Rh(III)-catalyzed oxidative *ortho*-C−H alkylation of 2,4-diarylquinazoline with potassium alkyltrifluoroborates

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Abstract

Alkyltrifluoroborates were used for Rh(III)-catalyzed *ortho*-alkylation of 2,4-disubstituted quinazoline via C-H bond activation. The reaction proceeded well with a broad substrate scope, providing a direct way to access high functional quinazoline core structure derivatives in yields up to 95%.

Keywords： 2,4-diarylquinazoline, alkylation, potassium alkyltrifluoroborate**s**

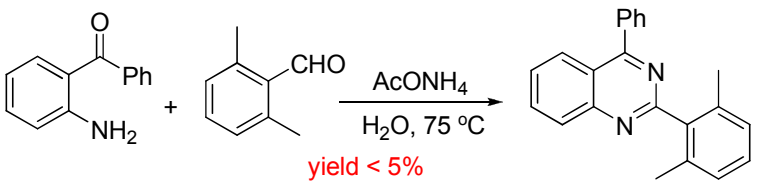
Introduction

The alkyl group, as one of the most common building blocks in small organic molecules, plays an vital role in a myriad of biological processes.[1] The introduction of a alkyl group, especially methyl, to a natural skeleton compound is also an essential process in organic and medicinal chemistry, due to its presence may alter the biological and physical properties of organic compounds.[2] The traditional methylating reagents, such as methyl iodide, dimethyl sulfate, diazomethane and dimethyl carbonate are still widely used in industry as well as in academic.[3] However, these hazardous and toxic alkylating reagents require strongly basic reaction conditions and frequently give both mono- and di-alkylated products. In the past decades, for chemists, much attention has been devoted to the development of new alkylating reagents. For example, alkyl halides,[4] alkylzinc halides,[5] alcohols,[6] alkanes,[7] alkenes,[8] allyl acetates,[9] amides,[10] amino acids,[11] ethers,[12] epoxides,[13] nitroalkanes,[14] organotin reagents,[15] peroxides,[16] α-diazoesters,[17] and organoboron reagents[18] have been reported as transitionmetal-catalyzed alkylation reagents. Among them, organoboron reagents owing to the advantage of commercial availability and excellent stability to air and moisture, have been extensively employed in C-H alkylation ever since a series of reports about alkylation of arenes by Yu group in 2006. [18a]

In recent years, Rh(III)-catalyzed reactions have been widely used in C-H activation of arenes with the coupling partners such as alkenes,[19] alkynes,[20] ketones and aldehydes,[21] imines,[22]azides,[23] isocyanates,[24] azides,[25] and strained rings.[26] However, there are only limited reports on rhodium catalyzed C-H activation of

arenes with organoboron. Li and co-workers revealed that aryl pyridine could be alkylated with alkyltrifluoroborates under rhodium catalysis in the presence of silver salt in 2015.[18g] Recently, Liu reported the Rh(III)-catalyzed site-selective C-H alkylation of pyridones using organoboron reagents.[18h] Soon afterward, our group disclosed rhodium(III)-catalyzed *ortho*-C-H alkylation of 2-arylbenzothiazoles and 2-arylthiazoles with potassium alkyltrifluoroborates.[18i]

Quinazoline or quinazolinone core structures are known as kinds of important potential biological active compounds.[27] In 2012, Durga reported a simple route to 2,4-disubstituted quinazolines in aqueous medium.[27d] In order to obtain methylated quinazoline, we use the traditional method to synthesize 2-(2,6-dimethylphenyl)-4-phenylquinazoline (Scheme **1**). However, the desired product was isolated in less than 5% yield due to steric effects. Therefore, more effective methods for the synthesis of 2-(2,6-dimethylphenyl)-4-phenylquinazoline are desirable. Recently, we have synthesized selectively alkylation and amidation quinazoline derivatives by rhodium-catalyzed regioselective direct C-H activation of 2,4-diarylquinazoline.[28] Based on these precedents, we here want to report Rh(III)-catalyzed *ortho* directing oxidative C-H alkylation of 2,4-diarylquinazoline with potassium alkyltrifluoroborates for synthesis of 2-(2,6-dimethylphenyl)-4-phenylquinazoline.



Scheme **1**. Synthesis of 2-(2,6-dimethylphenyl)-4-phenylquinazoline with traditional method

Experimental

General information

All solvents were dried and distilled according to standard procedures. All reactions were formed in reaction tubes. The Flash column chromatography was performed using silica gel (60 Åpore size, 32-63 mm, standard grade). Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25mm 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 0-20 Torr (house vacuum) at 25-35 ^{0}C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane (TMS) on the δ scale. HRMS was measured on TOF mass spectrometer equippedwith an ESI source.

General procedure

2,4-diphenylquinazoline **1a** (0.2 mmol), $MeBF_3K$ **2a** (0.8 mmol), $[RhCp^*Cl_2]_2$ (4.0 mol %), $AgSbF_6$ (16 mol %) and Ag_2CO_3 (0.36 mmol) in DCE (3 mL). After sealed, the tube was heated to 85℃. After completion of the reaction as indicated by TLC, the reaction mixture was extracted with EtOAc (3 mL*3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacum. The crude residue was purified by flash column chromatograph (EtOAc/Petroleum ether = 1:20) to give the desired product **3a**, as a light yellow solid.

***2-(2,6-dimethylphenyl)-4-p-tolylquinazoline*(4a).** Yellow solid, 91% yield, mp = 166-168 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4

Hz, 1H), 7.80 (t, *J* = 7.6Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.26 (d, *J* = 7.8Hz, 2H), 7.15-.07 (m, 1H), 7.02 (d, *J* = 7.6Hz, 2H), 2.35 (s, 3H), 2.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 163.9, 151.6, 140.2, 139.7, 135.8, 134.5, 133.7, 130.2, 129.3, 129.0, 128.3, 127.8, 127.5, 127.2, 121.2, 21.5, 20.2. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{21}N_2^+$: 325.1705; found: 325.1701.

***2-mesityl-4-p-tolylquinazoline*(4b).** Yellow solid, 90% yield, mp = 123-124 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.91-7.88 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.64-7.57 (m, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 6.95 (s, 2H), 2.46 (s, 3H), 2.32 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 164.1, 151.6, 140.1, 137.8, 136.9, 135.7, 134.5, 133.5, 130.2, 129.3, 129.0, 128.6, 127.3, 127.3, 121.1, 21.5, 21.2, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{23}N_2^+$: 339.1861; found: 339.1865.

***2-(4-methoxy-2,6-dimethylphenyl)-4-p-tolylquinazoline*(4c).** Yellow solid, 95% yield, mp = 185-186 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.91-7.89 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.63-7.59 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 6.69 (s, 2H), 3.82 (s, 3H), 2.47 (s, 3H), 2.21 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 163.8, 159.2, 151.5, 140.1, 137.6, 134.4, 133.5, 132.7, 130.1, 129.2, 128.9, 127.2, 127.1, 120.9, 113.2, 55.2, 21.4, 20.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{23}N_2O^+$: 355.1810; found: 355.1814.

***N,N,3,5-tetramethyl-4-(4-p-tolylquinazolin-2-yl)aniline*(4d).** Yellow solid, 92% yield, mp = 153-154 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.91-7.85 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H),

7.35 (d, *J* = 8.4 Hz, 2H), 6.53 (s, 2H), 2.95 (s, 6H), 2.46 (s, 3H), 2.23 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 164.4, 151.6, 150.7, 139.9, 136.9, 134.7, 133.3, 130.2, 129.2, 128.9, 127.0, 126.9, 120.8, 112.5, 40.81 , 21.5, 20.9. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{26}N_3^+$: 368.2127; found: 368.2124.

***2-(4-chloro-2,6-dimethylphenyl)-4-p-tolylquinazoline*(4e).** Yellow solid, 65% yield, mp = 112-114 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 1H), 7.95-7.91 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.66-7.62 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 2H), 7.14 (s, 2H), 2.47 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 162.9, 151.5, 140.3, 138.1, 137.9, 134.2, 133.7, 133.6, 130.1, 129.3, 128.9, 127.6, 127.2, 121.2, 21.44, 20.06. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{20}ClN_2^+$: 359.1315; found: 359.1314.

***2-(2,5-dimethylphenyl)-4-phenylquinazoline*(4f).** Yellow solid, 70% yield, mp = 163-164 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (t, *J* = 7.6 Hz, 2H), 7.90 -7.84 (m, 3H), 7.79 (s, 1H), 7.58-7.55 (m, 4H), 7.25-7.13 (m, 2H), 2.61 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 163.5, 151.6, 138.5, 137.4, 135.3, 134.2, 133.5, 131.2, 131.1, 130.0, 129.9, 129.8, 129.0, 128.5, 127.1, 126.9, 120.9, 20.9, 20.7.HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{19}N_2^+$: 311.1548; found: 311.1543.

***2-(2,6-dimethylphenyl)-4-phenylquinazoline*(4g).** Yellow solid, 93% yield, mp = 164-165 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (t, *J* = 9.2 Hz, 2H), 7.93 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1H), 7.82 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.63 (ddd, *J* = 8.4, 7.6, 1.2 Hz, 1H), 7.60-7.54 (m, 3H), 7.25-7.19 (m, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 163.9, 151.5, 137.2, 135.8, 133.7, 130.1, 129.9,

128.9, 128.5, 128.2, 127.8, 127.5, 127.0, 121.1, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{19}N_2^+$: 311.1548; found: 311.1543.

***2-(2,6-dimethylphenyl)-4-(4-fluorophenyl)quinazoline*(4h).** Yellow solid, 90% yield, mp = 153-155 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, J = 8.8, 4.0 Hz, 2H), 7.97-7.93 (m, 1H), 7.87-7.82 (m, 2H), 7.68-7.64 (m, 1H), 7.29-7.21 (m, 3H), 7.14 (d, J = 7.2 Hz, 2H), 2.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 163.9 (d, ^1J = 249 Hz), 163.8, 151.6, 139.4, 135.8, 133.8, 133.3 (d, ^3J = 3Hz), 132.1 (d, ^3J = 9 Hz), 129.1, 128.4, 127.8, 127.7, 126.7, 120.9, 115.7 (d, ^2J = 22 Hz), 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{18}FN_2^+$: 329.1454; found: 329.1449.

***2-(2,6-dimethylphenyl)-4-m-tolylquinazoline*(4i).** Yellow solid, 85% yield, mp = 153-154 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 14.4, 8.0 Hz, 2H), 7.93 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.65-7.60 (m, 3H), 7.45 (t, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.23-7.12 (m, 3H), 2.47 (s, 3H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 163.9, 151.5, 139.6, 138.4, 137.1, 135.7, 133.7, 130.7, 130.6, 128.9, 128.3, 128.2, 127.7, 127.4, 127.3, 127.1, 121.2, 21.5, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{21}N_2^+$: 325.1705; found: 325.1701.

***2-(2,6-dimethylphenyl)-4-(4-methoxyphenyl)quinazoline*(4j).** Yellow solid, 70% yield. mp = 165-167 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 8.4 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.91 (ddd, J = 8.4, 6.8, 1.2 Hz, 1H), 7.85-7.82 (m, 2H), 7.63 (ddd, J = 8.2, 7.2, 0.8 Hz, 1H), 7.23-7.19 (m, 1H), 7.14-7.07 (m, 4H), 3.90 (s, 3H), 2.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 163.9, 161.2, 151.6, 139.6, 135.8, 133.5, 131.8, 129.7, 128.9, 128.2, 127.7, 127.3, 127.1, 121.0, 114.0, 55.4, 20.1. HRMS (ESI):

m/z $[M + H]^+$ calcd for $C_{23}H_{21}N_2O^+$: 341.1654; found: 341.1649.

***2-(2,6-dimethylphenyl)-4-(naphthalen-1-yl)quinazoline*(4k).** Yellow solid, 71% yield. mp = 176-177 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 8.02 (dd, *J* = 6.8, 2.8 Hz, 1H), 7.96-7.91 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.64 -7.60 (m, 2H), 7.52-7.48 (m, 3H), 7.41-7.37 (m, 1H), 7.23-7.18 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 2.24 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 164.1, 151.1, 139.5, 135.6, 134.5, 134.1, 133.6, 131.6, 129.7, 128.9, 128.4, 128.3, 127.7, 127.6, 127.3, 126.7, 126.2, 126.1, 125.4, 125.0, 122.8, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{21}N_2^+$: 361.1705; found: 361.1707.

***2-(2,6-dimethylphenyl)-6-methoxy-4-o-tolylquinazoline*(4l).** Yellow solid, 78% yield, mp = 154-155 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 7.58 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.39-7.36 (m, 4H), 7.19 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 2.19 (s, 3H), 2.16 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 162.0, 158.4, 147.3, 139.6, 136.8, 135.9, 135.7, 130.6, 130.4, 129.1, 129.9, 128.1, 127.6, 126.8, 125.7, 122.9, 104.0, 55.7, 19.9, 19.8. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{23}N_2O^+$: 355.1810; found: 325.1816.

***2-(2,6-dimethylphenyl)-6-methoxy-4-p-tolylquinazoline*(4m).** Yellow solid, 83% yield, mp = 156-157 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 9.2 Hz, 1H), 7.74 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.58 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.47 (d, *J* = 2.8 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.22-7.11 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 3.88 (s, 3H), 2.47 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 162.0, 158.3, 147.8, 139.9, 139.6, 135.9, 134.7, 130.4, 129.7, 129.3, 128.1, 127.7, 126.3, 121.9, 104.4, 55.7, 21.4,

20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{23}N_2O^+$: 355.1810; found: 325.1816.

***2-(2,6-dimethylphenyl)-6-methoxy-4-m-tolylquinazoline*(4n)** Yellow solid, 80% yield, mp = 156-157 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 1H), 7.64 -7.57 (m, 3H), 7.46-7.43 (m, 2H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 3.87 (s, 3H), 2.46 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1671, 162.0, 158.30, 147.7, 139.6, 138.5, 137.5, 135.8, 130.5, 130.4, 130.3, 128.3, 128.2, 127.7, 126.8, 126.3, 121.9, 104.4, 55.7, 21.5, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{24}H_{23}N_2O^+$: 355.1810; found: 325.1816.

***2-(2,6-dimethylphenyl)-4-(4-fluorophenyl)-6-methoxyquinazoline*(4o).** Yellow solid, 95% yield, mp = 143-144 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.2 Hz, 1H), 7.86- 7.82 (m, 2H), 7.60 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.39 (d, *J* = 2.4 Hz, 1H), 7.28-7.19 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 2H), 3.88 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 163.7 (d, ^1J = 249 Hz), 161.9, 158.5, 147.8, 139.4, 135.8, 133.6 (d, ^2J = 33 Hz), 131.7 (d, ^3J = 9 Hz), 130.6, 128.2, 127.8, 126.5, 121.8, 115.9, 115.7 (d, ^2J = 22 Hz), 103.9, 55.7, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{20}FN_2O^+$: 359.1560; found: 359.1566.

***6-chloro-2-(2,6-dimethylphenyl)-4-o-tolylquinazoline*(4p).** Yellow solid, 65% yield, mp = 155-156℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.8 Hz, 1H), 7.86 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.70 (d, *J* = 2.4 Hz, 1H), 7.46-7.41 (m, 1H), 7.38-7.34 (m, 3H), 7.21 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 2.19 (s, 3H), 2.16 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 164.3, 149.5, 139.2, 135.9, 135.8, 135.5, 135.0, 133.4, 130.8, 130.6, 129.5, 129.2, 128.4, 127.7, 125.8, 125.8, 122.7, 19.9, 19.8.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{20}ClN_2^+$: 359.1315; found: 359.1319.

***6-chloro-2-(2,6-dimethylphenyl)-4-p-tolylquinazoline*(4q).** Yellow solid, 62% yield, mp = 156-158 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.76 (dd, *J* = 9.2, 24 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.17-7.12 (m, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 2.39 (s, 3H), 2.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 164.2, 150.1, 140.6, 139.3, 135.8, 134.6, 133.9, 133.2, 130.7, 130.1, 129.5, 128.5, 127.9, 125.9, 121.7, 21.5, 20.2. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{20}ClN_2^+$: 359.1315; found: 359.1319.

***6-chloro-2-(2,6-dimethylphenyl)-4-m-tolylquinazoline*(4r).** Yellow solid, 70% yield, mp = 157-158 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 2.4 Hz, 1H), 8.10 (d, *J* = 9.2 Hz, 1H), 7.86 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.61-7.57 (m, 2H), 7.47 (dd, *J* = 9.6, 4.0 Hz, 1H), 7.40 -7.33 (m, 1H), 7.22 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 2H), 2.47 (s, 3H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 1681, 164.2, 150.0, 139.2, 138.7, 136.6, 135.7, 134.7, 133.2, 131.0, 130.7, 130.4, 128.5, 128.4, 127.8, 127.1, 125.9, 121.7, 21.5, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{23}H_{20}ClN_2^+$: 359.1315; found: 359.1319.

***6-chloro-2-(2,6-dimethylphenyl)-4-(naphthalen-1-yl)quinazoline*(4s).** Yellow solid, 68% yield, mp = 183-184 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 9.2 Hz, 1H), 8.04 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.68- 7.60 (m, 3H), 7.54-7.48 (m, 2H), 7.43- 7.39 (m, 1H), 7.25- 7.19 (m, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 2.23 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 164.4, 149.7, 139.1, 135.6, 135.2, 133.8, 133.7, 133.3, 131.4, 130.6, 130.1, 128.5, 128.4, 127.8,

127.7, 126.9, 126.3, 125.9, 125.2, 125.0, 123.4, 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{26}H_{20}ClN_2^+$: 395.1315; found: 395.1315.

***6-chloro-2-(2,6-dimethylphenyl)-4-(4-fluorophenyl)quinazoline*(4t).** Yellow solid, 68% yield, mp = 138-139 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2H), 7.87 (dd, J = 9.2, 2.4 Hz, 1H), 7.85-7.81 (m, 2H), 7.30- 7.21 (m, 3H), 7.14 (d, J = 7.6 Hz, 2H), 2.18 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 164.2, 164.1 (d, ^1J = 249 Hz), 162.9, 150.1, 139.0, 135.7, 134.8, 133.5, 132.7 (d,^3J = 3.3 Hz), 132.1 (d, ^3J = 9 Hz), 130.8, 128.5, 127.9, 125.5, 121.5, 115.8 (d, ^2J = 22 Hz), 20.1. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{22}H_{17}ClFN_2^+$: 363.1064; found: 363.1069.

***2-(2-benzyl-6-methylphenyl)-4-(naphthalen-1-yl)quinazoline*(3u).** Yellow solid, 60% yield, mp = 183-185 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.94-7.90 (m, 2H), 7.62-7.57 (m, 2H), 7.51-7.45 (m, 3H), 7.34-7.29 (m, 2H), 7.20 (dd, J = 23.2, 7.6 Hz, 2H), 7.10-7.06 (m, 4H), 6.98-6.96 (m, 2H), 4.02 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.8, 150.9, 140.8, 139.4, 138.9, 136.2, 134.5, 1341, 133.6, 131.6, 129.7, 129.0, 128.8, 128.5, 128.4, 128.3, 128.1, 127.8, 127.7, 127.5, 127.3, 126.7, 126.2, 125.7, 125.0, 122.76, 39.66, 20.30. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{32}H_{25}N_2^+$: 437.2018; found: 437.2017.

***2-(2-cyclopropyl-6-methylphenyl)-4-(naphthalen-1-yl)quinazoline*(3v).** Yellow solid, 57% yield, mp = 180-181 ℃. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 1H), 8.06-8.00 (m, 1H), 7.99-7.90 (m, 2H), 7.73-7.67 (m, 1H), 7.66 -7.61 (m, 2H), 7.51 (dd, J = 8.0, 7.6 Hz, 3H), 7.40-7.34 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.4 Hz,

1H), 6.93 (d, *J* = 7.8 Hz, 1H), 2.23 (s, 3H), 1.82 (dt, *J* = 13.6, 6.8 Hz, 1H), 0.75-0.51 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 164.3, 151.1, 140.9, 140.5, 135.4, 134.6, 134.1, 133.7, 131.7, 129.7, 128.9, 128.5, 127.7, 127.6, 127.5, 127.3, 126.6, 126.2, 125.5, 125.1, 123.1, 122.8, 20.1, 14.0, 7.9. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{28}H_{23}N_2^+$: 387.1861; found: 387. 1866.

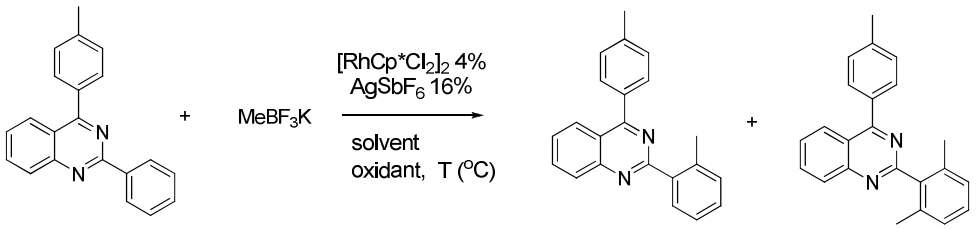
2-(o-tolyl)quinazoline (**3w**). yellow solid, 15% yield, mp = 36-39 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 8.01-7.96 (m, 1H), 7.84-7.82 (m, 1H), 7.60-7.54 (m, 1H), 7.50 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.43-7.34 (m, 4H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 159.9, 151.7, 140.4, 138.6, 137.4, 131.5, 130.9, 129.6, 128.6, 126.1, 122.9, 117.1, 114.5, 21.5. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{15}H_{13}N_2^+$: 221.1079; found: 221.1076.

Results and discussions

The methylation reaction of 2,4-diarylquinazoline is possible on the 2-aryl group or 4-aryl group. Therefore, initially, we selected 2-phenyl-4-(*p*-tolyl)quinazoline **1a** and potassium methyltrifluoroborate **2a** as the model substrate to optimize the reaction conditions. To our delight, a coupling occurred with $[RhCp^*Cl_2]_2$ (4.0 mol %) and $AgSbF_6$ (16 mol %), using AgF (2.8 equiv) as a oxidant in DCM (Table **1**, entry **1**) at 85℃, and the product **3a** was isolated in 15% yield. Interestingly, the methylation occured only on the 2-aryl group rather than the 4-aryl group by analyzing the ^{1}H-NMR, which was consistent with the results of our previous direct C-H amidation of 2,4-diarylquinazoline with sulfonyl azides[28]. The isolation of di-alkylated products **4a** caught our attention. In order to investigate the selectivity of the reaction, different

amounts of $MeBF_3K$ were studied (Table **1**, entry **2-4**). It was noteworthy that in all the tested cases, mono-methylation product and di-methylation were generated depending on the amount of $MeBF_3K$. Further studied showed that 4.0 equiv of $MeBF_3K$ provided a comparable yield of product **4a** with 84%. Next, other oxidants such as Ag_2CO_3, Ag_2O, AgOAc, $AgBF_4$, $AgNO_3$ were screened, and the results indicated that Ag_2CO_3 was the best choice, affording 89% yield (Table **1**, entry **5**). Ag_2O and AgOAc also accelerate this reaction with respectively less yields 81% and 40% (Table **1**, entries **6** and **7**), whereas $AgBF_4$ and $AgNO_3$ were totally ineffective (Table **1**, entries **8** and **9**). Screening of the solvent revealed that $ClCH_2CH_2Cl$ (DCE) seemed to be the crucial one with relatively higher yields 91% (Table **1**, entries **15**), and the coupling in other solvents afforded inferior results (Table **1**, entries **10-14**). To our delight, reducing the amount of oxidant Ag_2CO_3 to 1.8 equiv, the reaction was not affected (Table **1**, entry **16**). The reaction proceeded with poor efficiency when lowering the reaction temperature to 60℃, while elevating the reaction temperature to 95℃ or 100℃ could not make the reaction better than ever before (Table **1**, entries **17-19**). Moreover, product **4a** was isolated in 70 % yield using a lower loading of the catalyst ($[RhCp^*Cl_2]_2$ (1.0 mol %) and $AgSbF_6$ (4 mol %)) (Table **1**, entry **20**). In contrast, the reaction gave no conversion when $[RhCp^*Cl_2]_2$ was omitted (Table **1**, entry **21**).

Table **1**. Optimization Studies[a]



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

Entry	**2a** (equiv)	Oxidant (equiv)	Solvent	*T* (℃)	Yield **3a** (%)[b]	Yield **4a** (%)[b]
1	1.0	AgF (2.8)	DCM	85	15	6
2	1.5	AgF (2.8)	DCM	85	20	2
3	2.0	AgF (2.8)	DCM	85	30	30
4	4.0	AgF (2.8)	DCM	85	trace	84
5	4.0	Ag_2CO_3(2.8)	DCM	85	trace	89
6	4.0	Ag_2O (2.8)	DCM	85	trace	81
7	4.0	AgOAc (2.8)	DCM	85	trace	40
8	4.0	$AgBF_4$(2.8)	DCM	85	trace	trace
9	4.0	$AgNO_3$ (2.8)	DCM	85	trace	10
10	4.0	Ag_2CO_3 (2.8)	MeCN	85	trace	10
11	4.0	Ag_2CO_3 (2.8)	THF	85	trace	15
12	4.0	Ag_2CO_3 (2.8)	Toluene	85	trace	20
13	4.0	Ag_2CO_3 (2.8)	1,4-dioxane	85	trace	24
14	4.0	Ag_2CO_3 (2.8)	DMSO	85	trace	26
15	**4.0**	**Ag_2CO_3 (2.8)**	**DCE**	**85**	trace	**91**
16	**4.0**	**Ag_2CO_3 (1.8)**	**DCE**	**85**	trace	**91**
17	4.0	Ag_2CO_3 (1.8)	DCE	60	trace	85

18	4.0	Ag_2CO_3 (1.8)	DCE	95	trace	90
19	4.0	Ag_2CO_3 (1.8)	DCE	100	trace	90
20[c]	4.0	Ag_2CO_3 (1.8)	DCE	85	trace	70
21[d]	4.0	Ag_2CO_3 (1.8)	DCE	85	NR	NR

[a]Reactions were carried out using 2-*o*-tolyl-4-*p*-tolylquinazoline **1a** (0.2 mmol), $MeBF_3K$ **2a** (0.8 mmol), $[RhCp^*Cl_2]_2$ (4.0 mol %), $AgSbF_6$ (16 mol %) and oxidant in a solvent (3 mL) at 85°C.

[b] Isolated yield.

[c] Reaction was performed in the presence of $[RhCp^*Cl_2]_2$ (1.0 mol %) and $AgSbF_6$ (4 mol %).

[d] No catalyst was added.

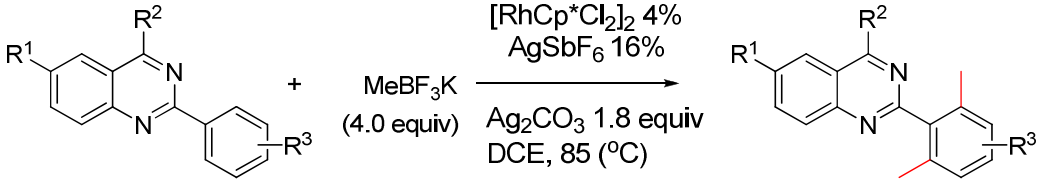
With the optimized conditions [**1a** (0.2 mmol), $MeBF_3K$ **2a** (0.8 mmol), $[RhCp^*Cl_2]_2$ (4.0 mol %), $AgSbF_6$ (16 mol %), and Ag_2CO_3 (0.36 mmol) in DCE (3 mL) at 85°C] in hand, the reaction scope was further explored, and the results were summarized in Table **2**. The results indicated that a broad range of quinazolinones could be well tolerated in this catalytic system. Firstly, the effect of a substituent on the phenyl ring at the 2-position was examined. Evidently, the substrates bearing electron-donor substitutions provided higher yields (**4b**, 90%; **4c**, 95%; **4d**, 92%) than the electron-withdrawing one (**4e**, 65%). It was noteworthy that methylation reacted at the less sterically hindered site to furnish the mono-product in good yield, when the substituted group at the *meta*-position of 2-phenyl ring (**4f**, 70%). No detectable di-methylation was noticed by TLC analysis during this reaction process. Thus, we can conclude herein that mono-methylation product can be obtained by steric hindrance regulated in these reactions. Fortunately, the reaction didn't occur when

2-(2,6-dimethylphenyl)-4-(naphthalen-1-yl)quinazoline was selected as the substrate under the standered reaction conditions(not list in Table **2**), and this also indicated the methylation occurred on the phenyl ring at the 2-position.

Then, the electronic effect of phenyl ring at the 4-position was also investigated. When R_2 was phenyl or 4-fluorophenyl, the reaction provided the corresponding desired product in excellent yield (**4g**, 93%; **4h,** 90%). In contrast, the electron donating substituents such as methyl and CH_3O- on 4-aromatic ring made great impact on the yield (**4i**, 85%; **4j**, 70%). Substrate with naphthalene substituted at 4-position was also tolerant with moderat yield (**4k**, 71%).

Next, we checked the mother aromatic ring of the quinazolinone. A group of quinazolinones were assessed. From the overall evaluation, the substrates with methoxyl group on the mother ring was favorable for the reaction, providing the desired product in higher yield (**4l-4o**, with 78%-95% yields) than those bearing electron-donor groups such as halogen respectively (**4p-4t,** with 62%-70% yields**)**.

Table **2**. Substrate exploration[a]



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

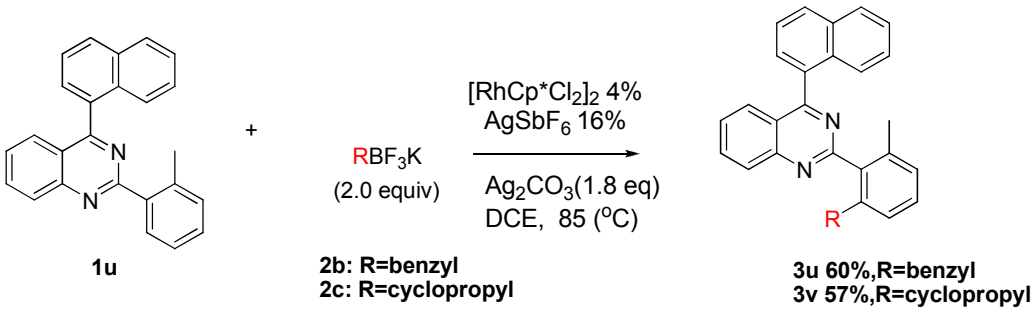
Entry	Substrate	R^1	R^2	R^3	Product (% yield)[a]
1	**1a**	H	4-methylphenyl	H	**4a** (91)
2	**1b**	H	4-methylphenyl	4-methyl	**4b** (90)

3	**1c**	H	4-methylphenyl	4-methoxy	**4c** (95)
4	**1d**	H	4-methylphenyl	4-N,N-dimethyl	**4d** (92)
5	**1e**	H	4-methylphenyl	4-chloro	**4e** (65)
6	**1f**	H	phenyl	3-methyl	**4f** (70)
7	**1g**	H	phenyl	H	**4g** (93)
8	**1h**	H	4-fluorophenyl	H	**4h** (90)
9	**1i**	H	3-methylphenyl	H	**4i** (85)
10	**1j**	H	4-methoxyphenyl	H	**4j** (70)
11	**1k**	H	naphthalen-1-yl	H	**4k** (71)
12	**1l**	methoxy	2-methylphenyl	H	**4l** (78)
13	**1m**	methoxy	4-methylphenyl	H	**4m** (83)
14	**1n**	methoxy	3-methylphenyl	H	**4n** (80)
15	**1o**	methoxy	4-fluorophenyl	H	**4o** (95)
16	**1p**	chloro	2-methylphenyl	H	**4p** (65)
17	**1q**	chloro	4-methylphenyl	H	**4q** (62)
18	**1**r	chloro	3-methylphenyl	H	**4**r (70)
19	**1s**	chloro	naphthalen-1-yl	H	**4s** (68)
20	**1t**	chloro	4-fluorophenyl	H	**4t** (68)

[a] Reactions were carried out using **1** (0.2 mmol), $MeBF_3K$ **2a** (0.8 mmol), $[RhCp^*Cl_2]_2$ (4.0 mol %), $AgSbF_6$ (16 mol %) and Ag_2CO_3 (0.36 mmol) in DCE (3 mL) at 85°C.

After finishing the above examined, we moved on to explore the other alkylation reagents. As a consequence potassium benzyltrifluoroborate (**2b**) and potassium

cyclopropyltrifluoroborate (**2c**) were selected to probe the substrates scope of quinazoline (Scheme **2**). To our delight, these two kinds of alkylation reagents can also be carried out in this reaction system. However, due to their steric effects, boron reagents containing a benzyl **2b** or cyclopropyl group **2c** only gave the corresponding benzylation product (**3u**, 60% yields) and the cycloalkylation product in moderate yields (**3v**, 57% yields). We concluded that steric hindrance effect was the main factor affecting 4-(naphthalen-1-yl)-2-*o*-tolylquinazoline alkylation on 2 aromatic ring. These results also revealed that the coupling partners in this catalytic system are not limited only to methyl boron reagent $MeBF_3K$ (**2a**).

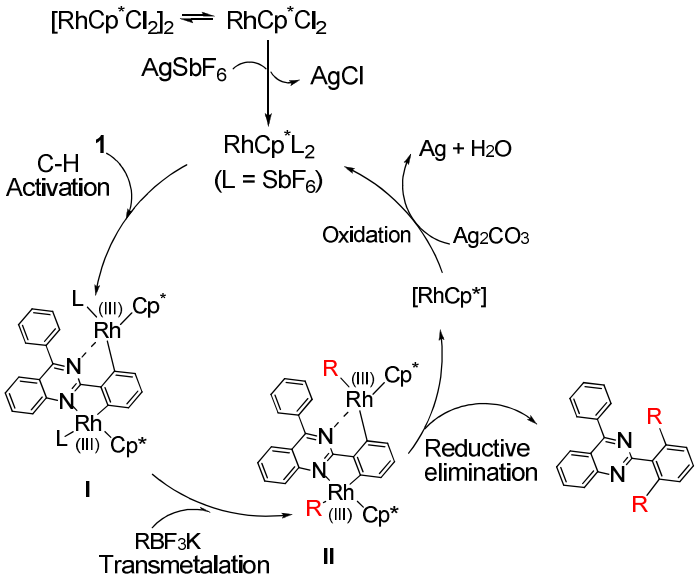


Scheme **2.** Reactions of different methylation reagents with 4-(naphthalen-1-yl)-2-*o*-tolylquinazoline

In order to gain an insight into the mechanism, other azine substrate such as 2-phenylquinoxalin (not list) was investigated under the standard conditions. However, the results indicated that this substrate did not tolerant the reaction conditions very well，giving the mono-alkyation product 2-(*o*-tolyl)quinazoline (**3w,** with only in 15% yields**)**. Also, it was quite interesting that 4-arylquinazoline did not undergo the standard reaction. It seems that the phenyl substitution would have resonance effect to favor the catalytic cycle.

On the base of recent Rh-catalyzed direct *ortho*-C-H bond functionalization of

arenes[18g,18h,18i], a plausible mechanistic pathway has been illustrated in Scheme **3**. Initially, intermediate **I**, generated by Rh(III)-promoted *ortho*-C-H bond activation, yield five-membered Rh intermediate **II** via transmetalation with boron reagent. Then the desired methylation product **3** along with Rh(I) species were formed via reductive elimination. Subsequently, Rh(I) species undergoes reoxidation by oxidant Ag_2CO_3 to regenerate the active cationic Rh(III) species for the following catalytic cycle.



Scheme **3.** Proposed catalytic pathway

Conclusion

In conclusion, we have developed an effective Rh(III)-catalyzed oxidative C-H methylation of 2,4-diarylquinazoline, which exerted several advantages: ligand free, practical reaction conditions, moderate to good yields. When both *ortho*-C-H sites on 2 aromatic ring are accessible, mono- and di-methyllation products will be generated, and this selectivity is controllable by the amount of methylation reagents. This methodology gave a rapid and straight forward synthesis of functionalized quinazolines which were potential biological compounds. Boron reagents containing a

benzyl or cyclopropyl group were also applied. However, the main factor affecting 2,4-diarylquinazoline methylation on 2 aromatic ring is steric hindrance effect.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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