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Suzuki-Miyaura cross-coupling of 3,4-disubstituted 5-bromoisoxazoles: An efficient access to trisubstituted isoxazoles

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ABSTRACT

The Suzuki-Miyaura cross-coupling of 3,4-disubstituted 5-bromoisoxazoles **1** at the C5 position has successfully proceeded in the presence of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$·HBF_4 catalysts to give the corresponding trisubstituted isoxazoles **3** in good to high yields while suppressing the formation of ketone **4** as a byproduct. The use of bulky phosphine ligand P(*t*-Bu)$_3$·HBF_4 is essential for the current transformation, and the formation of ketone **4**, which was a major product in the previous report, was able to be suppressed under the current conditions.

Introduction

Isoxazole is a five-membered heteroaromatic compound containing a nitrogen–oxygen bond in its ring. The ring structure has been recognized as a privileged framework in medicinal chemistry, because the isoxazole ring itself exhibits critical pharmacophores for biological activity [1]. This high utility as pharmaceuticals has encouraged the development of various synthetic approaches towards functionalized isoxazoles [2]. Most of them, however, are based on conventional ring construction strategies that often suffer from insufficient regioselectivity and poor availability of linear components. On the other hand, the direct functionalization approach has not been established mainly due to its lability under basic conditions. To resolve this situation, we have developed direct functionalization methods such as 4-isoxazolyl anion species [3], gold(I)-catalyzed S_EAr type reactions,[4] and rhodium (III)-catalyzed C—H functionalizations [5]. Turning our attention to cross-coupling strategy which enables regioselective installation of substituents on heteroarenes using readily available building blocks [6]. 3,5-disubstituted isoxazoles were successfully synthesized via Suzuki-Miyaura coupling (Scheme 1a) [7]. However, the synthesis of trisubstituted isoxazoles via cross-coupling reactions at the C5 position has not been well developed [8,9]. Furthermore, Jurberg *et al.* clearly pointed out the difficulty in cross-coupling of 3,4-disubstituted 5-(pseudo)halogenated isoxazole [10]. According to their report, 3,4-disubstituted 5-bromoisoxazoles such as **1a** did not participate in Suzuki-Miyaura coupling, and desired trisubstituted isoxazoles were not obtained at all (Scheme 1b). Intrigued by their report, we decided to investigate the cross-coupling reactions of 5-bromoisoxazoles **1** with aryl boronic acids **2** in detail and succeeded in synthesizing trisubstituted isoxazoles **3** (Scheme 1c).

Results and discussion

Based on the previous report by Jurberg and coworkers, we began with an investigation on Suzuki-Miyaura cross-coupling of 4-benzyl-5-bromo-3-phenylisoxazole (**1a**) and phenylboronic acid (**2a**) (Table 1). First, we treated **1a** and **2a** in combination with Pd(PPh_3)$_4$ (10 mol%) and Na_2CO_3 (4.0 equiv.) in 1,4-dioxane at 100 °C for 16 h, as following the previously reported combination. As a result, the desired product **3a** was not observed, though the ring-opening product **4a** was obtained in 22% yield along with 15% recovery of bromoisoxazole **1a**. This ring-opening process was also observed by Jurberg *et al.* when they employed isoxazolyl triflate instead of **1a** [10]. The ketone **4a** was presumably given by N—O bond cleavage of the intermediate generated via oxidative addition, followed by hydrolysis and decarboxylation [11]. Surprisingly, by simply changing the base from Na_2CO_3 to K_3PO_4, the desired trisubstituted isoxazole **3a** was produced in 67% yield (entry 2). In this case, ring-opening of the isoxazole ring also proceeded, resulting in the undesired ketone **4a** in a non-negligible yield (24%). To suppress the generation of the ring-opening product **4a**, condition screening was performed. The use of $Pd(OAc)_2$ without

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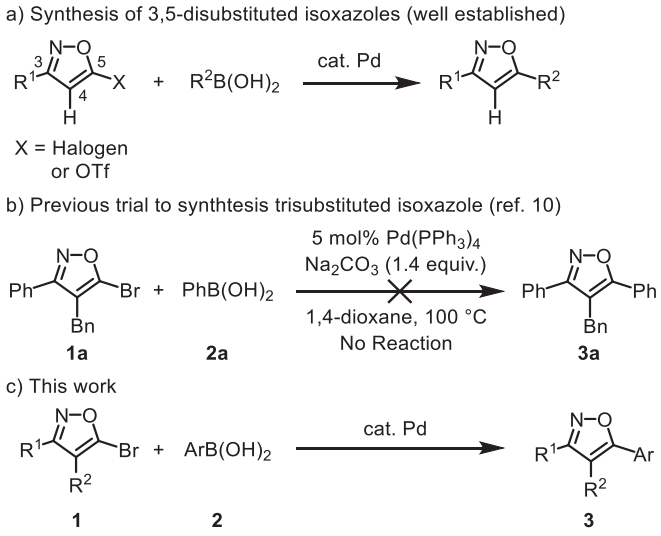


Scheme 1. Suzuki-Miyaura cross-coupling of the isoxazoles at the C5 position.

ligands resulted in low conversion of **1a** with a poor yield of **3a** (entry 3, 13% yield). In contrast, the combination of $Pd_2(dba)_3$ and P(*t*-Bu)$_3$·HBF$_4$ [12] gave only traceable amount of ketone **4a**, though approximately 40% of substrate **1a** was recovered (entry 4). With this promising palladium salt and ligand system, various solvents were investigated (entries 5–7 and see supporting information, Table S1). As a result, the combination of K_2CO_3 and DMF was found to be the best condition, and the trisubstituted isoxazole **3a** was obtained in 88% NMR yield (73% isolated yield) while suppressing the formation of ketone **4a** in 5% yield. (entry 7). Next, various phosphine ligands were examined (entries 8–16). Among them, bulky ligands such as P(*o*-Tol)$_3$ was found to exhibit an efficient catalytic activity to afford **3a** in high yield (entry 10, 87% yield) accompanied by 6% yield of ketone **4a**.

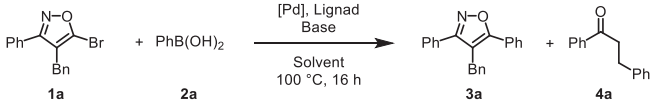
With the best conditions in our hand (Table 1, entry 7), we next examined the scope of Suzuki-Miyaura cross-coupling of 3,4-disubstituted 5-bromoisoxazole **1a** with various aryl boronic acids (Table 2). Aryl groups having both an electron donating group (entry 2) and electron withdrawing groups (entries 3–6) were introduced into C5 position of the isoxazole ring, and corresponding trisubstituted isoxazoles **3b-f** were provided in moderate to good yields (52–84%). The styrene derivative **3 g** was also obtained via the cross-coupling of **1a** with 4-vinylphenylboronic acid **2 g**, though the yield was rather sluggish (entry 6). Heteroaryl boronic acids, such as 4-pyridylboronic acid **2 h** and 2-thiopheneboronic acid **2i**, were coupled with substrate **1a** to afford **3 h** and **3i** in 54% and 57% yields, respectively (entries 7 and 8). Further, the cross-coupling using 2-naphthaleneboronic acid **2j** afforded the corresponding coupling product **3j** in 92% yield (entry 9). In all cases in Table 2, the formation of ketone **4a** via ring-opening of isoxazole ring was suppressed less than 7% yield.

Next, the scope of 5-bromoisoxazole **1** was investigated thorough coupling reaction with phenylboronic acid **2a** (Scheme 2). Interestingly, the corresponding ring-opening products **4** were not observed in all cases. With a benzyl group as R^2, 3-(hetero)aryl isoxazoles **3 k-m** were obtained in good to high yields (64–77%). Not only those 3-aryl isoxazoles, but also the 3-alkyl isoxazole **3n** was provided in 92% yield. Substituents on a benzyl group did not show any drastic effects, and the product **3o** was obtained in 64% yield. Finally, methyl or *n*-propyl group on the C4-position also gave the products **3p** and **3q** in good yields (84% and 52%, respectively).

Conclusion

In this study, we succeeded in the Suzuki-Miyaura cross-coupling of 3,4-substituted 5-bromoisoxazoles **1** at C5 position by optimization of reaction conditions, giving trisubstituted isoxazoles **3** while suppressing the formation of ketone **4** as a byproduct. The use of bulky phosphine ligand P(*t*-Bu)$_3$·HBF$_4$ is essential for the

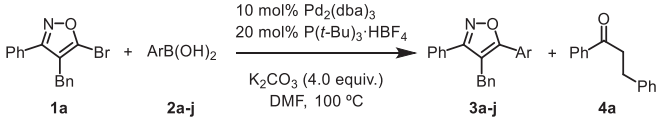
Table 1
Optimization of the Suzuki-Miyaura cross-coupling reaction for the synthesis of **3a**.[a]



Entry	Catalysts	Base	Solvent	Recovery of **1a** (%)[b]	**3a** (%)[b]	**4a** (%)[b]
1	$Pd(PPh_3)_4$	Na_2CO_3	1,4-dioxane	15	0	22
2	$Pd(PPh_3)_4$	K_3PO_4	1,4-dioxane	0	67	24
3	$Pd(OAc)_2$	K_3PO_4	1,4-dioxane	62	13	8
4	$Pd_2(dba)_3$, P(*t*-Bu)$_3$·HBF$_4$	K_3PO_4	1,4-dioxane	39	40	trace
5	$Pd_2(dba)_3$, P(*t*-Bu)$_3$·HBF$_4$	K_3PO_4	DMF	0	77	2
6	$Pd_2(dba)_3$, P(*t*-Bu)$_3$·HBF$_4$	Na_2CO_3	DMF	9	80	5
7	$Pd_2(dba)_3$, P(*t*-Bu)$_3$·HBF$_4$	K_2CO_3	DMF	0	88 (73)[c]	5
8	$Pd_2(dba)_3$, PCy_3	K_2CO_3	DMF	0	68	6
9	$Pd_2(dba)_3$, $P(CH_2CH_2CH_3)_3$	K_2CO_3	DMF	0	79	4
10	$Pd_2(dba)_3$, P(*o*-Tol)$_3$	K_2CO_3	DMF	0	87	6
11	$Pd_2(dba)_3$, $P(OPh)_3$	K_2CO_3	DMF	9	17	6
12	$Pd_2(dba)_3$, JohnPhos	K_2CO_3	DMF	0	50	5
13	$Pd_2(dba)_3$, XPhos	K_2CO_3	DMF	0	77	8
14	$Pd_2(dba)_3$, Xantphos	K_2CO_3	DMF	0	75	5
15	$Pd_2(dba)_3$, DPEphos	K_2CO_3	DMF	0	78	10
16	$Pd_2(dba)_3$, dppf	K_2CO_3	DMF	0	57	17

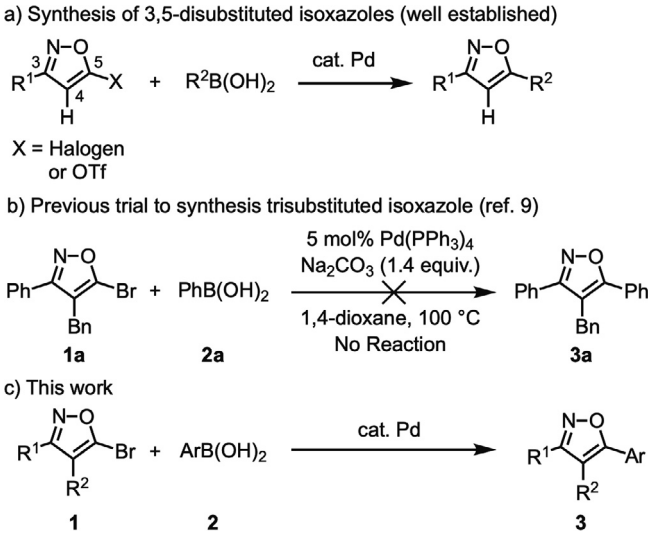
[a] Reagents and conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), Pd-catalyst (10 mol%), ligand (20 mol%), base (0.40 mmol), solvent (2 mL), 16 h. [b] NMR yield using 1,1-dibromomethane as an internal standard. [c] Isolated yield in parenthesis. Ph = phenyl, Bn = benzyl, Ac = acetyl, dba = dibenzylideneacetone, Bu = butyl, THF = tetrahydrofuran, DMF = *N*, *N*-dimethylformaldehyde, Cy = cyclohexyl, Tol = tolyl, JohnPhos = (2-biphenylyl)di-*tert*-butylphosphine, XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, DPEphos = bis[2-(diphenylphosphino)phenyl] ether, dppf = 1,1′-bis(diphenylphosphino)ferrocene.

Table 2
Suzuki-Miyaura cross-coupling of **3a** with various aryl boronic acids.



Entry	2	Ar	Yield (%)	
			3[a]	4a[b]
1	**2a**	phenyl	73	5
2	**2b**	4-$CH_3C_6H_5$	84	5
3	**2c**	4-ClC_6H_5	56	3
4	**2d**	4-$CF_3C_6H_5$	72	6
5	**2e**	3,5-$CF_3C_6H_3$	52	5
6	**2f**	4-$CHOC_6H_5$	61	4
7	**2g**	4-CH_2 = CHC_6H_5	43	trace
8	**2h**	4-pyridyl	54	2
9	**2i**	2-thienyl	57	7
10	**2j**	2-naphtyl	92	5

[a] Isolated yield.
[b] NMR yield using 1,1-dibromomethane as an internal standard.



Scheme 2. Suzuki-Miyaura cross-coupling of various 5- bromoisoxazoles **3** with phenylboronic acid.

current transformation. We are now in a position to synthesize a variety of trisubstituted isoxazoles, some of which are difficult to synthesize via the previously known methods. Further studies on cross-coupling for modular synthesis of multi-functionalized isoxazoles are ongoing in our laboratory.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Taiki Morita reports financial support was provided by Japan Society for the Promotion of Science (JSPS). Hiroyuki Nakamura reports a relationship with Japan Society for the Promotion of Science (JSPS) that includes: funding grants. Hiroyuki Nakamura reports a relationship with AMED that includes: funding grants.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153185.

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