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Derivatization of a tris-oxazole using Pd-catalyzed coupling reactions of a 5-bromooxazole moiety

Kazuaki Shibata [a], Masahito Yoshida [b], Takayuki Doi [a,b,*], Takashi Takahashi [a,*]

[a] Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro, Tokyo 152-8552, Japan
[b] Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aza-Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

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ABSTRACT

Modification at the C5 position of an oxazole ring contained in a 2,4-concatenated tris-oxazole by Pd-catalyzed coupling reactions was performed. Novel Pd-catalyzed amination and alkoxylation of a 5-bromooxazole derivative as well as Suzuki–Miyaura coupling and Migita–Stille coupling have been demonstrated. A wide variety of functional groups, including aryl, heteroaryl, primary and secondary amines, and phenol, were introduced in the 5-bromooxazole moiety in moderate to excellent yields using $Pd(OAc)_2$/S-PHOS or $Pd(OAc)_2$/X-PHOS as a catalyst.

Oxazole-containing natural products are attracting attention for their fascinating structures and broad range of biological activity.[1] Many researchers have investigated their total synthesis and that of their derivatives.[2] These natural products consist of not only a single oxazole but also two or more oxazoles concatenated at the 2- and 4-positions[3] such as in telomestatin (**1**),[4,5] YM-216391 (**2**),[6,7] and ulapualide A (**3**)[8,9] (Fig. 1). Since the oxazoles in these natural products possess a hydrogen, a methyl, or a phenyl group at the C5 position, these substituents may affect their biological activities. To elucidate the structure–activity relationships on the basis of the substituents on the 2,4-concatenated oxazoles, we need to develop an efficient synthetic method for introducing a wide variety of functional groups at the C5 position of an oxazole moiety.

Our strategy is therefore to introduce a 5-bromooxazole moiety in a 2,4-concatenated tris-oxazole in advance and selectively activate the bromide by Pd-catalyzed coupling reactions in the later stage of synthesis toward efficient diversification (Fig. 2). Herein, we report the synthesis and Pd-catalyzed coupling reactions of 5-bromooxazole-containing tris-oxazole that corresponds to the synthetic intermediate of the natural product telomestatin.[10–12]

Preparation of tris-oxazole **11** containing a 5-bromooxazole moiety is shown in Scheme 1. Commercially available Boc–Cys(*t*-Bu)–OH (**4**) was converted to 4-cyanooxazole **5** by the modified Harran procedure.[13] Boc protection of the carbamate with $(Boc)_2O$, followed by treatment with NH_3/MeOH and aqueous H_2O_2, provided amide **6** (68%) in two steps. After conversion of **6** to tetracarbamate with $(Boc)_2O$, methanolysis at the C terminus with K_2CO_3/MeOH, followed by a selective removal of the Boc group

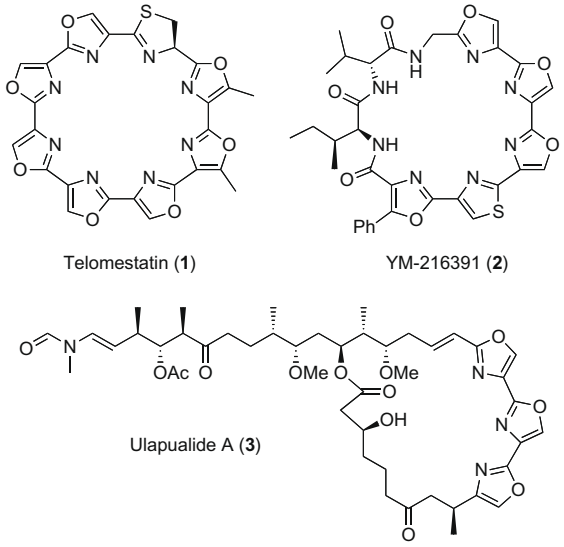

Figure 1. Tris-oxazole-containing natural products.

* Corresponding authors. Fax: +81 3 5734 2884.
E-mail addresses: doi_taka@mail.pharm.tohoku.ac.jp (T. Doi), ttak@apc.titech.ac.jp (T. Takahashi).

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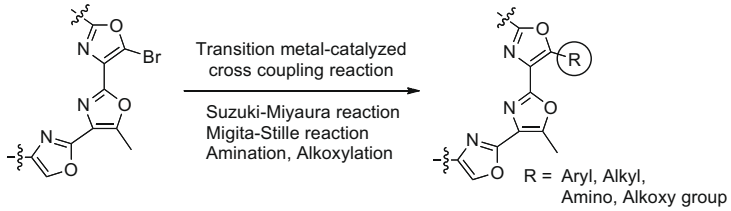
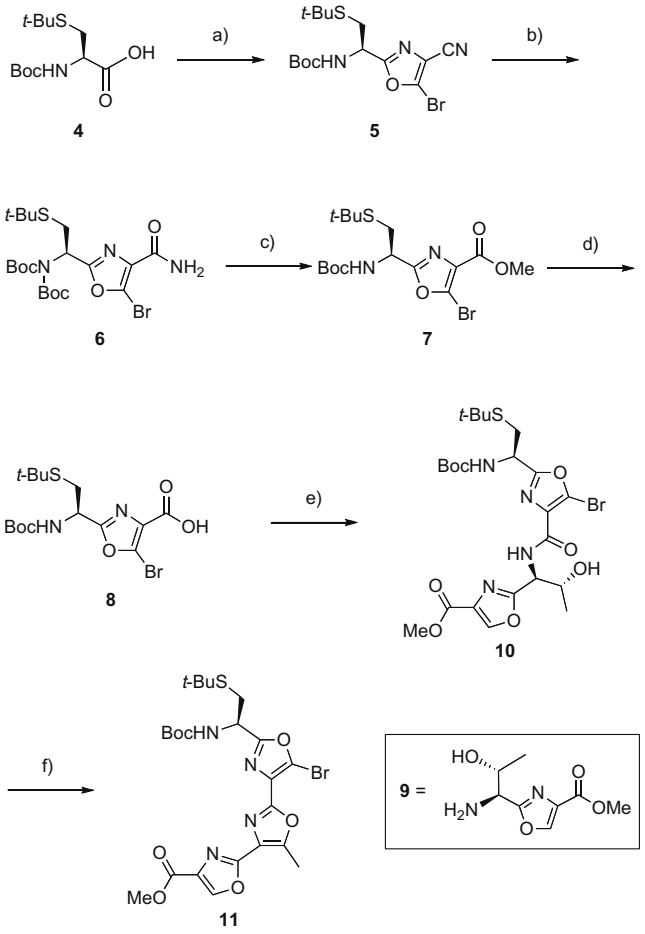


Figure 2. Our synthetic strategy for 5-functionalized tris-oxazole derivatives by Pd-catalyzed coupling reactions.

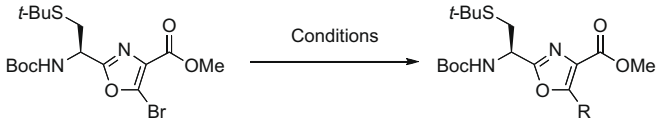


Scheme 1. Reagents and conditions: (a) (i) aminomalononitrile *p*-toluenesulfonate, EDCI, Py., rt, 20 h, (ii) *t*-BuONO, $CuBr_2$, CH_3CN, 0 °C to rt, 2 h, 28% (two steps); (b) (i) $(Boc)_2O$, NEt_3, DMAP, CH_2Cl_2, rt, 24 h, (ii) NH_3/MeOH, aq H_2O_2, dioxane, rt, 2 h, 68% (two steps); (c) (i) $(Boc)_2O$, DMAP, CH_3CN, rt, 2 h, (ii) K_2CO_3, THF–MeOH, rt, 3 h, (iii) TFA (2.0 equiv), CH_2Cl_2, rt, 6 h, 90% (three steps); (d) Me_3SnOH, $(CH_2Cl)_2$, 80 °C, 6 h, 92%; (e) **9**, PyBrop, DIEA, CH_2Cl_2, rt, 3 h, 90%; (f) (i) Burgess reagent, THF, 70 °C, 12 h, (ii) DBU, $BrCCl_3$, CH_2Cl_2, rt, 12 h, 76% (two steps).

with 2 equiv of TFA, afforded the desired 5-bromooxazole **7** (90% overall). Although hydrolysis of **7** with LiOH in THF–MeOH–H_2O gave a complex mixture, methyl ester **7** was converted to acid **8** by treatment with trimethyltin hydroxide (92%).[14] Amidation of **8** with amine **9** using PyBrop/DIEA provided bis-oxazole amide **10** (90%). Finally, cyclodehydration of **10** using Burgess reagent,[15] followed by a treatment with $BrCCl_3$/DBU,[16] afforded the expected tris-oxazole **11** (76%).

In our initial attempt at modification at the C5 position of an oxazole, we investigated various Pd-catalyzed coupling reactions of 5-bromooxazole **7**. Results are summarized in Table 1. Migita–Stille coupling of **7** with $PhSnBu_3$ in the presence of $PdCl_2(CH_3CN)_2$ proceeded at 80 °C to give **12a** in 94% (entry 1). Coupling reaction

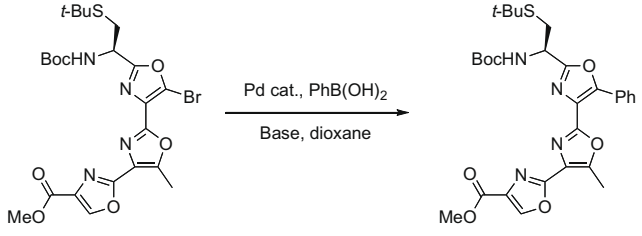
Table 1
Pd-catalyzed and Cu-mediated cross-coupling reactions of 5-bromooxazole **7**



Entry	R	Nucleophile	Catalyst	Additive	Product	Yield (%)
1[a]	Ph	$PhSnBu_3$	$PdCl_2(CH_3CN)_2$	—	**12a**	94
2[b]	Me	Me_4Sn	POPd	CuI	**12b**	85
3[c]	Ph	$PhB(OH)_2$	$PdCl_2(PPh_3)_2$	KF	**12a**	90
4[d]	$C_8H_{17}NH$	$C_8H_{17}NH_2$	$Pd(OAc)_2$	K_3PO_4	**12c**	80
5[e]	CF_3	$FSO_2CF_2CO_2Me$	—	CuI HMPA	**12d**	81

Reagents and conditions: (a) $PdCl_2(CH_3CN)_2$ (5 mol %), $PhSnBu_3$ (1.5 equiv), DMF (0.2 M), 80 °C, 12 h; (b) POPd (5 mol %), CuI (15 mol %), Me_4Sn (1.5 equiv), DMF (0.2 M), 80 °C, 12 h; (c) $PdCl_2(PPh_3)_2$ (5 mol %), $PhB(OH)_2$ (1.5 equiv), KF (2 equiv), dioxane (0.2 M), 60 °C, 12 h; (d) $Pd(OAc)_2$ (5 mol %), X-PHOS (10 mol %), $C_8H_{17}NH_2$ (2 equiv), K_3PO_4 (3 equiv), DME (0.2 M), 60 °C, 24 h; (e) CuI (1.2 equiv), $FSO_2CF_2CO_2Me$ (5 equiv), HMPA (5 equiv), DMF (0.05 M), 70 °C, 12 h. POPd = $PdCl_2[(t\text{-}Bu)_2P(OH)]_2$, X-PHOS = 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl.

Table 2
Suzuki–Miyaura cross-coupling of **11** with phenyl boronic acid

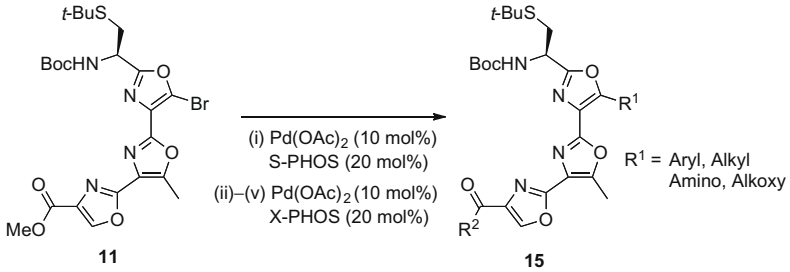


Entry	Pd cat.	Base	Temp (°C)	Time (h)	Yield (%)
1	$PdCl_2(PPh_3)_2$	KF	60	16	Trace
2	$Pd(Pt\text{-}Bu_3)_2$	KF	60	16	Trace
3	$Pd(OAc)_2$, L-1	KF	60	16	62
4	$Pd(OAc)_2$, L-2	KF	60	16	73
5	$Pd(OAc)_2$, L-3	KF	60	16	92
6	$Pd(OAc)_2$, L-3	KF	110	0.5	95
7	$Pd(OAc)_2$, L-3	K_3PO_4	60	16	79

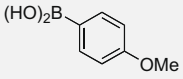
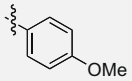
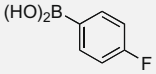
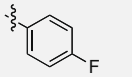
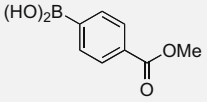
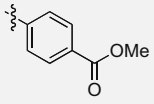
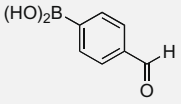
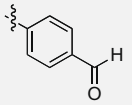
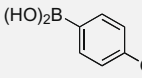
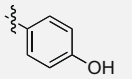
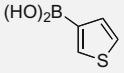
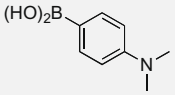
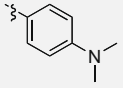
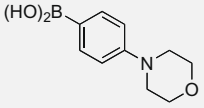
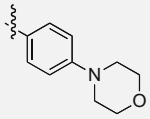
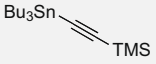
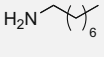
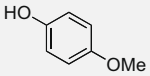
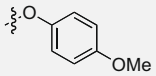
Reagents and conditions: Pd catalyst (10 mol %) or $Pd(OAc)_2$ (10 mol %)/ligand (20 mol %), $PhB(OH)_2$ (1.5 equiv), base (KF or K_3PO_4) (2 equiv), dioxane (0.2 M). L-1 = 2-(Di-*t*-butylphosphino)-2′-methylbiphenyl, L-2 = 2-(Dicyclohexylphosphino)-2′-methylbiphenyl, L-3 = 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-PHOS).

with Me_4Sn in the presence of POPd[17]/CuI yielded **12b** (85%; entry 2). Suzuki–Miyaura reaction of **7** with $PhB(OH)_2$ in the presence of $PdCl_2(PPh_3)_2$/KF afforded the expected **12a** in excellent yield (90%; entry 3). Racemization at the α-position of the modified cysteine residue is suppressed (<2%) under the reaction conditions (See Supplementary data).[18]

Table 3
Scope of the boronic acids in Suzuki–Miyaura reaction of **11** and other Pd-catalyzed cross-coupling reactions



11 **15**

Entry		Nucleophile	Conditions	Product	R^1	Yield (%)
1	**14a**		i	**15a** (R^2 = OMe)		91
2	**14b**		i	**15b** (R^2 = OMe)		80
3	**14c**		i	**15c** (R^2 = OMe)		74
4	**14d**		i	**15d** (R^2 = OMe)		62
5	**14e**		i or ii	**15e** (R^2 = OMe)		i: 53 ii: 84
6	**14f**		i or ii	**15f** (R^2 = OMe)		i:30 ii:91
7	**14g**		ii	**15g** (R^2 = OMe)		63
8	**14h**		ii	**15h** (R^2 = OMe)		68
9	**14i**		iii	**15i** (R^2 = OMe)		70
10	**14j**		iv	**16j** (R^2 = NHC_8H_{17})		70
11	**14k**		iv	**15k** (R^2 = OMe)		65
12	**141**		iv	**151** (R^2 = OMe)		69
13	**14m**		v	**15m** (R^2 = OMe)		43

Reagents and conditions: (i) KF (2 equiv), dioxane (0.2 M), 110 °C (MW), 0.5 h; (ii) KF (2 equiv), DME (0.2 M), 80 °C, 16 h; (iii) dioxane (0.2 M), 60 °C, 16 h; (iv) K_3PO_4 (3 equiv), DME (0.2 M), 80 °C, 24 h; (v) K_3PO_4 (2 equiv), dioxane (0.2 M), 80 °C, 16 h; nucleophile was used as 1.5 equiv (entries 1–9, and 13), 4 equiv (entry 10) and 2 equiv (entries 11 and 12).

Furthermore, we introduced an amino group at the C5 position of the oxazole by Pd-catalyzed amination.[19] Amination of **7** with octylamine in the presence of $Pd(OAc)_2$/X-PHOS at 60 °C provided the desired 5-(octylamino)oxazole **12c** (80%; entry 4). The methyl ester remains intact and racemization at the α-position of the modified cysteine residue is suppressed (<3%) under the reaction conditions.[18] Fluorinated small molecules are attractive compounds for medicinal chemistry and drug discovery.[20] Therefore, we also examined trifluoromethylation. Cu(I)-mediated nucleophilic substitution of **7** with $FSO_2CF_2CO_2Me$ provided 5-(trifluoromethyl)oxazole **12d** (81%; entry 5).[21]

According to the above result (Table 1, entry 3), we investigated the Suzuki–Miyaura coupling reaction of tris-oxazole **11** with $PhB(OH)_2$. Results are summarized in Table 2. Reaction in the presence of $PdCl_2(PPh_3)_2$/KF (entry 1) did not proceed; nor did reaction in the presence of $Pd(Pt\text{-}Bu_3)_2$ (entry 2). In view of the difficulty of

oxidative addition of **11** onto Pd(0) catalyst, we used more electron-rich ligands in this cross-coupling reaction because Buchwald and co-workers have reported that biaryl monophosphine ligands are highly effective for Suzuki–Miyaura reaction of heteroaryl halides with aryl boronic acids; reaction using $Pd(OAc)_2$/Buchwald monophosphine ligands (L-1, L-2, and L-3 in the Table)[22] proceeded to yield the desired **13** (entries 3–7). In particular, the use of L-3 (S-PHOS) yielded **13** in 92% yield (entry 5). After further optimization, cross-coupling reaction was completed within 30 min under microwave irradiation to yield **13** (95%; entry 6).

With optimized reaction conditions for Suzuki–Miyaura reaction of **11** in hand, we next examined a range of boronic acids and other cross-coupling reactions such as ethynylation, amination, and alkoxylation. Results are summarized in Table 3. *p*-Substituted aryl boronic acids **14a**–**d** yielded the corresponding products **15a**–**d** (62–91%; entries 1–4). *p*-Hydroxyphenyl derivative **14e** reacted incompletely (53%) even under microwave irradiation (entry 5). However, reaction in the presence of $Pd(OAc)_2$/X-PHOS/KF under conventional heating (80 °C, 16 h) was completed to yield **15e** (84%). When *p*-formylphenyl boronic acid **14d** was used for the coupling reaction, a small amount of debrominated product **15n** (R^1 = H, R^2 = OMe) was observed (<5%). Turning from microwave irradiation to conventional heating (DME, 80 °C, 16 h) in the presence of $Pd(OAc)_2$/X-PHOS provided the desired coupling products **15f**–**h** in acceptable yields (entries 6–8). Ethynylation of **11** by Migita–Stille coupling (entry 9) proceeded at 60 °C in the presence of $Pd(OAc)_2$/X-PHOS to yield **15i** (70%).

Amination of **11** with primary and secondary amines (entries 10–12) using K_3PO_4 at 80 °C afforded the corresponding coupling products **16j**, **15k**, and **15l** (65–70%). In entry 10, **16j** was obtained as a sole product formed by transamidation of the methyl ester with the less-hindered primary amine **14j**. In alkoxylation of **11**, coupling reaction of phenol **14m** with K_3PO_4 in the presence of $Pd(OAc)_2$/X-PHOS provided the expected **15m** (43%; entry 13). In this reaction, β-elimination of the *St*-Bu group was observed.[23]

In summary, we have demonstrated the modification of the C5 position of an oxazole ring contained in a 2,4-concatenated tris-oxazole derivative by means of Pd-catalyzed cross-coupling reactions. Novel Pd-catalyzed amination and alkoxylation of 5-bromooxazole as well as Suzuki-Miyaura coupling have been achieved. In the presence of $Pd(OAc)_2$/S-PHOS or $Pd(OAc)_2$/X-PHOS, a wide variety of functional groups, such as aryl, heteroaryl, primary and secondary amines, and phenol, were introduced in the 5-bromooxazole moiety in moderate to excellent yields. These modifications could be applied to diversification of natural products containing a 2,4-concatenated tris-oxazole. The synthesis of telomestatin derivatives utilizing this method is underway in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.064.

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