Synthesis and Reaction of the First Oxazol-4-ylboronates: Useful Reagents for the Preparation of the Oxazole-Containing Biaryl Compounds

Hiroshi Araki,[a] Tadashi Katoh,[b] Munenori Inoue*[a,c]

[a] Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8502, Japan

[b] Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan

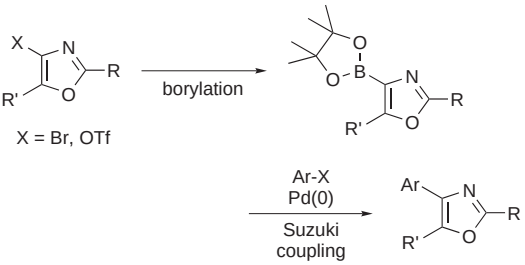
[c] Sagami Chemical Research Center, 2743-1 Hayakawa, Ayase, Kanagawa 252-1193, Japan
Fax +81(467)774113; E-mail: inoue@sagami.or.jp

Received 3 December 2005

Abstract: The first oxazol-4-ylboronates were prepared from the corresponding 4-bromo- and 4-trifluoromethanesulfonyloxy-oxazoles. The Suzuki coupling using the resulting boron reagents with various aryl halides, including benzene, pyridine, oxazole and thiazole rings, in the presence of palladium catalyst proceeded to produce the oxazole-containing biaryl compounds in moderate to good yields.

Key words: oxazoles, oxazol-4-ylboronates, Suzuki coupling, biaryl compounds, palladium-catalyzed cross-coupling

Oxazoles are an important class of heterocyclic compounds due to their occurrence in natural product chemistry, medicinal chemistry and materials science. A great number of literatures for their preparations and reactions have been reported and reviewed.[1] Among them, oxazole-containing biaryl structure is especially characteristic in natural product chemistry, where recently unprecedented natural products such as diazonamide A,[2a] the hennoxazoles[2b] the mycalolides,[2c] the sulfomycins,[2d] telomestatin,[2e] and YM-216391[2f] have been isolated and reported to exhibit a wide variety of biological activities. With increasing necessity for supplies of biaryl compounds, the transition-metal-catalyzed reaction of metallated heteroaromatic compounds with aromatic halides has been recognized as a powerful strategy for the biaryl synthesis.[3] In terms of the synthesis of the oxazole-containing biaryl compounds by palladium-catalyzed cross-coupling reaction using the metallated oxazoles, Dondoni et al. reported the synthesis of 2-stannyloxazoles and the Stille reaction of these stannanes to lead to the formation of 2-(hetero)aryloxazoles.[4] Since then, other groups have proved the efficiency of the stannyloxazoles to synthesize the (hetero)aryloxazole derivatives.[5] On the other hand, Anderson et al. disclosed the Negishi coupling of oxazol-2-ylzinc reagents with several aryl halides to produce the 2-substituted oxazoles and applied this methodology to the synthesis of the oxazole-containing partial ergot alkaloids.[6] In addition, to attain the purpose of establishing the oxazole-containing biaryl systems, the reaction of oxazolyl halides (triflates) with metallated arene derivatives was also utilized as an alternative method.[7] Although Suzuki coupling[8] is currently regarded as a powerful and general transition-metal-catalyzed cross-coupling reaction for the preparation of biaryl compounds including heterocyclic rings[9] due to their relatively low toxicity, easily availability, air stability, and wide functional-group tolerance, to our knowledge, there have been no reports with respect to the Suzuki coupling reaction using oxazolylboron reagents to date. In the course of our synthetic studies of the natural products containing oxazole rings, we have demonstrated the first preparation and reaction of oxazol-4-ylboronates for the biaryl synthesis in this paper (Scheme 1).

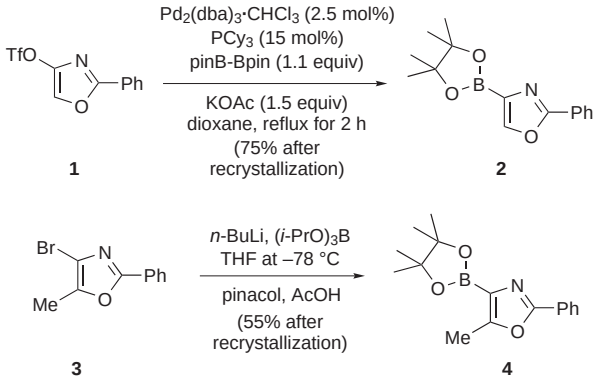


Scheme 1 Suzuki coupling of oxazol-4-ylboronate, leading to the oxazole-containing biaryl compound.

We first studied the synthesis of oxazol-4-ylboronates from the corresponding 4-trifluoromethanesulfonyloxy-oxazole and 4-bromooxazole as shown in Scheme 2. According to the normal reaction condition,[10] we have succeeded in the synthesis of 2-phenyloxazol-4-ylboronate **2** from the known 2-phenyl-4-trifluoromethanesulfonyloxyoxazole (**1**).[11] Borylation was achieved by treatment of **1** with 2.5 mol% of $Pd_2(dba)_3$ and 15 mol% of PCy_3 in the presence of 1.1 equivalents of bis(pinacolato)diboron (pinB-Bpin) and 1.5 equivalents of KOAc in refluxing dioxane to furnish the desired 2-phenyloxazol-4-ylboronate **2** in 75% yield after recrystallization.[12] On the other hand, lithiation of the known 4-bromo-5-methyl-2-phenyloxazole (**3**)[13] with *n*-BuLi, followed by borylation with triisopropyl borate at –78 °C and transesterification with pinacol afforded the expected 5-methyl-2-phenyloxazol-4-ylboronate **4** in 55% yield after recrystallization.[14] These boron reagents are stable under Ar at room temperature and can be stored for a long time.

With the desired oxazol-4-ylboronates in hand, we turned our attention to the Suzuki coupling reaction using these

SYNLETT 2006, No. 4, pp 0555–0558
Advanced online publication: 20.02.2006
DOI: 10.1055/s-2006-932471; Art ID: U30705ST



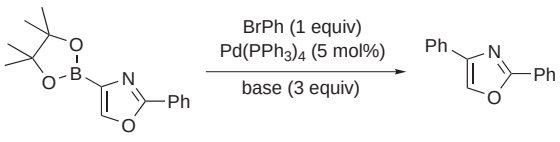
Scheme 2 Preparation of oxazol-4-ylboronates (**2** and **4**).

boron reagents. The reaction conditions were standardized by optimization of the coupling reaction of 2-phenyloxazolylboronate **2** with one equivalent of bromobenzene in the presence of 5 mol% of $Pd(PPh_3)_4$ under various reaction conditions as summarized in Table 1. In entries 1–6, we initially investigated the base (3 equiv) for the coupling reaction in refluxing dioxane. Na_2CO_3 and Et_3N were not effective for the reaction, producing a low yield of 2,4-diphenyloxazole (**5**, entries 1 and 2).[13] *t*-BuOK was strong enough to destroy the boronate to give a complex mixture (entry 3). In the case of using KF, moderate yield (41%) of **5** was afforded (entry 4). K_2CO_3 and K_3PO_4 were found to be the most effective base to furnish a 71% yield of **5** (entries 5 and 6). In testing four solvents (dioxane, DMF, toluene, and MeCN), it was found that DMF was the best solvent in this coupling reaction (entry 7), in which 88% yield of **5** was obtained in a short reaction time, while other solvents also worked well to produce **5** in 67–78% (entries 6, 8, 9).

Next, we explored the applicability of the Suzuki coupling of oxazolylboron reagents (**2** and **4**) with other aromatic halides, possessing benzene, pyridine, oxazole, and thiazole rings, to synthesize the oxazole-containing biaryl compounds by applying our preliminary reaction condition [Ar-X (1 equiv), $Pd(PPh_3)_4$ (5 mol%), K_2CO_3 (3 equiv), DMF, 100 °C][15,16] as shown in Table 2. All reactions went to completion within three hours to give rise to the desired coupling products in moderate to high yields. When the aryl bromide having electron-withdrawing group was used (entry 1), the reaction proceeded smoothly to give a good yield of the 2,4-diaryloxazole, however, the presence of electron-donating or stereocongested substitutes markedly decreased the yield of the coupling products due to the slow reaction, which resulted in the formation of homocoupling product (entries 2 and 3).[17] Heteroaromatic (pyridine, oxazole, and thiazole rings) halides were also coupled with **2** and **4** without any difficulty (entries 5–7, 9, 10). This single-step reaction to elaborate the heteroaromatic–oxazole linkage would be especially useful for the synthesis of natural products possessing the oxazole-containing biaryl structure. Comparing the reactivity of **2** with that of **4**, the 5-methyl group effected an increase of the yield (entries 8–10). In addition, the coupling reaction of **2** with the vinyl bromide derivative also proceeded to give the corresponding vinyloxazole (entry 4).

In conclusion, we have successfully synthesized oxazol-4-ylboronates (**2** and **4**) from the corresponding 4-bromo and 4-trifluoromethanesulfonyloxyoxazoles. The palladium-catalyzed Suzuki cross-coupling reaction of these boronates with several aryl halides, involving benzene, pyridine, oxazole, and thiazole rings, gave rise to the 4-

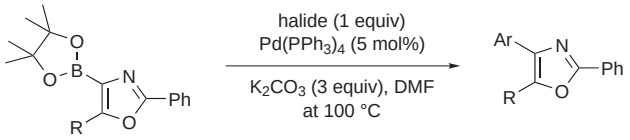
Table 1 Reaction of 2-Phenyloxazol-4-ylboronate **2** with Bromobenzene under Various Conditions

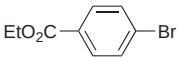
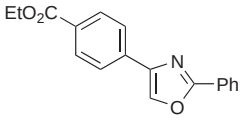
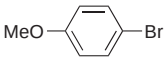
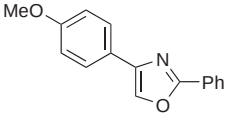
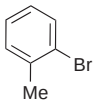
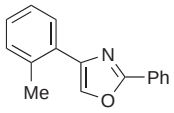
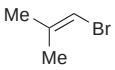
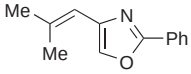
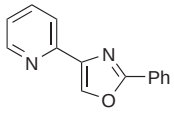
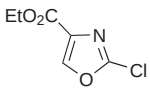
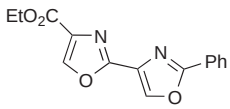
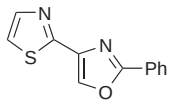
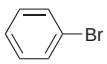
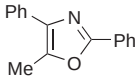
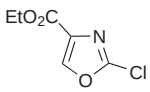
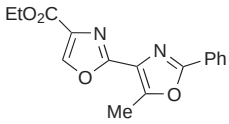
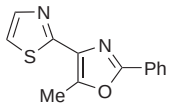


Entry	Solvent	Base	Temperature	Time (h)	Yield (%)[a]
1	Dioxane	Na_2CO_3	Reflux	24	16
2	Dioxane	Et_3N	Reflux	16	8
3	Dioxane	*t*-BuOK	Reflux	16	Complex mixture
4	Dioxane	KF	Reflux	8	41
5	Dioxane	K_3PO_4	Reflux	1	71
6	Dioxane	K_2CO_3	Reflux	1.5	71
7	DMF	K_2CO_3	100 °C	0.5	88
8	Toluene	K_2CO_3	100 °C	1.0	78
9	MeCN	K_2CO_3	Reflux	1.5	67

[a] Isolated yields after chromatography.

Table 2 Suzuki Coupling of Oxazolylboronates with Various Aryl Halides



Entry	R	Halide	Time (h)	Product	Yield (%)[a]	^{1}H NMR (500 MHz, $CDCl_3$), δ
1	H		0.5		83	1.42 (t, *J* = 7.1 Hz, 3 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 7.46–7.52 (m, 3 H), 7.89–7.92 (m, 2 H), 8.06 (s, 1 H), 8.09–8.15 (m, 4 H)
2	H		1		56	3.86 (s, 3 H), 6.95–6.99 (m, 2 H), 7.45–7.50 (m, 3 H), 7.74–7.77 (m, 2 H), 7.88 (s, 1 H), 8.09–8.13 (m, 2 H)
3	H		3		54	2.51 (s, 3 H), 7.25–7.33 (m, 5 H), 7.45–7.51 (m, 3 H), 7.82 (s, 1 H), 7.91–7.94 (m, 1 H), 8.11–8.15 (m, 2 H)
4	H		1.5		65	1.94 (s, 3 H), 2.01 (s, 3 H), 6.13 (s, 1 H), 7.42–7.48 (m, 3 H), 7.56 (s, 1 H), 8.02–8.07 (m, 2 H)
5	H		3		73	7.23 (ddd, *J* = 1.0, 4.9, 7.5 Hz, 1 H), 7.46–7.52 (m, 3 H), 7.79 (dt, *J* = 1.7, 7.7 Hz, 1 H), 8.02 (d, *J* = 7.9 Hz, 1 H), 8.12–8.16 (m, 2 H), 8.32 (s, 1 H), 8.61 (br d, *J* = 4.3 Hz, 1 H)
6	H		0.5		71	1.41 (t, *J* = 7.1 Hz, 3 H), 4.43 (q, *J* = 7.1 Hz, 2 H), 7.48–7.53 (m, 3 H), 8.12–8.16 (m, 2 H), 8.32 (s, 1 H), 8.43 (s, 1 H)
7	H		3		80	7.40 (d, *J* = 3.2 Hz, 1 H), 7.48–7.52 (m, 3 H), 7.88 (d, *J* = 3.2 Hz, 1 H), 8.11–8.15 (m, 2 H), 8.28 (s, 1 H)
8	Me		1		98	2.62 (s, 3 H), 7.31–7.35 (m, 1 H), 7.42–7.48 (m, 5 H), 7.72–7.75 (m, 2 H), 8.07–8.10 (m, 2 H)
9	Me		1		84	1.41 (t, *J* = 7.1 Hz, 3 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 2.82 (s, 3 H), 7.46–7.50 (m, 3 H), 8.08–8.13 (m, 2 H), 8.30 (s, 1 H)
10	Me		2		88	2.81 (s, 3 H), 7.34 (d, *J* = 3.3 Hz, 1 H), 7.45–7.49 (m, 3 H), 7.88 (d, *J* = 3.3 Hz, 1 H), 8.06–8.10 (m, 2 H)

[a] Isolated yields after chromatography.

aryl- and 4-heteroaryloxazole derivatives. Applying this method to the synthesis of natural products is currently in progress, and will be discussed in due course.

Acknowledgment

We are grateful to professor emeritus J. Tsuji (Tokyo Institute of Technology) for helpful discussions. We also thank Dr. T. Mori (Tokyo Institute of Technology) for his assistance in MS spectra measurements.

References and Notes

(1) For a recent review, see: Palmer, D. C.; Venkatraman, S. *Oxazoles: Synthesis, Reactions and Spectroscopy*, In *The Chemistry of Heterocyclic Compounds, Part A*, Vol 60; Palmer, D. C., Ed.; John Wiley and Sons: New York, **2003**, 1–390; and references therein.

(2) (a) Lindquist, N.; Fenical, W.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 2303. (b) Ichiba, T.; Yoshida, W. Y.; Scheuer, P. J.; Higa, T.; Gravalos, D. G. *J. Am. Chem. Soc.* **1991**, *113*, 3173. (c) Fusetani, N.; Yasumuro, K.;

Matsunaga, S.; Hashimoto, K. *Tetrahedron Lett.* **1989**, *30*, 2809. (d) Egawa, Y.; Umino, K.; Tamura, Y.; Shimizu, M.; Kaneko, K.; Sakurazawa, M.; Awataguchi, S.; Okuda, T. *J. Antibiot.* **1969**, *22*, 12. (e) Shinya, K.; Wierzba, K.; Matsuo, K.; Ohtani, T.; Yamada, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1262. (f) Sohda, K.; Nagai, K.; Yamori, T.; Suzuki, K.; Tanaka, A. *J. Antibiot.* **2005**, *58*, 27. (g) Sohda, K.; Hiramoto, M.; Suzumura, K.; Takebayashi, Y.; Suzuki, K.; Tanaka, A. *J. Antibiot.* **2005**, *58*, 32.

(3) Undheim, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol 1; Negishi, E., Ed.; John Wiley and Sons: New York, **2002**, 409–492; and references therein.

(4) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 693.

(5) (a) Barrett, A. G. M.; Kohrt, J. T. *Synlett* **1995**, 415. (b) Collins, I.; Castro, J. L.; Street, L. J. *Tetrahedron Lett.* **2000**, *41*, 781. (c) Clapham, B.; Sutherland, A. J. *J. Org. Chem.* **2001**, *66*, 9033.

(6) (a) Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583. (b) Anderson, B. A.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8634. (c) Vedejs, E.; Luchetta, L. M. *J. Org. Chem.* **1999**, *64*, 1011.

(7) (a) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623. (b) Boto, A.; Ling, M.; Meek, G.; Pattenden, G. *Tetrahedron Lett.* **1998**, *39*, 8167. (c) Liu, C.-M.; Chen, B.-H.; Liu, W.-Y.; Wu, X.-L.; Ma, Y.-X. *J. Organomet. Chem.* **2000**, *598*, 348. (d) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2002**, *4*, 2905. (e) Hodgetts, K. J.; Kershaw, M. T. *Org. Lett.* **2003**, *5*, 2911. (f) Maekawa, T.; Sakai, N.; Tawada, H.; Murase, K.; Hazama, M.; Sugiyama, Y.; Momose, Y. *Chem. Pharm. Bull.* **2003**, *51*, 565. (g) Young, G. L.; Smith, S. A.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 3797.

(8) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

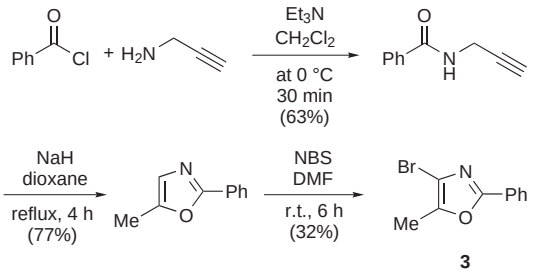
(9) Tyrrell, E.; Brookes, P. *Synthesis* **2004**, 469; and references therein.

(10) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508. (b) Ishiyama, T.; Itoh, Y.; Kitano, T.; Miyaura, N. *Tetrahedron Lett.* **1997**, *38*, 3447.

(11) Schaus, J. V.; Panek, J. S. *Org. Lett.* **2000**, *2*, 469.

(12) **Preparation of 2-Phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (2).**
A suspension of $Pd_2(dba)_3{\cdot}CHCl_3$ (120 mg, 0.13 mmol) and tricyclohexylphosphine (220 mg, 0.78 mmol) in 1,4-dioxane (60 mL) was stirred for 30 min at r.t. under Ar. Bis(pinacolato)diboron (1.46 g, 5.7 mmol), 2-phenyl-4-trifluoromethanesulfonyloxyoxazole (**1**, 1.53g, 5.2 mmol) and KOAc (769 mg, 7.8 mmol) were successively added to the resulting solution. After being at reflux for 2 h, the reaction mixture was diluted with Et_2O (300 mL). The resulting mixture was washed with H_2O (100 mL) and then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 20:1 to 1:1) to give 2-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (**2**). After recrystallization from hot hexane, pure **2** (1.06 g, 75%) was obtained as colorless needles; mp 124–125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (12 H, s), 7.44 (3 H, m), 8.07 (1 H, s), 8.14 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 24.8, 84.3, 126.9, 127.3, 128.6, 130.4, 148.0, 162.8; IR (neat) 2996, 2973, 1567, 1363, 1319, 1081, 692 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{15}H_{18}BNO_3$ [M$^+$]: 271.1380; found: 271.1374.

(13) (a) Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2665. (b) The method reported in ref. 13a is inconvenient to synthesize **3**. We developed the alternative method to prepare bromide **3** from benzoyl chloride and propargylamine as follows (Scheme 3).



Scheme 3

(14) **Preparation of 5-Methyl-2-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)oxazole (4).**
n-BuLi in *n*-hexane (1.58 M, 0.42 mL, 0.67 mmol) was added to a stirred solution of 4-bromo-5-methyl-2-phenyloxazole (**3**, 144 mg, 0.65 mmol) in THF (3 mL) at –78 °C under Ar. After 30 min, triisopropylborate (0.17 mL, 0.73 mmol) was added to the resulting solution and stirred for 1 h at the same temperature. The reaction mixture was allowed to warm to r.t. and stirred for 1 h. Pinacol (86 mg, 0.73 mmol) and glacial AcOH (42 μL, 0.73 mmol) were added to the resulting solution and the resulting mixture was stirred for 1 h. The reaction mixture was diluted with Et_2O (30 mL) and washed with H_2O (10 mL) and then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 1:1) to give 5-methyl-2-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-oxazole (**4**). After recrystallization from hot hexane, pure **4** (95 mg, 55%) was obtained as colorless needles; mp 108–109 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (12 H, s), 2.56 (3 H, s), 7.41 (3 H, m), 8.10 (2 H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 11.8, 24.9, 83.9, 126.5, 127.6, 128.5, 129.9, 160.1, 161.0. IR (neat): 2979, 1593, 1407, 1382, 1317, 1141, 1085, 1050, 696 cm^{-1}. HRMS (EI): *m/z* calcd for $C_{16}H_{20}BNO_3$ [M$^+$]: 285.1536; found: 285.1532.

(15) Although both K_2CO_3 and K_3PO_4 worked well in the coupling reaction of **2** with bromobenzene, we chose K_2CO_3 as a base for further applications due to its milder basicity.

(16) **General Procedure of the Suzuki Coupling [Synthesis of 2,4-Diphenyloxazole (5)].**
A solution of **2** (60 mg, 0.22 mmol), bromobenzene (23 μL, 0.22 mmol), tetrakis(triphenylphosphine)palladium(0) (13 mg, 11 μmol) and K_2CO_3 (92 mg, 0.66 mmol) in DMF (1 mL) was heated at 100 °C for 30 min under Ar. The reaction mixture was diluted with Et_2O (30 mL) and washed with H_2O (10 mL) and then dried over Na_2SO_4. Concentration of the solvent in vacuo gave a residue, which was purified by silica gel column chromatography (hexane–EtOAc, 20:1) to give 2,4-diphenyloxazole (**5**, 43 mg, 88%) as a white solid. All characterization data of **5** were compatible with the literature.[13]

(17) Self-coupling reaction of the borane reagent **2** occurred to give 2,2′-diphenyl-4,4′-bioxazole in ca. 20% yield. This undesired event sometimes happened in slow Suzuki reaction, see: Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* **1996**, *61*, 2346.