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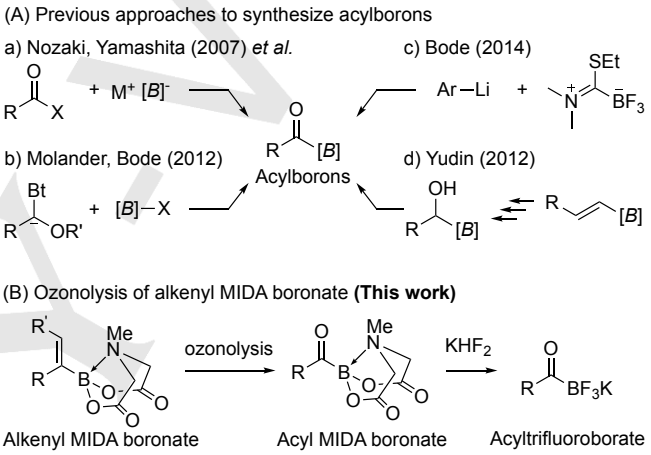
Synthesis of Acylborons by Ozonolysis of Alkenylboronates: Preparation of an Enantioenriched Amino Acid Acylboronate

Jumpei Taguchi,[a] Toshiki Ikeda,[a] Rina Takahashi,[a] Ikuo Sasaki,[b] Yasushi Ogasawara,[a] Tohru Dairi,[a] Naoya Kato,[a] Yasunori Yamamoto,[a] Jeffrey W. Bode*[c] and Hajime Ito*[a]

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

Acylborons are studied enthusiastically due to their unique reactivity.[1,2,3] In 2012, Bode and Molander reported rapid and highly chemoselective amide-bond forming reaction between potassium acyl trifluoroborates (KATs) and hydroxylamines that is called KAT ligation.[2a] This reaction proceeds without any condensation reagents or catalysts under mild conditions at dilute concentrations in aqueous media at room temperature, and tolerates unprotected functional groups. Since these features are attractive for bioconjugation, KAT ligation has been applied to site-specific functionalization of unprotected peptides.[2b,2c,2d] Conjugation between peptides consisting of natural amino acids with KAT ligation has, however, not been achieved. To accomplish this, a route to α-amino acylborons is required, but currently there has been no reported preparations of α-amino acylborons.

Herein, we report a concise acylboron synthesis by the ozonolysis of alkenyl MIDA (*N*-methyliminodiacetic acid) boronates (Scheme 1B). 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,[4] and they are transformed to MIDA boronates easily by Burke's method;[5] and (b) ozonolysis can be conducted under mild 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 1. (A) Previous approaches to synthesize acylborons. (B) Acylboron synthesis by ozonolysis of alkenyl MIDA boronate. Bt = benzotriazole, MIDA = *N*-methyliminodiacetic acid.

There are only four known approaches for preparation of acylborons (Scheme 1A). First one is the reaction of a boryl metal species and carbonyl electrophile such as acyl chlorides (Scheme 1A-a).[6a–6d] In the second approach, acyl anion equivalents trap boryl electrophiles to afford acylborons (Scheme 1A-b).[3e,6e] In the third, Bode developed a reagent derived from thioformamide that acts as electrophilic KAT equivalent in 2014. This reagent reacts with aryl or heteroaryl lithium reagent to give KAT in one step (Scheme 1A-c).[6f] In each of these three approaches, a highly reactive and unstable nucleophile, such as boryl metal species or organolithium compounds are required and thus they exhibit low functional group tolerance. The only exception is the Pd-catalyzed borylation reaction of acyl chlorides with a boryl-zinc reagent reported by Aldridge in 2015, although access to the boron species is challenging.[6d] Yudin developed a conceptually new acylboron synthesis containing Dess-Martin oxidation of α-hydroxy boronate. This method proceeds under relatively mild condition and is the only reported procedure for α-heteroatom substituted acylboron, such as α-bromo acylboron or oxalyl boron, but this approach requires multi-step reaction from alkenylboronate (Scheme 1A-d).[3a] Despite these advances, it has been difficult to prepare more functionalized acylboron such as α-amino acylboron, which contains an amino-substituted stereocenter at the α-position. Furthermore, one great concern

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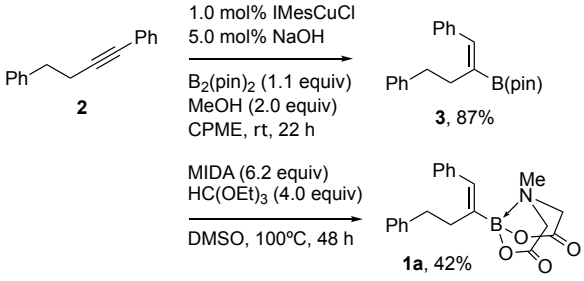
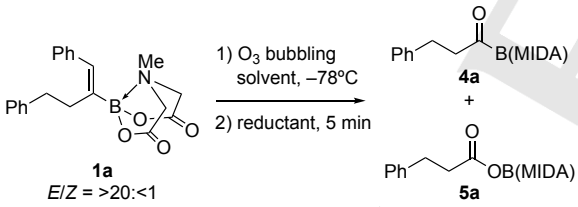
for application of KAT ligation to peptide synthesis is there is no information on the configurational stability of optically active α-amino acylboron in the ligation step.



Scheme 2. Preparation of alkenyl MIDA boronate **1a**.

Based on the known tolerance of MIDA boronates to ozonolysis, we sought to employ alkenyl MIDA boronates as precursors to KATs.[7] We selected **1a** as a model compound, as it can be easily prepared by Cu(I)-catalyzed protoboration of alkyne **2**,[4c,4e] followed by conversion of pinacol boronate **3** to MIDA boronate **1a**, according to a modified procedure based on the Burke's method (Scheme 2).[5c] When the ozonolysis of **1a** was conducted in acetone at –78ºC, 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 addition to **4a**.[8] The ratio of **4a** and **5a** was determined by ^{11}B NMR as 87:13.[9] The ozonolysis of potassium alkenyl trifluoroborate was also investigated; however, the crude solution contained a complex mixture and we could not detect the desired acyl trifluoroborate. To improve selectivity of **4a** over **5a**, we investigated the reaction solvent. Ozonolysis in acetonitrile or EtOAc decreased the ratio of **4a**:**5a** (entry 2: 70:30, and entry 3: 56:44). 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).[10]

Table 1. Optimization of reaction conditions[a].



Entry	Solvent	Reductant	Yield (%)[b]	**4a**:**5a** Ratio[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, –78ºC. b) Me_2S (excess), acetone, –78ºC, 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, –78ºC.

We next investigated the scope of this reaction with respect to the alkenyl MIDA boronates. The substrates were prepared from alkynes according to the procedure depicted in Scheme 2. The ozonolysis of **1b** proceeded in high yield with high selectivity (Table 2, entry 1: 87%, 94:6), and ozonolysis of **1c**, which had a sterically hindered secondary alkyl group also proceeded in high yield with high selectivity (entry 2: 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 (entry 3: 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. 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 (entry 8: 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 substrates bearing exomethylene moiety can also be employed for this reaction.

Next, synthesis of α-amino alkenyl boronates were investigated. 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 analog in good yields and high selectivity (entries 9–12, **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 1).

We applied this protocol to the synthesis of an optically active, *L*-alanine type acylboron (Scheme 3). Optically 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.[4f] Exchange of the boron ligands afforded alkenyl MIDA boronate (*S*)-**1n** in 39% yield. Ozonolysis of (*S*)-**1n** gave alanine acylboron analog (*S*)-**4n** in high yield with high selectivity (93%, >95:<5) and high enantiospecificity (99% ee).[11] This compound would be difficult

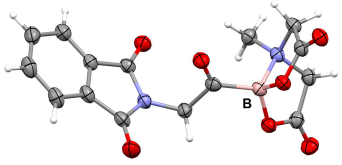


Figure 1. Crystal Structure of **4j**·CH_3CN. CH_3CN was omitted for clarification.

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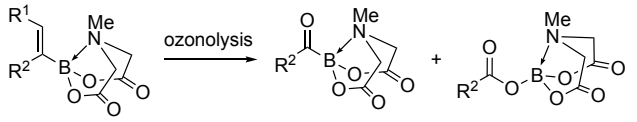
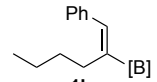
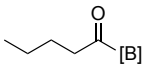
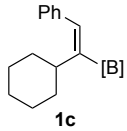
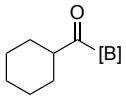
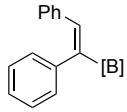
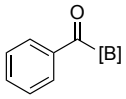
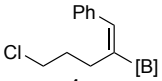
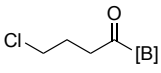
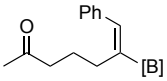
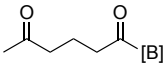
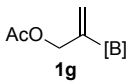
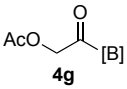
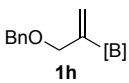
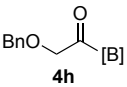
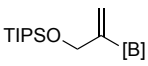
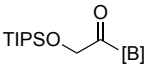
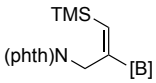
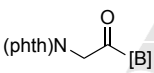
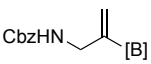
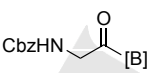
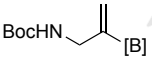
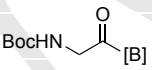
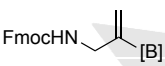
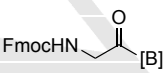
Table 2. Substrate scope.[a]



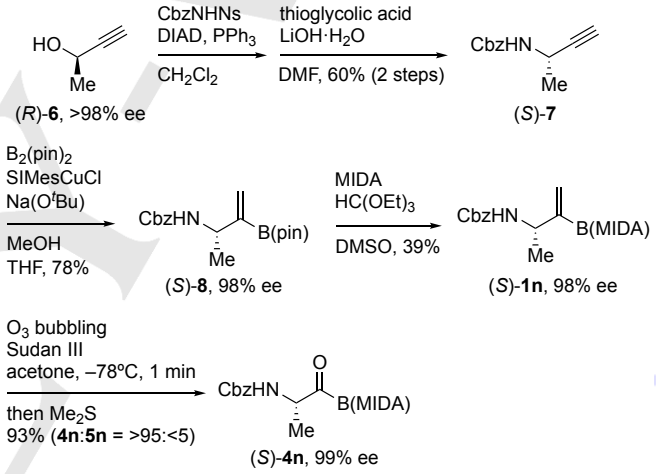
1b–1m **4b–4m** **5b–5m**

entry	substrate	product	condition	yield (%)[b]	**4**:**5** ratio[c]
1	 **1b**	 **4b**	A	87	94:6
2	 **1c**	 **4c**	A	84	>95:<5
3	 **1d**	 **4d**	A B	- 90	64:36 >95:<5
4	 **1e**	 **4e**	A	94	84:16
5	 **1f**	 **4f**	A B	88 88	85:15 >95:<5
6	 **1g**	 **4g**	A B	85 81	93:7 95:5
7	 **1h**	 **4h**	A B	84 80	82:18 85:15
8	 **1i**	 **4i**	A	66	74:26
9	 **1j**	 **4j**	A	90	>95:<5
10	 **1k**	 **4k**	A	88	90:10
11	 **1l**	 **4l**	A	91	95:5
12[d]	 **1m**	 **4m**	A	65	93:7

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

to synthesize by conventional methods because their harsh conditions will cause racemization at α-position.

α-Amino acylboron compounds could potentially be used as a building block in peptide conjugation using KAT ligation. As a preliminary experiment 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 4).[3g] According to the reported procedure, MIDA-protected **4m** could easily be converted to potassium acyl trifluoroborate **9** in 85% yield (Scheme 4A).[2c] 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 4B). The diastereomeric ratio of **14** was 98:2, indicating that α-amino acylborons have configurational stability under the ligation conditions.



Scheme 3. Synthesis of alanine type acyl MIDA boronate (*S*)-**4n**.

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, 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 was achieved. The development of a method to install acylborons onto the *C*-terminus of protein will be a great step in achieving protein-protein conjugation by KAT ligation.

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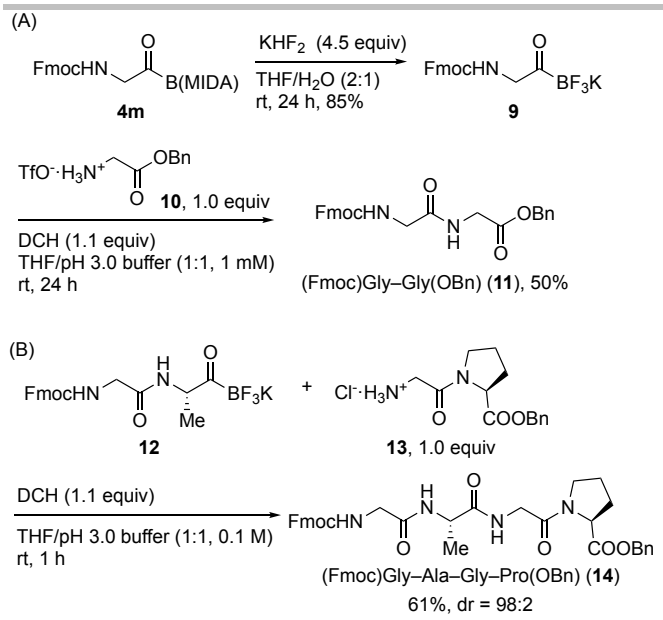

Scheme 4. Oligopeptide synthesis between α-amino KAT and amino acid using chlorinating agent in water. (A) Dipeptide synthesis in highly diluted solution. (B) Preservation of stereochemistry in tetrapeptide synthesis.

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Keywords: Amino acids · Boron · Chemical ligation · MIDA boronate · Ozonolysis

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[8] In 2012, Yudin has also reported that acyloxy MIDA boronate could be synthesized by the oxidation of acyl MIDA boronates using *m*-CPBA (See ref. 3a)

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

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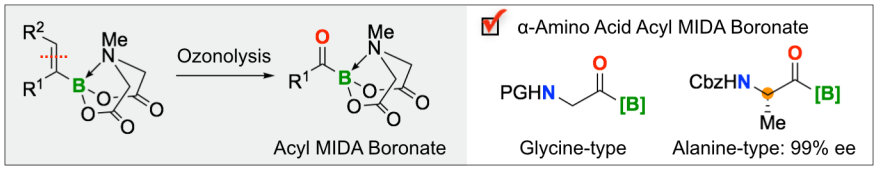

Highly functionalized acylborons were easily prepared by ozonolysis of alkenyl MIDA boronates. The first synthesis of α-amino acylborons including the enantiopure alanine-type acylboron was achieved using this method. They are essential for the protein–protein conjugation by KAT ligation. Oligopeptide synthesis using α-amino acylborons revealed that peptide-bond-formation proceed even in highly diluted aqueous medium and alanine-type acylboron is configurationally stable under ligation condition.

Jumpei Taguchi, Toshiki Ikeda, Ikuo Sasaki, Rina Takahashi, Yasushi Ogasawara, Tohru Dairi Naoya Kato Yasunori Yamamoto, Jeffrey W. Bode and Hajime Ito**

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