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CONVENIENT SYNTHESIS OF PHARMACOLOGICALLY ACTIVE ORTHO-SUBSTITUTED BIARYL OXAZOLINES VIA THE SUZUKI REACTION

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We describe an efficient protocol for the Suzuki–Miyaura synthesis of ortho-substituted biphenyl oxazolines from 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline and aryl boronic acids or aryl boronates. The Suzuki coupling is carried out in the presence of $Pd(PPh_3)_4$ and sodium carbonate in aqueous tetrahydrofuran. The scope and limitations of the reaction are discussed.

Keywords: Biaryls; cross-coupling; oxazolines; palladium catalyst; Suzuki coupling

INTRODUCTION

Biaryls are important substructures found in many biologically active compounds (Fig. 1). The special utility of ortho-biaryls may arise from the gauche conformation imposed by repulsive unbonded interactions and the ability of this twisted architecture to interact with some conserved protein structure, which results in broad pharmacological activity. Biaryls have been successfully utilized as lipophilic peptidomimetics and as replacements for more complex hydrocarbon skeletons. These include the angiotensin II receptor antagonists[1] exemplified by telmisartan[2–4] (**1**), losartan (**2**), and the hypolipidemic xenalipin (**3**).

RESULTS AND DISCUSSION

In the course of our research efforts, we required access to novel biaryl oxazolines. Adapting published methods based on oxazoline chemistry[5–11] and preparation of these biaryl oxazolines[12] resulted in multistep sequences, which often involved chromatographic separations and gave poor overall yields. Until now, these biaryl oxazolines have been synthesized by nucleophilic aromatic substitution on

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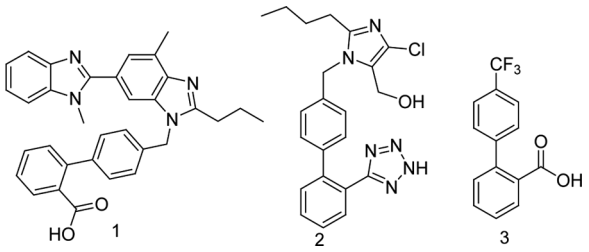
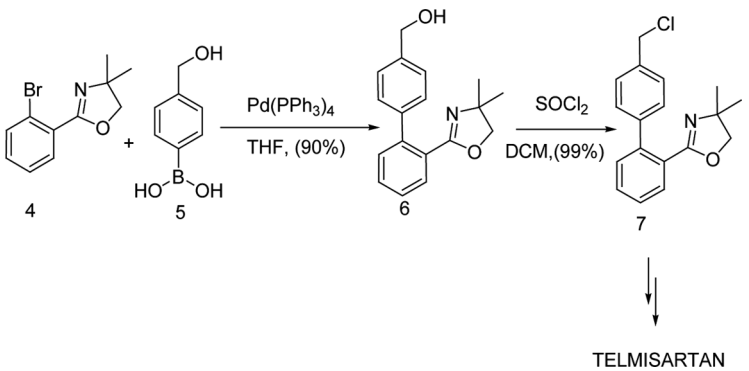


Figure 1. Angiotensin II receptor antagonists telmisartan, losartan, and hypolipidemic agent, xenalipin.

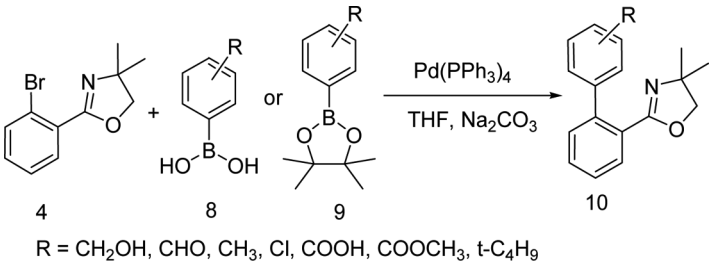
aryloxazolines, but we thought that these could also be prepared by the Suzuki coupling reaction. The Suzuki reaction has evolved as a powerful tool for the construction of C–C bonds in organic chemistry.

We initially chose the oxazoline moiety as a carboxy synthon because of its ortho-metalling properties, its stability to many common reaction conditions, its use as a versatile synthetic intermediate, and the recovery of the parent acid under mild conditions. With 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (**4**) in hand, several Suzuki coupling reactions were carried out. This compound was prepared by standard methods in a very good yield. As part of our initial strategy toward the synthesis of biaryl oxazolines derivatives, we first planned to apply a Suzuki coupling between 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline **4** (which was prepared from commercially available 2-bromo benzoic acid as per literature procedure[5]) and 4-(hydroxymethyl) phenyl boronic acid as shown in Scheme 1. Under optimal reaction conditions [5 mol% Pd $(PPh_3)_4$, 2 equiv of 2 M Na_2CO_3, and aqueous tetramethylsilane (THF) as solvent], Suzuki coupling afforded biaryl product **6** in more than 90% yield.

With the success of the Suzuki coupling reaction, biaryl oxazoline (**6**) was prepared efficiently in multigram quantities via this route as shown in Scheme 1. After Suzuki coupling, the biaryl oxazoline (**6**) on reaction with thionyl chloride at 0–5 °C for 2 h gave the key intermediate 2-(4′-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole (**7**) in more than 99% yield.



Scheme 1. Convergent scheme for 2-(4′-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole.



Scheme 2. Ortho-substituted biaryl oxazolines synthesis via Suzuki coupling.

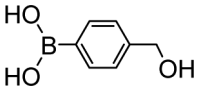
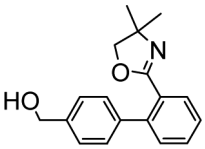
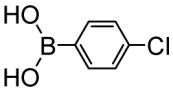
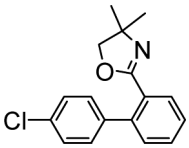
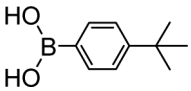
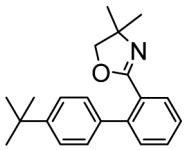
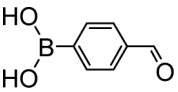
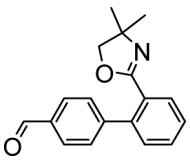
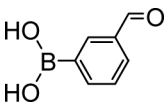
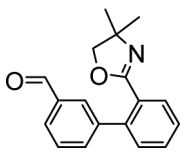
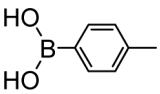
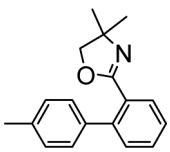
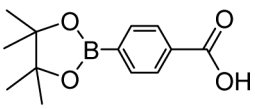
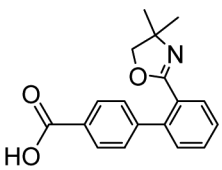
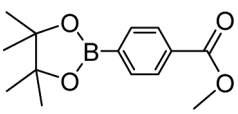
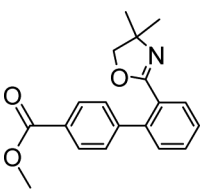
The two-step sequence has greatly improved the synthesis of biaryl oxazoline (**7**) over the literature procedure[12]: it gave better yield (overall yield 90%), needed less preparation time, and required only one-column separation. With these Suzuki coupling conditions, we were able to access other functionalized biaryl oxazolines. We applied this method to prepare a set of substituted biaryl oxazolines using similar reaction conditions (Table 1). In general, these Suzuki coupling conditions worked well between aryl boronic acids (entries 1–6) or aryl boronates (entries 7 and 8) with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline.

With 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline in hand, several Suzuki coupling reactions were carried out. First, the coupling reaction with 4-(hydroxymethyl)phenylboronic acid was examined, mainly because the coupling reaction would provide a two-step method to synthesize 2-(4′-chloromethyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole, which is key intermediate of telmisartan, an angiotensin II receptor antagonist useful in the treatment of hypertension, heart diseases, heart strokes, and bladder diseases. The reaction indeed gave the intermediate (Table 1, entry 1) in 90% yield using 5% $Pd(PPh_3)_4$ and in 75% yield using 1% $Pd(PPh_3)_4$ catalyst.

To examine the scope of the reaction, 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline was subjected to similar conditions with 4-chloro phenylboronic acid and gave the desired product in about 82% yield (entry 2). The effect of substituents was investigated with various aryl boronic acids and aryl boronates. In entries 2–6, the reactions with electron-rich and electron-poor substituents proceeded smoothly to give corresponding biphenyl oxazolines in moderate to good yields. Under these conditions, 4-(methoxycarbonyl)benzene boronicacid pinacol ester did not react with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline in aqueous THF conditions even after prolonged stirring; substituting aqueous THF with dimethylformamide (DMF) gave the product in only 5% yield (entry 7). The poor yield is probably due to the presence of the polar carboxyl group. When the carboxylic acid group was converted to methyl ester, the reaction proceeded smoothly with 65% yield (entry 8). *para*-Substituted boronic acids or boronates (entries 1–4, 6, and 8) effectively coupled with 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline to give the product in moderate to good yields, better than the *meta*-substituted boronic acids.

In summary, we have described a simple and efficient method for the preparation of ortho-substituted biphenyl oxazolines. This method provides a ready alternative to the synthesis of a wide variety of biaryl carboxylic acids and biaryl nitriles.

Table 1. Coupling reactions of 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline with aryl boronic acids and aryl boronates

Entry	Arylboronic acid	Product	Time (h)	Yield (%)
1			3	90
2			2	82
3			3	80
4			8	76
5			8	60
6			6	85
7			24	5
8			4	65

EXPERIMENTAL

Materials and Instruments

All aryl boronic acids, aryl boronates, solvents, and reagents were purchased from Aldrich and Alfa Aesar suppliers and were used without further purification. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. Thin-layer chromatography (TLC) was performed on Merck precoated silica-gel $60F_{254}$ plates. ^{1}H and ^{13}C NMR spectra were recorded in dimethylsulfoxide (DMSO-d_6) at 400 MHz on a Varian Gemini 400-MHz Fourier transform (FT) NMR spectrometer. The chemical shifts were reported in δ ppm relative to tetramethylsilane (TMS). The mass spectra were recorded on Shimadzu LCMS-QP 800 liquid chromatography–mass spectrometry (LC-MS) and AB-4000 Q-trap LC-MS/MS instruments. Elemental analyses were performed on a Flash EA-1112 instrument. Melting points were obtained by using the open capillary method and are uncorrected.

Typical Procedure for Suzuki Coupling

$Pd(PPh_3)_4$ (5 mol%) was added to a degassed solution of aryl boronic acid or aryl boronates (1.0 equiv) and 2-(2-bromophenyl)-4,4-dimethyl-2-oxazoline (1.5 equiv) in 2.0 M sodium carbonate solution (10 mL) and THF (10 mL). The mixture was heated at 60 °C under N_2 for the time indicated in Table 1 [reaction progress was monitored by thin-layer chromatography (TLC)]. After cooling to rt, the solution was diluted with ethyl acetate, washed with H_2O and brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by silica-gel column chromatography using ethyl acetate and heptanes as an eluent to give the coupling products.

Data for [2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-yl]-methanol (Entry 1)

Melting point: 98–100 °C (lit.[12] mp 97–100 °C); ^{1}H NMR ($CDCl_3$) (δ ppm): 7.74 (m, 1H, ArH, $J = 7.4$ Hz), 7.49 (m, 1H, ArH, $J = 7.4$ Hz), 7.40–7.39 (m, 2H, ArH), 7.38 (d, 2H, ArH, $J = 8.0$ Hz), 7.35 (d, 2H, ArH, $J = 8.0$ Hz), 4.75 (s, 2H, $-CH_2$), 3.80 (s, 2H, $-CH_2$), 1.30 (s, 6H, $2 \times -CH_3$); ^{13}C NMR ($CDCl_3$) (δ ppm): 28.7, 66.3, 68.1, 78.9, 127.1, 126.9, 127.7, 128.5, 129.4, 129.4, 130.2, 137.2, 140.2, 141.2, 164.9; MS (m/z): 282 [$M^+ + 1$]. Anal. calcd. for $C_{18}H_{19}NO_2$ (281): C, 76.84; H, 6.81; N, 4.98; O, 11.37. Found: C, 77.02; H, 6.81; N, 4.90.

Data for 2-(4′-Chloro-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydro-oxazole (Entry 2)

An oil; ^{1}H NMR ($CDCl_3$) (δ ppm): 7.60–7.43 (m, 3H, ArH), 7.41 (m, 1H, ArH, $J = 7.4$ Hz), 7.39 (d, 2H, ArH, $J = 8.4$ Hz), 7.24 (d, 2H, ArH, $J = 8.4$ Hz), 3.81 (s, 2H, $-CH_2$), 1.3 (s, 6H, $2 \times -CH_3$); ^{13}C NMR ($CDCl_3$) (δ ppm): 28.6, 68.2, 78.9, 126.7 127.1, 127.7, 128.5, 129.1, 129.7, 130.2, 134.2, 137.7, 139.7, 164.9; MS (m/z): 286

[$M^+ + 1$]. Anal. calcd. for $C_{17}H_{16}ClNO$ (285): C, 71.45; H, 5.64; Cl, 12.41; N, 4.90; O, 5.60. Found: C, 71.51; H, 5.62; N, 4.90.

Data for 2-(4′-*tert*-Butyl-biphenyl-2-yl)-4,4-dimethyl-4,5-dihydro-oxazole (Entry 3)

An oil; ^{1}H NMR ($CDCl_3$) (δ ppm): 7.57–7.40 (m, 3H, ArH), 7.39 (m, 1H, ArH, $J = 7.4$ Hz), 7.37 (d, 2H, ArH, $J = 8.4$ Hz), 7.22 (d, 2H, ArH, $J = 8.4$ Hz), 3.76 (s, 2H, $-CH_2$), 1.26 (s, 9H, $3 \times -CH_3$), 1.18 (s, 6H, $2 \times -CH_3$); ^{13}C NMR ($CDCl_3$) (δ ppm): 28.6, 31.3, 35.2, 68.1, 78.9, 127.27, 127.28, 127.78, 129.4, 129.5, 130.2, 136.6, 137.8, 140.2, 151.6, 164.8; MS (*m*/*z*): 308 [$M^+ + 1$]. Anal. calcd. for $C_{21}H_{25}NO$ (307): C, 82.04; H, 8.20; N, 4.56; O, 5.20. Found: C, 82.09; H, 8.29; N, 4.55.

Data for 2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carbaldehyde (Entry 4)

An oil; ^{1}H NMR (DMSO-d_6) (δ ppm): 10.0 (s, 1H, –CHO), 7.91 (d, 2H, ArH, $J = 8.4$ Hz), 7.73 (d, 1H, ArH, $J = 8.4$ Hz), 7.48 (d, 2H, ArH, $J = 7.8$ Hz), 7.44–7.34 (m, 2H, ArH), 7.30 (m, 1H, ArH, $J = 7.4$ Hz), 3.80 (s, 2H, $-CH_2$), 1.12 (s, 6H, $2 \times -CH_3$); ^{13}C NMR (DMSO-d_6) (δ ppm): 28.0, 68.0, 78.9, 128.0, 128.5, 129.5, 129.6, 130.4, 130.5, 131.2, 135.3, 140.2, 147.0, 161.8, 193.2; MS (*m*/*z*): 280 [$M^+ + 1$]. Anal. calcd. for $C_{18}H_{17}NO_2$ (279): C, 77.40; H, 6.13; N, 5.01; O, 11.46. Found: C, 77.02; H, 6.30; N, 5.04.

Data for 2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-3-carbaldehyde (Entry 5)

An oil; ^{1}H NMR (DMSO-d_6) (δ ppm): 10.05 (s, 1H, –CHO), 7.92 (s, 1H, ArH), 7.86 (d, 1H, ArH, $J = 7.6$ Hz), 7.80 (d, 1H, ArH, $J = 7.2$ Hz), 7.68 (d, 1H, ArH, $J = 7.6$ Hz), 7.59–7.53 (m, 2H, ArH), 7.51–7.40 (m, 2H, ArH), 3.80 (s, 2H, $-CH_2$), 1.27 (s, 6H, $2 \times -CH_3$); ^{13}C NMR (DMSO-d_6) (δ ppm): 28.6, 68.1, 78.9, 128.0, 128.7, 129.0, 129.5, 129.6, 130.4, 130.5, 130.8, 131.2, 133.3, 140.2, 141.7, 166.9, 191.6; MS (*m*/*z*): 280 [$M^+ + 1$]. Anal. calcd. for $C_{18}H_{17}NO_2$ (279): C, 77.40; H, 6.13; N, 5.01; O, 11.46. Found: C, 77.02; H, 6.30; N, 5.04.

Data for 4,4-Dimethyl-2-(4′-methyl-biphenyl-2-yl)-4,5-dihydro-oxazole (Entry 6)

Melting point: 56–58 °C (lit.[12] mp 57–59 °C); ^{1}H NMR ($CDCl_3$) (δ ppm): 7.57–7.37 (m, 3H, ArH), 7.35 (m, 1H, ArH, $J = 7.4$ Hz), 7.22 (d, 2H, ArH, $J = 8.4$ Hz), 7.19 (d, 2H, ArH, $J = 8.4$ Hz), 3.82 (2H, s, $-CH_2$), 2.32 (s, 3H, $-CH_3$), 1.30 (s, 6H, $2 \times -CH_3$); ^{13}C NMR ($CDCl_3$) (δ ppm): 21.2, 28.6, 68.1, 78.9, 127.2, 127.2, 127.7, 129.3, 129.4, 129.5, 130.2, 136.6, 137.8, 140.2, 164.9; MS (*m*/*z*): 266 [$M^+ + 1$]. Anal. calcd. for $C_{18}H_{19}NO$ (265): C, 81.48; H, 7.22; N, 5.28; O, 6.03. Found: C, 81.41; H, 7.20; N, 5.25.

Data for 2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carboxylic Acid (Entry 7)

Melting point: 191–193 °C (lit.[12] mp 191–193 °C); ^{1}H NMR (DMSO-d_6) (δ ppm): 12.9 (broad-s, 1H, –COOH), 7.94 (d, 2H, ArH, $J = 8.4$ Hz), 7.64 (m, 1H, ArH, $J = 7.4$ Hz), 7.56 (m, 1H, ArH, $J = 7.4$ Hz), 7.45–7.42 (m, 2H, ArH), 7.41 (d, 2H, ArH, $J = 8.4$ Hz), 3.76 (s, 2H, $-CH_2$), 1.15 (s, 6H, 2 × $-CH_3$); ^{13}C NMR (DMSO-d_6) (δ ppm): 28.1, 68.0, 78.9, 128.0, 128.3, 128.9, 129.5, 130.0, 130.4, 130.5, 131.2, 140.4, 145.2, 162.1, 167.7; MS (m/z): 296 [$M^+ + 1$]. Anal. calcd. for $C_{18}H_{17}NO_3$ (295): C, 73.20; H, 5.80; N, 4.74; O, 16.25. Found: C, 73.30; H, 5.79; N, 4.70.

Data for 2′-(4,4-Dimethyl-4,5-dihydro-oxazol-2-yl)-biphenyl-4-carboxylic Acid Methyl Ester (Entry 8)

An oil; ^{1}H NMR ($CDCl_3$) (δ ppm): 7.96 (d, 2H, ArH, $J = 8.4$ Hz), 7.66 (m, 1H, ArH, $J = 7.4$ Hz), 7.56 (m, 1H, ArH, $J = 7.4$ Hz), 7.48–7.44 (m, 2H, ArH), 7.42 (d, 2H, ArH, $J = 8.4$ Hz), 3.84 (s, 3H, $-CH_3$), 3.76 (s, 2H, $-CH_2$), 1.15 (s, 6H, 2 × $-CH_3$); ^{13}C NMR ($CDCl_3$) (δ ppm): 24.6, 47.4, 62.8, 74.7, 123.0, 123.1, 123.6, 124.0, 124.5, 125.2, 125.5, 125.8, 135.8, 141.1, 158.3, 162.3; MS (m/z): 310 [$M^+ + 1$]. Anal. calcd. for $C_{19}H_{19}NO_3$ (309): C, 73.77; H, 6.19; N, 4.53; O, 15.51. Found: C, 73.56; H, 6.23; N, 4.59.

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