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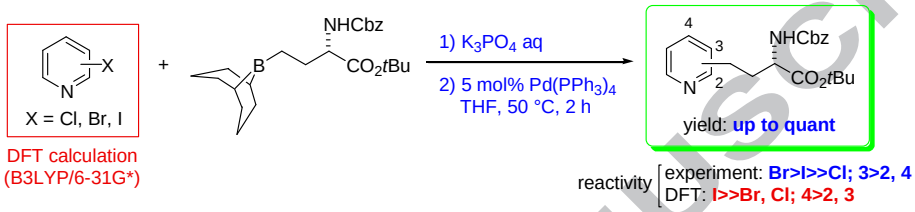

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Suzuki-Miyaura cross-coupling reaction of monohalopyridines and L-aspartic acid derivative

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ABSTRACT

Suzuki-Miyaura cross-coupling reaction of halogenated pyridines and a borated L-aspartic acid derivative was conducted. The reactivity of chloro-, bromo-, and iodo-pyridines with substituents at the C2, C3, and C4 positions was investigated. Electron density of halogenated pyridines was also estimated by density functional theory (DFT) calculations. The order of experimental yield of halogen substituents was Br>I>>Cl and C3>C2, C4 whereas the DFT results indicated the reactivity order as I>>Br, Cl and C4>C2, C3. Optimized experimental conditions (3-bromopyridine) afforded the coupling product quantitatively.

Introduction

Suzuki-Miyaura cross-coupling is a powerful C-C bond-forming reaction.[1,2] Despite its usefulness, few reports exist that describe Suzuki-Miyaura cross-coupling reaction between pyridine rings and borated amino acids. Expanding the scope of the cross-coupling reaction could lead to a practical method for preparation of naturally occurring pyridinium amino acids, such as the chronic obstructive pulmonary disease (COPD) biomarkers desmosine (**1**) and isodesmosine (**2**),[3-5] as illustrated in Figure 1.

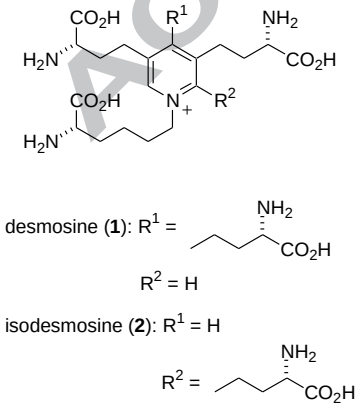

Figure 1. Structures of desmosine and isodesmosine.

In 2014, we reported Negishi cross-coupling reaction between monohalopyridines and a protected L-aspartic acid.[6] The results showed that reactivity of the halogen substituents on the pyridine was in the order of I>Br>>Cl but was not related to the position.[6] However, a theoretical explanation of these results has not been reported nor have other cross-coupling reactions between pyridine rings and amino acid derivative been investigated. The present report describes Suzuki-Miyaura cross-coupling reaction of monohalopyridines and a protected amino acid along with the optimization of reaction conditions. The effect of halogen substituents (Cl, Br, I) at different positions (C2, C3, C4) on the pyridine ring on the reaction was investigated experimentally and calculationally.

Results and discussion

For study of the Suzuki-Miyaura cross-coupling reaction, *tert*-butyl-20-(*S*)-benzyloxycarbonylamino-but-19-enolate (**3**)[7] was chosen as the amino acid substrate. Segment **3** was synthesized from commercially available *N*-carbobenzoxy-L-methionine (**S1**) in three steps in overall 19% yield (see Supporting Information). Optical rotation of synthetic **3** ($[\alpha]_D^{20}$ -15.6) was good agreement with reported one ($[\alpha]_D^{20}$ -16.5).[7] The olefin segment **3** was prepared for hydroboration before the coupling reaction.

Reaction conditions of Suzuki-Miyaura cross-coupling between 2.3 equivalents of borated segment (**4**) and 3-bromopyridine (**5**) were investigated (Table 1). Reactions were conducted after hydroboration of olefin **3**, which was prepared with 4.6 equivalents of 9-borabicyclo[3.3.1]nonane (9-BBN) solution in tetrahydrofuran (THF).[8] First, [1,1'-

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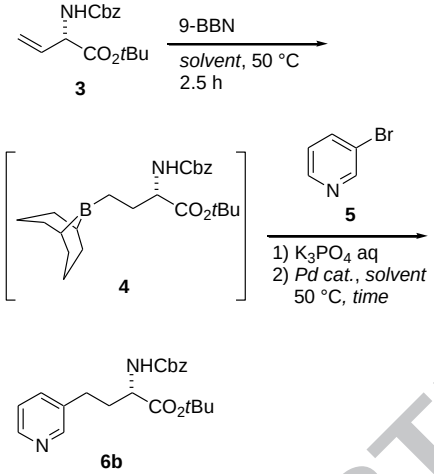
bis(diphenylphosphino)ferrocene]dichloropalladium (II) [Pd(dppf)Cl_2] or tetrakis(triphenylphosphine)palladium (0) [Pd(PPh_3)$_4$] was used as the catalyst in *N*,*N*-dimethylformamide (DMF) (entries 1 and 2, Table 1).[9] Reactions proceeded for 20 h to afford the coupling product (**6b**) in 15% and 16% yield, respectively. These unsatisfying yields might be due to isomerization of the olefin, caused by DMF. When the solvent was changed to THF, the yield of **6b** improved dramatically to quantitative (entry 3, Table 1). However, when [1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium (II) dichloride (Pd-PEPPSI-IPr)[10] and a combination of tris(dibenzylideneacetone)dipalladium (0) [Pd_2(dba)$_3$] and tri(2-furyl)phosphine [P(2-furyl)$_3$] were used in THF, yields were 0% and 51%, respectively (entries 4 and 5, Table 1). The coupling product **6b** could be obtained almost quantitatively, even if reaction time was shortened to 4 h or 2 h (entries 6 and 7, Table 1). The yield of entry 6 was the same using either K_3PO_4 or K_2CO_3 as the base (data not shown).

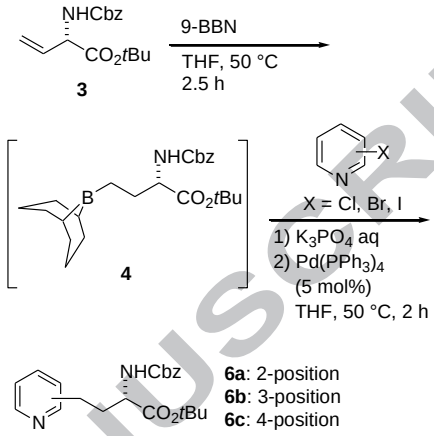
Table 1. Investigation of Suzuki-Miyaura cross-coupling reaction with **4**.



Entry	Solvent	Pd cat. (mol %)	Time (h)	Yield (%)
1	DMF	Pd(dppf)Cl_2	20	15
2	DMF	Pd(PPh_3)$_4$ (5)	20	16
3	THF	Pd(PPh_3)$_4$ (5)	20	Quant
4	THF	Pd-PEPPSI-IPr (5)	20	0
5	THF	Pd_2(dba)$_3$ (2.5), P(2-furyl)$_3$(10)	20	51
6	THF	Pd(PPh_3)$_4$ (5)	4	99
7	THF	Pd(PPh_3)$_4$ (5)	2	Quant

Using the optimized conditions (entry 7, Table 1), reactivity of different halogenated pyridines with chloro, bromo, and iodo substituents at the C2, C3, and C4 positions of the pyridine ring was investigated (Table 2). Cross-coupling reaction with 2- and 3-chloropyridine did not provide the desired products (**6a**, **6b**), and starting materials were not recovered (entries 1 and 2, Table 2). In contrast, the coupling product (**6c**) was obtained from 4-chloropyridine in 18% yield (entry 3, Table 2). Reactions of 2- and 3-bromopyridines gave the corresponding products (**6a**, **6b**) in nearly quantitative yields (entries 4 and 5, Table 2). Reaction with 4-bromopyridine resulted in a lower yield (40%) than those for 2- and 3-bromopyridines (entry 6, Table 2). In addition, reactions with 2- and 3-iodopyridines afforded the desired products (**6a**, **6b**) in moderate yields (57% and 80%, respectively) (entries 7 and 8, Table 2). 4-Iodopyridine gave the corresponding product **6c** in a low 27% yield (entry 9, Table 2). Thus, order of reactivity was Br>I>>Cl and C3>C2, C4.

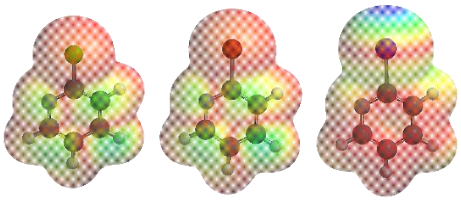
Table 2. Suzuki-Miyaura cross-coupling reaction of **4** and monohalopyridines **6a-c.**



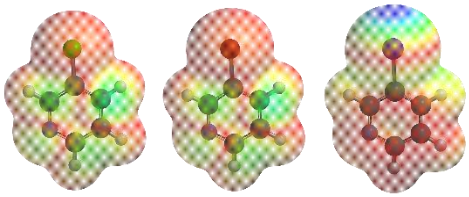
Entry	Position	X	Yield (%)
1	2	Cl	0
2	3	Cl	0
3	4	Cl	18
4	2	Br	98
5[a]	3	Br	Quant
6	4	Br	40
7	2	I	57
8	3	I	80
9	4	I	27

[a] Entry is the same as entry 7 in Table 1

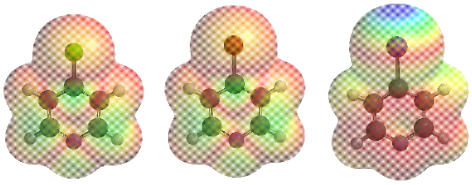
Oxidative addition is often the rate-determining step of a Suzuki-Miyaura cross-coupling reaction,[2] and is affected by C-X bond energy, the HOMO of the palladium species, and the LUMO of the halopyridines.[11] Studies on the LUMO of halopyridines was expected to explain the reactivity of the reaction. Therefore, DFT calculations (B3LYP/6-31G*) were conducted to compute electron density distributions (Figure 2). While iodopyridines were significantly different from other halopyridines, 4-chloropyridine and 4-bromopyridine were only slightly different. These results suggest that the iodopyridines were more reactive because oxidative addition to the bond between pyridine and iodide proceeded easily. Theoretical considerations indicated that reactivity of halogen substituents on the pyridine ring was in the order I>>Br, Cl, and reactivity of the substituent positions was in the order C4>C2, C3. However, the experimental results suggested that 4-bromopyridine and the iodopyridines were so reactive that interfering side reactions inhibited the coupling reactions. In contrast, reaction of 4-chloropyridine proceeded because of the high reactivity of C4-substituted pyridines. Negishi cross-coupling reaction between monohalopyridines and amino acid derivatives demonstrated that experimental reactivity was in the order I>Br>>Cl.[6] The calculation results were consistent with those of the reported Negishi cross-coupling reaction.



(a) 2-Halopyridines (left: 2-chloropyridine; center: 2-bromopyridine; right: 2-iodopyridine)



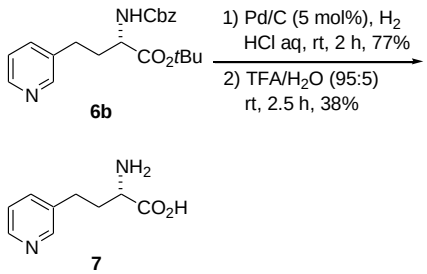
(b) 3-Halopyridines (left: 3-chloropyridine; center: 3-bromopyridine; right: 3-iodopyridine)



(c) 4-Halopyridines (left: 4-chloropyridine; center: 4-bromopyridine; right: 4-iodopyridine)

Figure 2. LUMO maps of monohalopyridines. Compounds (from left to right) are chloropyridines (yellow), bromopyridines (red), and iodopyridines (blue). Blue areas indicate localization of LUMO, resulting in easier oxidative addition.

The antimicrobacterial activities of the coupling product (**6b**) and free amino acid (**7**) against *Escherichia coli b/r* and *Bacillus subtilis* were assessed using the disc diffusion method. Amino acid **7** was prepared from **6b** in two steps (Scheme 1). Both products were dissolved in 1% aq. dimethyl sulfoxide (DMSO) and each disc was loaded with 0.1 mg of the compound. A 1% DMSO solution and 0.1 mg/disc concentration of ampicillin were used as controls. The minimal inhibitory concentration (MIC) assay of the products (**6b**, **7**) was conducted. However, the compounds did not have significant activity against either bacteria (>0.4 mg/mL).



Scheme 1. Preparation of **7**.

Conclusion

Optimization of Suzuki-Miyaura cross-coupling reactions between a borated aspartic acid derivative and a pyridine containing a halogen (Cl, Br, I) at different positions (C2, C3, C4) on the pyridine ring was investigated. 3-Bromopyridine produced a quantitative yield of the coupling product, which was the best yield. Localizations of the LUMO of the monohalopyridines were also determined using DFT calculations. The experimental yield was in the order Br>I>>Cl, C3>C2, C4 whereas the calculated reactivity was in the order of I>>Br, Cl, and C4>C2, C3. These results will be applied to additional reactions to obtain more amino acid derivatives including a pyridine ring.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/...

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Highlights

- Suzuki-Miyaura coupling of halopyridines and boronated amino acid was conducted.
- Protected boronated L-aspartic acid was prepared from protected L-methionine.
- The reaction proceeded quantitatively when using 3-bromopyridine.
- Electron density of monohalopyridines was estimated by DFT calculations.