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Pd(II)-catalyzed *ortho* arylation of 2-arylbenzothiazoles with aryl iodides via benzothiazole-directed C–H activation

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ABSTRACT

A novel and efficient method for the arylation of 2-arylbenzothiazoles is described via C–H activation. The desired C_{Ar}–C_{Ar} bond formation proceeded efficiently with good functional-group tolerance and high regioselectivity. Proposed mechanism for the arylation of 2-arylbenzothiazole is depicted.

1. Introduction

Construction of carbon–carbon bond is fundamental to all of organic chemistry. Aryl–aryl bonds are founded in diverse natural products, medicinal agents, and organic materials. Metal complexes-catalyzed reactions for the formation of C_{Ar}–C_{Ar} bonds are widely used in organic synthesis. Transition metal-catalyzed cross-couplings are among the most traditional synthetic methods [1–9], such as the Suzuki–Miyaura reaction, Stille reaction, Kumada reaction, and Negishi reaction. However, the formation of these bonds involved nucleophilic aromatic substitution reactions between electron-deficient organic halides and stoichiometric amounts of organometallic reagents, both coupling components must be functionalized. The required organometallic nucleophilic reagents are often not commercially available or are relatively expensive. Their preparation process usually involves many synthetic steps, during which undesired byproducts are formed. Therefore, transition metal-catalyzed direct arylation reaction through cleavage of C–H bond is an alternative to the traditional strategy. The C–H activation [10–17] progress involves just one or no functionalized coupling components, which represent an environmentally and economically more attractive method. The most widely studied area in this field is transitional metal-catalyzed ligand-directed C–H activation followed by cross-coupling to form C(sp2)–C(sp2), C(sp2)–C(sp3), and C(sp3)–C(sp3) bonds. For example, amide [18], oxime ether [19], pyridine [20–22], oxazoline [23,24], and carboxylic acid [25,26] serve as directing groups for Pd-catalyzed *ortho*-arylation have been extensively studied.

As a privileged fragment, 2-arylbenzothiazole core is found in many natural products and pharmaceuticals that exhibit remarkable biological activities [27–30]. Typical examples include [^{11}C]PIB (an agent in clinical trials for early diagnosis of Alzheimer's disease) [31,32] GW610 (antitumor agent) [30], and 5F203 (antitumor agent) [33] (Fig. 1). Many efforts continue to be given to the development of new 2-arylbenzothiazole structures and new methods for their constructions [34–38]. As a part of our continuing efforts for the expeditious synthesis of biologically relevant heterocyclic compounds [39–46], herein we would like to report our recent efforts towards the synthesis of diverse 2-arylbenzothiazoles via Pd-catalyzed C–H activation reactions.

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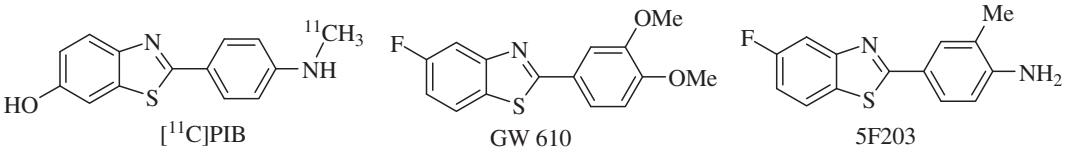


Fig. 1. Potential therapeutic/diagnostic 2-arylbenzothiazoles.

2. Experimental

2.1. General remarks

All reactions were performed in reaction tubes under nitrogen atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ using a Bruker Avance (AV400) spectrometer in parts per million from internal tetramethylsilane on the δ scale. HRMS were obtained using a Nova NanoSEM 200 (FEI) instrument with ESI ionization.

2.2. General procedure for C–H bond activation/arylation of 2-arylbenzothiazoles **1** with aryl iodides **2**

In a 20 mL Teflon tube, a mixture of 2-phenylbenzothiazole **1** (0.3 mmol, 1.0 equiv), aryl iodides **2** (1.2 mmol, 4.0 equiv), AgOAc (1.5 mmol, 5.0 equiv), and $Pd(OAc)_2$ (10 mol%) in dried TFA (2.0 mL) was stirred at 90 °C for 12–72 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature, the resulting mixture was extracted with ethyl acetate (3 × 20 mL), The organic layer was evaporated under vacuum, and then the residue was purified by flash column chromatography on silica gel to provide the corresponding pure product **3** and (or) **4**.

2.2.1. 2-(4,4″-Dimethyl-[1,1′:3′,1″-terphenyl]-2′-yl)benzo[d]thiazole, **3a**

White powder; yield: 97 mg (83%); mp 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 6H), 6.96 (d, J = 7.6 Hz, 4H), 7.14 (d, J = 7.6 Hz, 4H), 7.26 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 121.3, 123.3, 124.7, 125.5, 128.7, 129.2, 129.4, 129.6, 131.4, 136.5, 136.6, 137.8, 142.9, 152.6, 167.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{22}NS$: 392.1473; found: 392.1468.

2.2.2. 2-([1,1′:3′,1″-Terphenyl]-2′-yl)benzo[d]thiazole, **3b**

Colorless oil; yield: 67.7 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.17 (m, 7H), 7.24–7.27 (m, 4H), 7.33 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.3, 123.3, 124.8, 125.6, 127.0, 127.9, 129.3, 129.6, 129.8, 131.5, 136.5, 140.7, 142.9, 152.5, 167.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{18}NS$: 364.116; found: 364.1156.

2.2.3. 2-(4,4″-Dimethyl-[1,1′:3′,1″-terphenyl]-2′-yl)-6-methylbenzo[d]thiazole, **3c**

Yellow powder; yield: 82.6 mg (68%); mp 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 6H), 2.29 (s, 3H), 6.86 (d, J = 8.0 Hz, 4H), 7.06 (d, J = 8.0 Hz, 5H), 7.31 (s, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.43–7.47 (m, 1H), 7.64 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 21.5, 121.0, 122.8, 127.1, 128.6, 129.2, 129.4, 129.5, 131.6, 134.7, 136.5, 136.8, 137.9, 142.9, 150.8, 166.1; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{24}NS$: 406.1629; found: 406.1630.

2.2.4. 2-(4,4″-Dimethoxy-[1,1′:3′,1″-terphenyl]-2′-yl)-6-methylbenzo[d]thiazole, **3d**

Yellow powder; yield: 69.5 mg (53%); mp 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.68 (s, 6H), 6.68 (d, J = 7.2 Hz, 4H), 7.14–7.18 (m, 5H), 7.39–7.43 (m, 3H), 7.51 (t, J = 8.0 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 55.1, 113.3, 121.0, 122.8, 127.1, 129.3, 129.6, 130.4, 131.6, 133.2, 134.8, 136.8, 142.6, 150.8, 158.5, 166.2; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{24}NO_2S$: 438.1528; found: 438.1522.

2.2.5. 2-(4,4″-Dichloro-[1,1′:3′,1″-terphenyl]-2′-yl)-6-methylbenzo[d]thiazole, **3e**

Yellow powder; yield: 80.1 mg (60%); mp 176–178 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 7.03 (d, J = 8.4 Hz, 4H), 7.08–7.12 (m, 5H), 7.32–7.37 (m, 3H), 7.47 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 121.1, 122.9, 127.6, 128.2, 129.7, 129.8, 130.6, 131.7, 133.2, 135.3, 136.6, 139.0, 141.9, 150.7, 164.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{18}Cl_2NS$: 446.0537; found: 446.0540.

2.2.6. 6-Chloro-2-(4,4″-dimethyl-[1,1′:3′,1″-terphenyl]-2′-yl)benzo[d]thiazole, **3f**

Yellow powder; yield: 105.8 mg (83%); mp 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 6H), 6.86 (d, J = 8.0 Hz, 4H), 7.04 (d, J = 8.0 Hz, 4H), 7.17 (dd, J = 2.0, 8.8 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.42–7.47 (m, 2H), 7.64 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 120.9, 124.0, 126.4, 128.7, 129.2, 129.4, 129.8, 130.7, 131.1, 136.7, 137.7, 137.8, 142.9, 151.2, 167.8; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{21}ClNS$: 426.1083; found: 426.1078.

2.2.7. 2-([1,1′:3′,1″-Terphenyl]-2′-yl)-6-chlorobenzo[d]thiazole, **3g**

Yellow oil; yield: 89.3 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04–7.05 (m, 6H), 7.13–7.17 (m, 5H), 7.36 (d, J = 7.6 Hz, 2H), 7.46 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.9, 124.0, 126.5, 127.1, 128.0, 129.3, 129.6, 129.9, 130.8, 131.2, 137.7, 140.6, 143.0, 151.2, 167.5; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{17}ClNS$: 398.077; found: 398.0765.

2.2.8. 6-Chloro-2-(4,4″-dichloro-[1,1′:3′,1″-terphenyl]-2′-yl)benzo[d]thiazole, **3h**

Yellow powder; yield: 86.3 mg (62%); mp 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.18 (m, 8H), 7.33 (dd, J = 2.0, 8.8 Hz, 1H), 7.43 (d, J = 7.6 Hz, 2H), 7.58 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.0, 124.2, 126.8, 128.3, 129.8, 130.1, 130.6, 131.1, 131.2, 133.4, 137.6, 138.8, 141.9, 151.1, 166.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{15}Cl_3NS$: 465.9991; found: 465.9985.

2.2.9. 2-(4,4″-Dimethyl-[1,1′:3′,1″-terphenyl]-2′-yl)-6-fluorobenzo[d]thiazole, **3i**

Yellow oil; yield: 92.0 mg (75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 6H), 6.85 (d, J = 8.0 Hz, 4H), 6.93 (dt, J = 2.4, 8.8 Hz, 1H),

7.04 (d, J = 8.0 Hz, 4H), 7.15 (dd, J = 2.4, 8.0 Hz, 1H), 7.32 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.67 (dd, J = 9.2, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 107.4 (d, $^2J_{C-F}$ = 27.0 Hz), 114.2 (d, $^2J_{C-F}$ = 24.0 Hz), 124.1 (d, $^3J_{C-F}$ = 9.0 Hz), 128.7, 129.2, 129.4, 129.8, 131.2, 136.7, 137.6 (d, $^3J_{C-F}$ = 11.0 Hz), 137.8, 143.0, 149.3, 160.1 (d, $^1J_{C-F}$ = 244.0 Hz), 166.9 (d, $^4J_{C-F}$ = 4.0 Hz); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{27}H_{21}FNS$: 410.1379; found: 410.1373.

2.2.10. 2-([1,1′:3′,1″-Terphenyl]-2′-yl)-6-fluorobenzo[d]thiazole, ***3j***

Yellow oil; yield: 83.4 mg (73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91–6.96 (m, 2H), 7.04–7.08 (m, 6H), 7.11–7.16 (m, 4H), 7.37 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 7.2 Hz, 1H), 7.62–7.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.3 (d, $^2J_{C-F}$ = 27.0 Hz), 114.3 (d, $^2J_{C-F}$ = 24.0 Hz), 124.1 (d, $^3J_{C-F}$ = 9.0 Hz), 127.1, 127.9, 129.3, 129.6, 129.8, 131.3, 137.5 (d, $^3J_{C-F}$ = 12 Hz), 140.6, 143.0, 149.2, 161.2 (d, $^1J_{C-F}$ = 244.0 Hz), 166.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{25}H_{17}FNS$: 382.1066; found: 382.1060.

2.2.11. 6-Chloro-2-(5′-methoxy-4,4″-dimethyl-[1,1′:3′,1″-terphenyl]-2′-yl)benzo[d]thiazole, ***3k***

Yellow powder; yield: 71 mg (52%); mp 158–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 6H), 3.88 (s, 3H), 6.92–7.00 (m 6H), 7.13 (d, J = 8.0 Hz, 4H), 7.27 (dd, J = 2.0, 8.8 Hz, 1H), 7.56 (s, 1H), 7.72 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 55.5, 114.9, 120.8, 123.8, 123.9, 126.3, 128.7, 129.1, 130.5, 136.8, 137.8, 137.9, 144.5, 151.2, 160.1, 168.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{23}ClNOS$: 456.1189; found: 456.1183.

2.2.12. 6-Chloro-2-(5′-methoxy-[1,1′:3′,1″-terphenyl]-2′-yl)benzo[d]thiazole, ***3l***

Yellow powder; yield: 76.8 mg (60%); mp 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.91 (s, 2H), 7.01–7.11 (m, 6H), 7.12–7.20 (m, 5H), 7.45 (d, J = 1.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 115.1, 120.8, 123.9, 124.0, 126.4, 127.2, 128.0, 129.2, 130.6, 137.9, 140.7, 144.6, 151.2, 160.2, 167.7; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{19}ClNOS$: 428.0876; found: 428.0870.

2.2.13. 6-Chloro-2-(4,4″,5′-trimethoxy-[1,1′:3′,1″-terphenyl]-2′-yl)benzo[d]thiazole, ***3m***

Yellow oil; yield: 96.4 mg (66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 6H), 3.90 (s, 3H), 6.70 (d, J = 8.4 Hz, 4H), 6.95 (s, 2H), 7.16 (d, J = 8.4 Hz, 4H), 7.29 (dd, J = 2.0, 8.8 Hz, 1H), 7.60 (s, 1H), 7.43 (d, J = 8.4 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 55.1, 55.5, 113.4, 114.8, 120.8, 123.9, 126.3, 130.3, 130.5, 133.1, 137.9, 144.2, 151.2, 158.7, 160.1, 168.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{23}ClNO_3S$: 488.1087; found: 488.1082.

2.2.14. 2-(5′-Methoxy-[1,1′:3′,1″-terphenyl]-2′-yl)benzo[d]thiazole, ***3n***

Colorless oil; yield: 62.5 mg (53%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.99 (s, 2H), 7.05–7.18 (m, 6H), 7.19–28 (s, 5H), 7.32 (t, J = 7.6 Hz, 1H), 7.71(d, J = 7.6 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.6, 112.9, 119.5, 120.9, 121.8, 122.9, 123.7, 125.2, 125.9, 126.6, 127.1, 134.4, 138.5, 142.1, 150.4, 157.9, 164.4; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{20}NOS$: 394.1266; found: 394.1260.

2.2.15. 2-(4′-Methyl-[1,1′-biphenyl]-2-yl)benzo[d]thiazole, ***4a***

Colorless oil; yield: 11.7 mg (13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.16 (d, J = 7.6 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.0 Hz, 1H), 7.41–7.52 (m, 4H), 7.72 (d, J = 7.6 Hz, 1H), 8.08 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 120.3, 121.1, 123.8, 124.8, 126.5, 128.0, 128.8, 129.0, 129.3, 129.9, 131.5, 135.6, 136.1, 136.5, 140.6, 151.6, 167.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{16}NS$: 302.1003; found: 302.0998.

2.2.16. 2-([1,1′-Biphenyl]-2-yl)benzo[d]thiazole [47], ***4b***

Colorless oil; yield: 8.6 mg (10%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.39 (m, 6H), 7.42–7.57 (m, 4H), 7.71 (d, J = 7.6 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.3, 123.2, 124.9, 125.9, 127.8, 128.3, 130.0, 130.1, 130.5, 130.9, 132.6, 136.6, 140.2, 141.7, 152.7, 167.9; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{14}NS$: 288.0847; found: 288.0840.

2.2.17. 6-Chloro-2-(5-methoxy-4′-methyl-[1,1′-biphenyl]-2-yl)benzo[d]thiazole, ***4k***

Yellow powder; yield: 10.9 mg (10%); mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.81 (s, 3H), 6.81 (d, J = 2.4 Hz, 1H), 6.94 (dd, J = 2.4, 8.4 Hz, 1H), 7.08–7.20 (m, 4H), 7.29 (dd, J = 2.0, 8.8 Hz, 1H), 7.57 (d, J = 2.0 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 55.5, 113.6, 116.0, 120.8, 123.5, 125.1, 126.5, 129.2, 129.8, 130.4, 131.9, 137.0, 137.7, 138.1, 143.5, 151.3, 160.9, 168.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{17}ClNOS$: 366.0719; found: 366.0715.

2.2.18. 6-Fluoro-2-(4-methyl-[1,1′-biphenyl]-2-yl)benzo[d]thiazole, ***4o***

Colorless powder; yield: 59.3 mg (62%); mp 105–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.16–7.20 (m, 1H), 7.24–7.40(m, 8H), 7.88 (s, 1H), 7.97 (dd, J = 4.8, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 106.3 (d, $^2J_{C-F}$ = 27.0 Hz), 113.5 (d, $^2J_{C-F}$ = 24.0 Hz), 122.9 (d, $^3J_{C-F}$ = 9.0 Hz), 126.7, 127.3, 129.0, 129.6, 129.8, 130.0, 131.0, 136.5 (d, $^3J_{C-F}$ = 11.0 Hz), 136.7, 137.9, 139.0, 148.3 (d, $^4J_{C-F}$ = 1.0 Hz), 159.2 (d, $^1J_{C-F}$ = 244.0 Hz), 166.8 (d, $^4J_{C-F}$ = 3.0 Hz); HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{15}FNS$: 320.0909; found: 320.0903.

2.2.19. 2-(4′-Chloro-4-methyl-[1,1′-biphenyl]-2-yl)-6-fluorobenzo[d]thiazole, ***4p***

Colorless powder; yield: 62.5 mg (59%); mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 7.16–7.34 (m, 7H), 7.40 (dd, J = 2.4, 8.0 Hz, 1H), 7.84 (s, 1H), 7.98 (dd, J = 4.8, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 106.5 (d, $^2J_{C-F}$ = 26.0 Hz), 113.6 (d, $^2J_{C-F}$ = 24.0 Hz), 123.1 (d, $^3J_{C-F}$ = 9.0 Hz), 127.5, 129.7, 129.8, 130.0, 130.2, 131.0, 132.8, 136.4 (d, $^3J_{C-F}$ = 11.0 Hz), 136.5, 137.0, 137.5, 148.3, 159.2 (d, $^1J_{C-F}$ = 244.0 Hz), 166.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{14}ClFNS$: 354.052; found: 354.0515.

2.2.20. 2-(4-Chloro-[1,1′-biphenyl]-2-yl)benzo[d]thiazole, ***4q***

Yellow powder; yield: 84.7 mg (88%); mp 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16–7.29 (m, 7H), 7.31–7.38 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.3, 122.4, 124.2, 125.0, 127.1, 127.5, 128.8, 128.9, 129.1, 131.1, 132.9, 133.1, 135.7, 138.2, 139.2, 151.7, 165.0; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{13}ClNS$: 322.0457; found: 322.0452.

2.2.21. 2-(4-Chloro-4′-methoxy-[1,1′-biphenyl]-2-yl)benzo[d]thiazole, ***4r***

Yellow powder; yield: 50.5 mg (48%); mp 91–92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.78 (d, J = 8.8 Hz, 2H), 7.10 (d, J = 8.8 Hz, 2H), 7.20–7.26 (m, 2H), 7.33–7.36 (m, 2H), 7.61 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 8.04 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 54.3, 113.0, 120.3, 122.4, 124.1, 125.0, 128.9, 129.0, 130.1, 130.4, 131.3, 132.6, 133.2, 135.7, 138.9, 151.6, 158.8, 165.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{20}H_{15}ClNOS$: 352.0563; found: 352.0057.

2.2.22. 2-(4,4′-Dichloro-[1,1′-biphenyl]-2-yl)benzo[d]thiazole, ***4s***

Yellow powder; yield: 59.6 mg (56%); mp 89–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.4 Hz, 2H), 7.20–7.27 (m, 4H),

7.35–7.39 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 120.4, 122.4, 124.4, 125.2, 127.7, 129.0, 129.3, 130.1, 131.0, 133.0, 133.2, 133.4, 135.4, 136.6, 137.7, 151.6, 164.6; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{19}H_{12}Cl_2NS$: 356.0068; found: 356.0062.

2.2.23. 2-(3-Methoxy-[1,1′-biphenyl]-2-yl)-6-methylbenzo[d] thiazole, **4t**

Colorless oil; yield: 67.5 mg (68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.77 (s, 3H), 6.97 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.10–7.17 (m, 3H), 7.21 (d, J = 9.2 Hz 1H), 7.23–7.27 (m, 2H), 7.45 (t, J = 8.0 Hz, 1H), 7.51 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 56.1, 110.1, 121.0, 122.1, 122.6, 122.9, 127.0, 127.2, 127.9, 129.3, 130.8, 134.8, 136.9, 140.3, 143.9, 151.2, 158.0, 163.3; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{21}H_{18}NOS$: 332.1109; found: 332.1105.

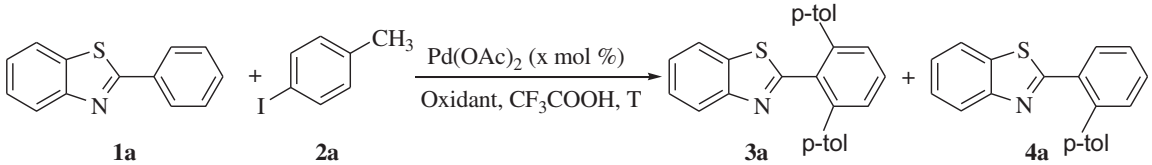
3. Results and discussion

Initially, we studied the coupling of 2-phenylbenzo[d]thiazole **1a** with 1-iodo-4-methylbenzene **2a** in the presence of $Pd(OAc)_2$ to afford **3a** (Table 1). The effects of different oxidants, temperatures, and solvents were systematically investigated. Unfortunately, it failed to provide the desired arylated product when $Cu(OAc)_2$, BQ (1,4-benzoquinone), and oxone were used as oxidant (Table 1, entries 1–3). The use of $PhI(OAc)_2$ as oxidant delivered the desired ortho-diarylated product **3a** in 5% yield, and trace of monoarylated product **4a** (Table 1, entry 4), while AgOAc afforded the **3a** in an encouraged 31% yield (Table 1, entry 5). Further study showed that elevated amount of $Pd(OAc)_2$ led to higher 41% yield (Table 1, entry 5). Examination of the loading of oxidant revealed that the yield was found to grow with increasing oxidant amount (Table 1, entries 6 and 7). Lower yield was obtained when combination of AgOAc and $Cu(OAc)_2$ as oxidant (Table 1, entry 8). No reaction occurred without catalysts or oxidants. Examination of the temperature effect showed that the best results being obtained at relatively high temperature 90 °C (Table 1, entry 9), while inferior results were obtained when the reaction temperature was more than 100 °C (Table 1, entry 11). When trifluoroacetic acid (TFA) was changed to HOAc or 1,4-dioxane, only trace desired product was observed (Table 1, entries 12 and 13). Thus, under optimized conditions [$Pd(OAc)_2$ (10 mol %), AgOAc (5.0 equiv), TFA, 90 °C], the *ortho*-diarylated product **3a**, was obtained in 83% isolated yield, with 13% yield of *ortho*-monoarylated product **4a**.

With this promising result in hand, we started to investigate the scope of this reaction under the optimized conditions. As summarized in Table 2, benzothiazole-directed C–H activation can be extended to a wide variety of substrates. A range of 2-arylbenzothiazoles coupled with aryl iodides to give the corresponding arylated products in moderate to good yields. Electron factors determined the reactivity of the substrates. Substrates aryl iodides or 2-arylbenzothiazoles could tolerate various functional groups such as CH_3, OCH_3, and Cl. Better results were obtained when aryl iodide containing a moderately electron-donating group (CH_3) **2a** or electron-neutral group (H) **2b** was employed. To strong electron-withdrawing group such as NO_2, the desired product was not observed (Table 2, entry 9). For example, 6-chloro-2-phenylbenzo[d]thiazole **1c** reacted with 1-iodo-4-methylbenzene **2a** led to the desired product **3f** in 83% yield (Table 2, entry 6), while 62% yield of **3h** was afforded when 1-chloro-4-iodobenzene **2d** was utilized in the reaction (Table 2, entry 8). Good results were observed when 6-fluoro-2- phenylbenzo[d]thiazole **1d** reacted with **2a** and **2b** (Table 2, entries 10 and 11). When R^2 was a strong electron-donating group (OCH_3), the reactions also occurred smoothly to afford the corresponding products, just in relatively low yield. For instance, reaction of 6-chloro-2-(4-methoxyphenyl) benzo[d]thiazole **1e** with **2a** gave rise to the diarylated cross-coupling product **3k** in 52% yield (Table 2, entry 12). The position of substituent R^2 had a critical effect on the arylation reaction. The arylation showed high regioselectivity for cross-coupling at the less hindered ortho-position for 2-arylbenzothiazoles containing a meta-substituent (Table 2, entries 16–20). In case of ortho-substituted 2-arylbenzothiazole, the arylation occurred at the other ortho-position in good yield (Table 2, entry 21).

Based on known metal-catalyzed directing-group-assisted C–H bond activation reaction and an analogy for the reaction of 2-

Table 1
Optimization of reaction conditions.[a]

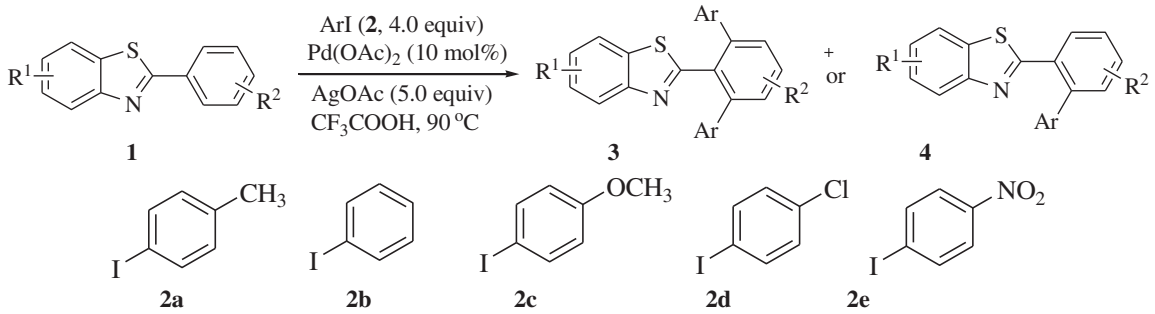


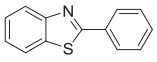
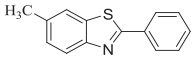
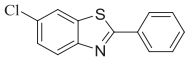
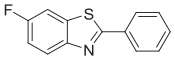
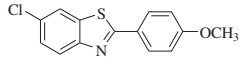
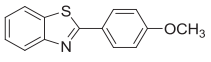
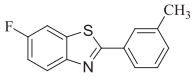
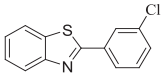
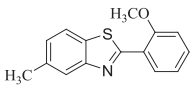
1a **2a** **3a** **4a**

Entry	x	Oxidant (equiv)	T/°C	Yield (%)[b]/3	Yield (%)[b]/4
1	5	$Cu(OAc)_2$ (2.5)	80	–	–
2	5	BQ (2.5)	80	–	–
3	5	Oxone (2.5)	80	–	–
4	5	$PhI(OAc)_2$ (2.5)	80	5	Trace
5	5	AgOAc (2.5)	80	31	3
6	10	AgOAc (2.5)	80	41	5
7	10	AgOAc (5.0)	80	49	8
8	10	AgOAc/$Cu(OAc)_2$(5.0/2.5)	80	44	6
9	10	AgOAc (2.5)	90	73	11
10	10	AgOAc (5.0)	90	83	13
11	10	AgOAc (5.0)	100	60	9
12[c]	10	AgOAc (5.0)	90	Trace	–
13[d]	10	AgOAc (5.0)	90	Trace	–

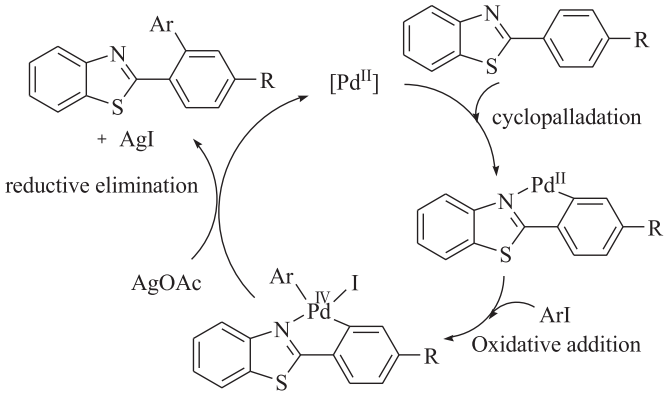
[a] Reaction conditions: 2-phenylbenzo[d]thiazole **1a** (0.3 mmol), 1-iodo-4-methylbenzene **2a** (1.2 mmol, 4.0 equiv), solvent (2 mL), 48 h.
[b] Isolated yield based on 2-phenylbenzo[d]thiazole **1a**.
[c] HOAc as solvent.
[d] 1,4-Dioxane as solvent.

Table 2
C–H bond activation/arylation of 2-arylbenzothiazoles **1** with aryl iodides **2**.[a]



Entry	Substrate **1**	**2**	*t* [h]	Yield (%)[b]/**3**	Yield (%)[b]/**4**
1	 **1a**	**2a**	48	83/**3a**	13/**4a**
2	**1a**	**2b**	72	62/**3b**	10/**4b**
3	 **1b**	**2a**	48	68/**3c**	Trace
4	**1b**	**2c**	24	53/**3d**	Trace
5	**1b**	**2d**	72	60/**3e**	Trace
6	 **1c**	**2a**	48	83/**3f**	Trace
7	**1c**	**2b**	72	75/**3g**	Trace
8	**1c**	**2d**	72	62/**3h**	Trace
9	**1c**	**2e**	72	–	Trace
10	 **1d**	**2a**	48	75/**3i**	Trace
11	**1d**	**2b**	72	73/**3j**	Trace
12	 **1e**	**2a**	72	52/**3k**	10/**4k**
13	**1e**	**2b**	72	60/**3l**	Trace
14	**1e**	**2c**	72	66/**3m**	Trace
15	 **1f**	**2b**	72	53/**3n**	Trace
16	 **1g**	**2b**	36	–	62/**4o**
17	**1g**	**2d**	48	–	59/**4p**
18	 **1h**	**2b**	36	–	88/**4q**
19	**1h**	**2c**	36	–	48/**4r**
20	**1h**	**2d**	48	–	56/**4s**
21	 **1i**	**2b**	12	–	68/**4t**

[a] Reaction conditions: 2-arylbenzothiazole **1** (0.3 mmol), aryl iodide **2** (1.2 mmol, 4.0 equiv), CF_3COOH (2 mL), 90 °C, 12–72 h.
[b] Isolated yield based on 2-arylbenzothiazole **1**.



Scheme 1. Proposed mechanism for Pd-catalyzed directed arylation with Ag^{I}/Ar–I.

arylbenzoxazole [18–24], a possible reaction mechanism for the arylation of 2-arylbenzothiazole is depicted in Scheme 1. The proposed catalytic cycle involves the following steps: (i) cyclopalladation of 2-arylbenzothiazole via C–H activation, (ii) oxidation addition of Pd(II) to Pd(IV), (iii) reductive elimination affording monoarylated product **4** and Pd(II). The monoarylated product **4** could re-enter the catalytic cycle to ultimately yield the corresponding diarylated compound **3**.

4. Conclusion

In summary, we have described a novel and efficient method for the arylation of 2-arylbenzothiazoles via C–H activation. The desired C_{Ar}–C_{Ar} bond formation proceeded efficiently with good functional-group tolerance and high regioselectivity. Proposed mechanism for the arylation of 2-arylbenzothiazole is depicted. The application of benzothiazole as a directing group to construct a C-heteroatom bond is underway in our laboratory.

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Appendix A. Supporting information

Supplementary data related to this article can be found online at doi:10.1016/j.jorganchem.2012.03.030.

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