, 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.

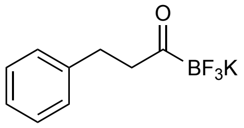
Potassium trifluoro(thiophene-2-carbonyl)borate (2i).



2i

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.[5] ^{1}H NMR (396 MHz, DMSO-d6, δ): 1.98 (s, 6H), 2.17 (s, 3H), 6.65 (s, 2H). ^{13}C NMR (100 MHz, acetone-d6, δ): 128.722 (*C*H), 131.3 (*C*H), 134.6 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.32 (q, *J* = 49.8 Hz). ^{19}F NMR (372 MHz, acetone-d6, δ): –146.03 (q, *J* = 45.5 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_5H_3O^{10}BF_3S$, 177.99916; found, 177.99902.

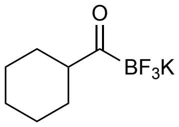
Potassium trifluoro(3-phenylpropanoyl)borate (2j).



2j

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.[4] ^{1}H NMR (396 MHz, acetone-d6, δ): 2.73 (s, 4H), 7.09–7.27 (m, 5H). ^{13}C NMR (100 MHz, acetone-d6, δ): 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. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.91 (q, J = 52.2 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.6 (q, J = 49.2 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_9H_9O^{10}BF_3$, 200.07403; found, 200.07387.

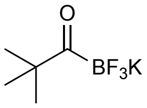
Potassium cyclohexanecarbonyl trifluoroborate (2k).



2k

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-d6, δ): 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). ^{13}C NMR (100 MHz, acetone-d6, δ): 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. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.86 (q, J = 55.0 Hz). ^{19}F NMR (372 MHz, acetone-d6, δ): –147.7 (q, J = 53.1 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_7H_{11}O^{10}BF_3$, 178.08968; found, 178.08940.

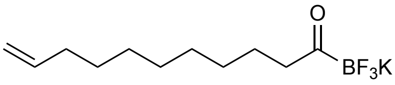
Potassium trifluoro(pivaloyl)borate (2l).



2l

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-d6, δ): 1.01 (s, 9H). ^{13}C NMR (99 MHz, acetone-d6, δ): 25.6 (CH$_3$), 44.1 (CH$_3$). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.69 (q, J = 54.7 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –144.1 (q, J = 53.1 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_5H_9O^{10}BF_3$, 152.07403; found, 152.07371.

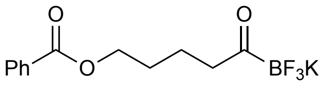
Potassium trifluoro(undec-10-enoyl)borate (2m).



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**. ^{1}H 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). ^{13}C NMR (100 MHz, DMSO-d6, δ): 22.2 (CH_2), 28.3 (CH_2), 28.6 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 29.3 (CH_2), 33.2 (CH_2), 44.2 (CH_2), 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-d6, δ): –0.95 (q, J = 54.3 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.95 (q, J = 49.4 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{11}H_{19}O^{10}BF_3$, 234.15229; found, 234.15230.

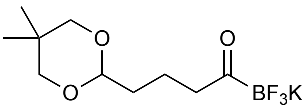
Potassium [5-(benzoyloxy)pentanoyl]trifluoroborate (2n).



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**. ^{1}H 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). ^{13}C NMR (100 MHz, acetone-d6, δ): 21.3 (CH_3), 125.8 (CH), 130.0 (CH), 131.7 (CH), 132.1 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.45 (q, J = 52.3 Hz). ^{19}F NMR (372 MHz, acetone-d6, δ): –144.98 (q, J = 49.3 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{12}H_{13}O_3{}^{10}BF_3$, 272.09516; found, 272.09512.

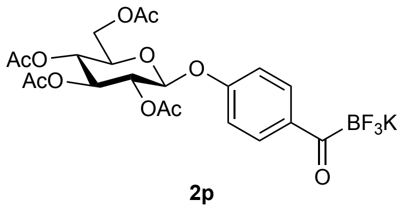
Potassium [4-(5,5-dimethyl-1,3-dioxan-2-yl)butanoyl]trifluoroborate (2o).



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**. ^{1}H 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). ^{13}C NMR (100 MHz, acetone-d6, δ): 17.9 (CH_2), 22.0 (CH_3), 23.4 (CH_3), 30.7 (C), 35.7 (CH_2), 44.9 (C), 77.5 (CH_2), 103.1 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.94 (q, J = 56.3 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –149.8 (q, J = 49.2 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{10}H_{17}O_3{}^{10}BF_3$, 252.12646; found, 252.12656.

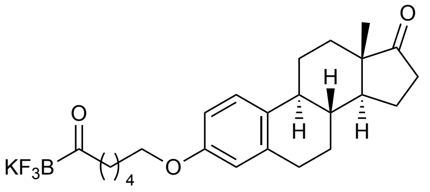
Potassium trifluoro(4-{[(2S,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yl]oxy}benzoyl)borate (2p).



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**. ^{1}H 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), 5.16 (t, *J* = 8.9 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). ^{13}C NMR (100 MHz, acetone-d6, δ): 20.6 (*C*H$_3$), 20.7 (*C*H$_3$), 62.8 (*C*H$_2$), 69.3 (*C*H), 72.0 (*C*H), 72.7 (*C*H), 73.4 (*C*H), 98.9 (*C*H), 116.4 (*C*H), 131.3 (*C*H), 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. ^{11}B NMR (127 MHz, acetone-d6, δ): –0.03 (q, *J* = 54.3 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –144.4 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{21}H_{23}O_{11}{}^{10}BF_3$, 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).

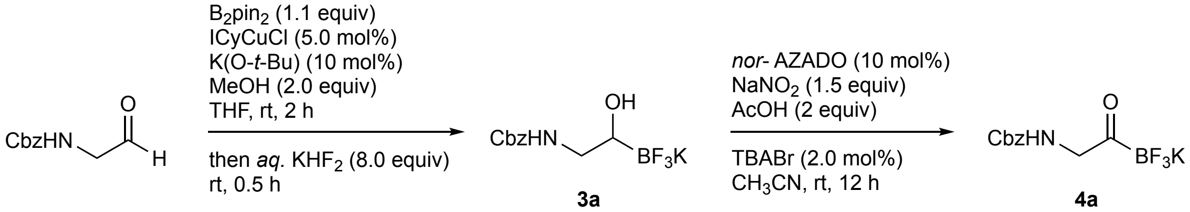


2q

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**. ^{1}H 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). ^{13}C NMR (100 MHz, methanol-d3, δ): 14.3 (*C*H$_3$), 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. ^{11}B NMR (127 MHz, methanol-d3, δ): –0.00 (q, *J* = 10.9 Hz). ^{19}F NMR (372 MHz, methanol-d3, δ): –149.37 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{24}H_{31}O_3{}^{10}BF_3$, 434.23601; found, 434.23719.

Synthesis of α-amino KAT.

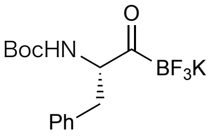
Potassium {[(benzyloxy)carbonyl]glycyl}trifluoroborate (4a).



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 DMF. ^{1}H NMR (396 MHz, DMSO-d6, δ): 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). ^{13}C NMR (99 MHz, DMSO-d6, δ): 46.0 (CH_2), 64.9 (CH_2), 127.7 (*C*H), 128.4 (*C*H), 137.5 (*C*), 156.1 (*C*). ^{11}B NMR (127 MHz, DMSO-d6, δ): 3.34 (brs). ^{19}F NMR (373 MHz, DMSO-d6, δ): –146.7 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{10}H_{12}O_3N^{10}BF_3$, 261.09041; found, 261.09066.

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, CD_3CN, δ): 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). ^{13}C NMR (99 MHz, DMSO-d6, δ): 52.4 (CH_2), 65.1 (CH_2), 127.67 (*C*H), 127.73 (*C*H), 128.4 (*C*H), 137.4 (*C*), 156.1 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadropolar relaxation. ^{11}B NMR (127 MHz, CD_3CN, δ): –1.13 (q, *J* = 49.0 Hz). ^{19}F NMR (373 MHz, CD_3CN, δ): –149.3 (q, J = 41.7 Hz). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{10}H_{10}O_3N^{10}BF_3$, 259.07476; found, 259.07520.

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

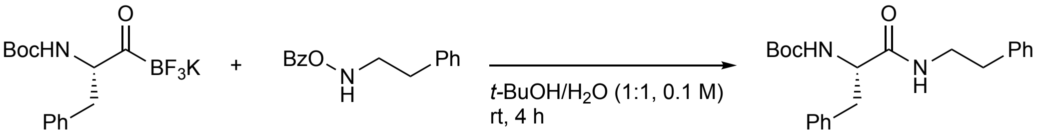


4b

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,δ): 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, 1 H), 5.46 (brd, *J* = 8.3 Hz, 1H), 7.11 (t, *J* = 6.9 Hz, 1H), 7.16–7.32 (m, 4H). ^{13}C NMR (100 MHz, acetone-d6, δ): 28.8 (CH_3), 38.6 (CH_2), 56.8 (*C*H), 68.0 (br, B–*C*), 78.2 (*C*), 126.2 (*C*H), 128.7 (*C*H), 130.5 (*C*H), 141.9 (*C*), 157.3 (*C*). ^{11}B NMR (127 MHz, acetone-d6, δ): 4.44 (brs). ^{19}F NMR (372 MHz, acetone-d6, δ): –143.3* (s), –145.8 (s). HRMS-ESI (m/z): [M–K]$^-$ calcd for $C_{14}H_{20}O_3N^{10}BF_3$, 317.15301; found, 317.15342. Specific rotation of **3b** could not be measured due to low solubility of **3b**.

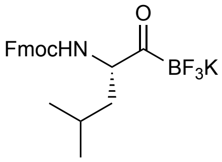
4b (85.2 mg, 0.24 mmol, white solid) was prepared in 80% yield from **3b** (107.4 mg, 0.50 mmol). ^{1}H NMR (396 MHz, acetone-d6, δ): 1.37 (s, 9H), 3.19 (dd, *J* = 4.6, 13.7 Hz, 1H), 3.32 (dd, *J* = 5.7, 13.7 Hz, 1H), 4.62 (q, *J* = 5.9 Hz, 1H), 5.41 (brd, *J* = 5.9 Hz, 1H), 7.06–7.23 (m, 5H). ^{13}C NMR (100 MHz, acetone-d6, δ): 28.7 ($\mathit{C}H_3$), 35.7 ($\mathit{C}H_2$), 62.7 (*C*H), 78.4 (*C*), 126.6 (*C*H), 128.5 (CH), 130.9 (CH), 139.3 (C), 155.8 (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): –0.30 (q, *J* = 45.8 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –147.2 (d, J = 56.9 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{14}H_{18}O_3N^{10}BF_3$, 315.13736; found, 315.13798. $[\alpha]_D^{19.7}$ +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: t_R = 11.17 min., (L)-isomer: t_R = 13.24 min.



4b **S4** **S5**

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



4c

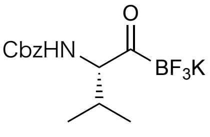
N-Fmoc leucinal (1.81 g, 5.36 mmol) was prepared in 54% yield from *N*-Boc-Phe-OH (3.53 g, 10 mmol) according to the procedure for the synthesis of *N*-Boc phenylalaninal. The NMR spectra data was consistent with those reported in the literature.[11] The ee of value of Fmoc-leucinal was determined by HPLC analysis of the corresponding alcohol after reduction with $NaBH_4$. Daicel CHIRALPAK® OJ-3, 2-PrOH/Hexane = 15.0/85.0, 0.5 mL/min, 40 °C, (D)-isomer: t_R = 22.05 min., (L)-isomer: t_R = 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**. ^{1}H 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). ^{13}C NMR (100 MHz, DMSO-d6, δ): 22.1* ($\mathit{C}H_3$), 22.3 ($\mathit{C}H_3$), 23.8 ($\mathit{C}H_3$), 24.0* ($\mathit{C}H_3$), 24.5 (*C*H), 24.6* (*C*H), 41.1 ($\mathit{C}H_2$), 46.9 (*C*H), 52.8 (*C*H), 53.5* (*C*H), 65.1 ($\mathit{C}H_2$), 67.9 (br, B–*C*), 120.1 (*C*H), 125.3* (*C*H), 125.4 (*C*H), 127.06 (*C*H), 127.11* (*C*H), 127.6 (*C*H), 140.7 (*C*), 144.0 (*C*), 144.2* (*C*), 155.8* (*C*), 156.1 (*C*). ^{11}B NMR (127 MHz, DMSO-d6, δ): 3.64 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –146.2 (s), –143.9* (s). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{21}H_{24}O_3N^{10}BF_3$, 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 Et_2O. ^{1}H NMR (392 MHz, acetone-d6, 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-d6, δ): 22.0 (CH_3), 24.1 (CH_3), 25.6 (*C*H), 39.9 (CH_2), 48.1 (*C*H), 61.1 (*C*H), 66.9 (CH_2), 120.8 (*C*H), 126.2 (d, *J* = 3.8 Hz, *C*H), 127.9 (*C*H), 128.5 (*C*H), 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-d6, δ): –0.19 (q, *J* = 56.7 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –146.9 (s). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{21}H_{22}O_3N^{10}BF_3$, 403.16866; found, 403.16919. $[\alpha]_D^{22.6}$ +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 {[(benzyloxy)carbonyl]-L-valyl}trifluoroborate (4d).



4d

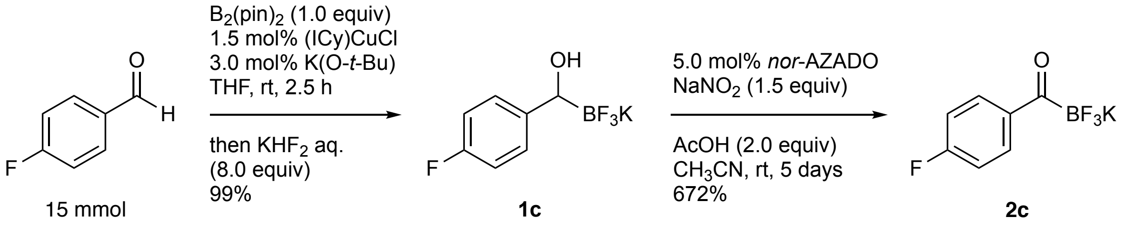
N-Cbz valinal was prepared in 48% yield over two steps from *N*-Boc-Phe-OH according to the reported procedure.[12] The spectra data was consistent with those reported in the literature.[13] **3d** (301 mg, 0.88 mmol) was prepared in 50% yield from *N*-Cbz valinal (235 mg, 1.76 mmol) according to the procedure for the synthesis of **1a**. ^{1}H NMR (396 MHz, acetone-d6, 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-d6, δ): 18.2 (CH_3), 20.9 (CH_3), 29.5 (*C*H), 59.2 (*C*H), 64.5 (CH_2), 127.3 (*C*H), 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-d6, δ): 4.03 (brs). ^{19}F NMR (373 MHz, acetone-d6, δ): –147.8 (s). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{13}H_{18}O_3N^{10}BF_3$, 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-d6, 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-d6, δ): 16.6 (CH_3), 21.2 (CH_3), 29.0 (*C*H), 66.5 (CH_2), 67.2 (*C*H), 128.6 (*C*H), 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-d6, δ): –1.27 (q, *J* = 50.6 Hz). ^{19}F NMR (373 MHz, acetone-d6, δ): –148.0 (d, J = 57.0 Hz). HRMS-ESI (m/z): $[M–K]^-$ calcd for $C_{13}H_{16}O_3N^{10}BF_3$, 301.12171; found, 301.12202. $[\alpha]_D^{18.2}$ +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.

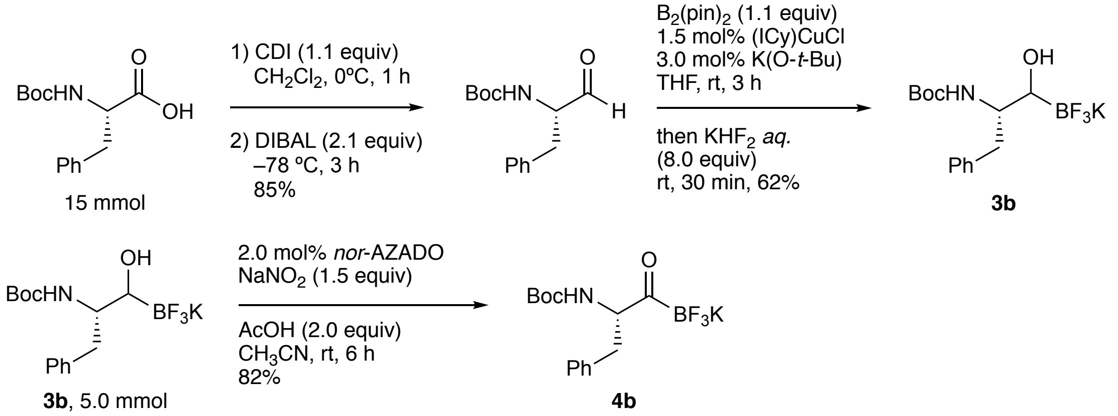
Gram-scale synthesis of 2c and 6b.

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 $NaNO_2$ (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, CH_3CN (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 Et_2O 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.[9] **3b** (3.08 g, 8.63 mmol) was prepared in 62% yield from 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 Et_2O, **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 $NaNO_2$ (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, CH_3CN (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 Et_2O/hexane to give KAT **4b** (1.45 g, 82%) as a white solid.

References

20) Scharnagl, F. K.; Bose, S. K.; Marder, T. B.; *Org. Biomol. Chem*. **2017**, *15*, 1738. b) Noda, H.; Bode, J. W. *Org. Biomol. Chem*. **2016**, *14*, 16.

21) Molander, G. A.; Raushel, J.; Ellis, N. M. *J. Org. Chem*. **2010**, *75*, 4304.

22) a) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem., Int. Ed*. **2012**, *51*, 5683; b) Noda, H.; Bode, J. W. *Chem. Sci.* **2014**, *5*, 4328; c) Noda, H.; Bode, J. W. *J. Am. Chem. Soc*. **2015**, *137*, 3958.

23) a) Shiro, T.; Schuhmacher, A.; Jackl, M. K.; Bode, J. W. *Chem. Sci.* **2018**, *9*, 5191; b) Jackl, M. K.; Schuhmacher, A.; Shiro, T.; Bode, J. B. *Org. Lett.* **2018**, *20*, 4044.

24) a) Taguchi, J.; Ikeda, T.; Takahashi, R.; Sasaki, I.; Ogasawara, Y.; Dairi, T.; Kato, N.; Yamamoto, Y.; Bode, J. W.; Ito, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 13847; b) Lepage, M. L.; Lai, S.; Peressin, N.; Hadjerci, R.; Patrick, B. O.; Perrin D. M. *Angew. Chem*., *Int. Ed.* **2017**, *56*, 15257.

25) He, Z.; Trinchera, P.; Adachi, S.; St Denis, J. D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11092.

26) Taguchi, J.; Takeuchi, T.; Takahashi, R.; Ito, H. *To be submitted.*

27) a) D. S. Laitar, E. Y. Tsui, J. P. Sadighi, J. Am. Chem. Soc. 2006, 128, 11036; b) G. A. Molander, S. R. Wisniewski J. Am. Chem. Soc. 2012, 134, 1685; c) K. Kubota, E. Yamamoto, H. Ito, J. Am. Chem. Soc. 2015, 137, 420; d) B. Carry, L. Zhang, M. Nishiura, Z. Hou, Angew. Chem., Int. Ed. 2016, 55, 6257.

28) a) G. A. Molander, M. Ribagorda J. Am. Chem. Soc. 2003, 125, 11148; b) G. A. Molander, R. Figueroa Org. Lett. 2006, 8, 75; c) G. A. Molander, D. E. Petrillo, J. Am. Chem. Soc. 2006, 128, 9634; d) G. A. Molander, D. J. Cooper J. Org. Chem. 2007, 72, 3558; e) E. P. Gillis, M. D. Burke, J. Am. Chem. Soc. 2008, 130, 14084; f) D. S. Kim, K. Bolla, S. Lee, J. Ham, Tetrahedron 2011, 67, 1062.

29) Albright, J. D.; Goldman L. *J. Am. Chem. Soc*. **1965**, *87*, 4214.

30) Hayashi, M.; Sasano, Y.; Nagasawa, S.; Shibuya, M.; Iwabuchi, Y. *Chem. Pharm. Bull*. **2011**, *59*, 1570.

31) Ivkovic, J.; Lembacher-Fadum, C.; Breinbauer, R. *Org. Biomol. Chem.* **2015**, *13*, 10456.

32) Santoro, O.; Collado, A.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. *Chem. Commun.* **2013**, *49*, 10483.

33) Erös, G.; Kushida, Y.; Bode, J. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 7604.

References

34) Scharnagl, F. K.; Bose, S. K.; Marder, T. B.; *Org. Biomol. Chem*. **2017**, *15*, 1738. b) Noda, H.; Bode, J. W. *Org. Biomol. Chem*. **2016**, *14*, 16.

35) Molander, G. A.; Raushel, J.; Ellis, N. M. *J. Org. Chem*. **2010**, *75*, 4304.

36) a) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem., Int. Ed*. **2012**, *51*, 5683; b) Noda, H.; Bode, J. W. *Chem. Sci.* **2014**, *5*, 4328; c) Noda, H.; Bode, J. W. *J. Am. Chem. Soc*. **2015**, *137*, 3958.

37) a) Shiro, T.; Schuhmacher, A.; Jackl, M. K.; Bode, J. W. *Chem. Sci.* **2018**, *9*, 5191; b) Jackl, M. K.; Schuhmacher, A.; Shiro, T.; Bode, J. B. *Org. Lett.* **2018**, *20*, 4044.

38) a) Taguchi, J.; Ikeda, T.; Takahashi, R.; Sasaki, I.; Ogasawara, Y.; Dairi, T.; Kato, N.; Yamamoto, Y.; Bode, J. W.; Ito, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 13847; b) Lepage, M. L.; Lai, S.; Peressin, N.; Hadjerci, R.; Patrick, B. O.; Perrin D. M. *Angew. Chem*., *Int. Ed.* **2017**, *56*, 15257.

39) He, Z.; Trinchera, P.; Adachi, S.; St Denis, J. D.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 11092.

40) Taguchi, J.; Takeuchi, T.; Takahashi, R.; Ito, H. *To be submitted.*

41) a) D. S. Laitar, E. Y. Tsui, J. P. Sadighi, J. Am. Chem. Soc. 2006, 128, 11036; b) G. A. Molander, S. R. Wisniewski J. Am. Chem. Soc. 2012, 134, 1685; c) K. Kubota, E. Yamamoto, H. Ito, J. Am. Chem. Soc. 2015, 137, 420; d) B. Carry, L. Zhang, M. Nishiura, Z. Hou, Angew. Chem., Int. Ed. 2016, 55, 6257.

42) a) G. A. Molander, M. Ribagorda J. Am. Chem. Soc. 2003, 125, 11148; b) G. A. Molander, R. Figueroa Org. Lett. 2006, 8, 75; c) G. A. Molander, D. E. Petrillo, J. Am. Chem. Soc. 2006, 128, 9634; d) G. A. Molander, D. J. Cooper J. Org. Chem. 2007, 72, 3558; e) E. P. Gillis, M. D. Burke, J. Am. Chem. Soc. 2008, 130, 14084; f) D. S. Kim, K. Bolla, S. Lee, J. Ham, Tetrahedron 2011, 67, 1062.

43) Albright, J. D.; Goldman L. *J. Am. Chem. Soc*. **1965**, *87*, 4214.

44) Hayashi, M.; Sasano, Y.; Nagasawa, S.; Shibuya, M.; Iwabuchi, Y. *Chem. Pharm. Bull*. **2011**, *59*, 1570.

45) Ivkovic, J.; Lembacher-Fadum, C.; Breinbauer, R. *Org. Biomol. Chem.* **2015**, *13*, 10456.

46) Santoro, O.; Collado, A.; Slawin, A. M. Z.; Nolan, S. P.; Cazin, C. S. J. *Chem. Commun.* **2013**, *49*, 10483.

47) Erös, G.; Kushida, Y.; Bode, J. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 7604.

List of Pudlications

Chapter 1

Catalyst-Controlled Regiodivergent C–H Borylation of Multifunctionalized Heteroarenes Using Iridium Complexes
Sasaki, I.; Taguchi, J.; Hiraki, S.; Ito, H.; Ishiyama, T.
Chem. Eur. J. **2015***, 21*, 9236–9241.

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.
Chem. Asian J. **2016**, *11*, 1400–1405.

Chapter 3

Synthesis of Acylborons by Ozonolysis of Alkenylboronates: Preparation of an Enantioenriched Amino Acid Acylboronate
Taguchi, J.; Ikeda, T.; Takahashi, R.; Sasaki, I.; Ogasawara, Y.; Dairi, T.; Kato, N.; Yamamoto, Y.; Bode, J. W.; Ito, H.
Angew. Chem., Int. Ed. **2017**, *56*, 13847–13851.

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
Sasaki, I.; Ikeda, T.; Amou, T.; Taguchi, J.; Ito, H.; Ishiyama, T.
Synlett **2016**, *27*, 1582–1586.

Acknowledgements

The studies presented in this thesis have been carried out under the direction of Professor Doctor Hajime Ito at the Faculty of Engineering of Hokkaido University during 2013–2019. The studies are concerned with the development of Iridium-catalyzed C–H borylation reactions and the development of novel method to synthesize acylboron compounds.

At first and foremost the author would like to express his deepest gratitude to Prof. Hajime Ito, whose constant guidance and enormous supports and insightfull foments we invaluable throughout this study. The author particularly indebted to Prof. Tatsuo Ishiyama for his helpful advice and stimulating discussions during the cource of his study. The author would also like to thank Prof. Jeffery W. Bode for his kind advise to our collaboration research. The author also would like to thank Prof. Ikuo Sasaki for his kind advise and heartly encouragement during the course of this study. The author would also like to thank Prof. Tomohiro Seki and Dr. Mingoo Jin for their help analyzing the X-ray crystallography data. The author would also like to thank Prof. Yasunori Yamamoto and Prof. Tohru Dairi, Prof. Yasushi Ogasawara for their help analyzing the HPLC data. The author is grateful to thank Prof. Eiji Yamamoto, Prof. Koji Kubota and other members of the Prof. Ito's research group for their good collaboration and for providing a good working atmosphere. This work supported by Reserch Fellowships of the Japan Society for the Promotion of Science for Young Scientists.

Jumpei Taguchi

Graduate school of chemical sciences and engineering
Hokkaido Univerity
2019