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Rhodium-Catalyzed Regioselective *Ortho*-Allylation of 2,4-Diarylquinazolines with Allylic Acetate

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Abstract

In this paper, a rhodium-catalyzed regioselective reaction of 2,4-diarylquinazolines with allylic acetate is described, leading to allylated quinazoline derivatives with high efficiency and good tolerance of functional groups. By switching to 2-arylquinazolin-4-ones, tandem C-H activation and aza-Michael addition are involved, leading to 1,6-dimethyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one derivatives with high efficiency.

Keywords: Rhodium, C-H activation, allyl acetate, 2,4-diarylquinazoline, allylation

Introduction

As we know, the allylated *N*-containing compounds are widely distributed in the genera *Aspergillus* and *Penicillium* of ascomycota.¹ This building blocks are known as pivotal scaffold found in a number of natural products and synthetic bioactive molecules (Figure 1).² Due to the versatility of olefinic transformations, many useful methods for introduction such a prevalence group to a natural skeleton have been developed.^{3,4} Among them, transition-metal-catalyzed C-H bond functionalization has become the most straightforward protocol to allylated molecules, due to its remarkable potential for step economy.⁵ Moreover, rhodium catalyst has emerged as a popular and efficient direct C-H functionalization tool for allylation. For example, Bergman and Ellman reported Rh(III)-catalyzed direct allylation of a ketoxime with allyl acetate affording a terminal alkene.⁶ Glorius described Rh(III)-catalyzed terminal allylation of indoles and benzamides with allylic carbonates.⁷ Interestingly, internal allylation of benzamides with allylic acetates to provide conjugated olefins under Rh(III)-catalysis were also demonstrated by Loh.⁸ Moreover, direct C-H allylations of benzamides using corresponding allenes as allyl sources under Rh(III)-catalysis were reported by Ma,⁹ and Cramer¹⁰. In addition, Wang disclosed the Rh(III)-catalyzed direct C-H allylation reaction to deliver allylic alcohols in the presence of 4-vinyl-1,3-dioxolan-2-ones.¹¹

On the other hand, the quinazoline core structure is widely found in many bioactive

molecules.¹² Thus, the construction of quinazolines and their derivatives

Figure 1. Selected examples for allylated products.

has become the intensive research focus of organic chemist. In the past decade, a variety of synthetic methods¹³⁻¹⁵ were developed to construct diverse functionalized quinazolines. Our group reported direct arylation *via* C-H bond activation, specifically leading to 2-aryl functionalized product with the assistance of quinazoline core.¹⁶ Results of density functional theory (DFT) calculations indicated that the quinazoline core is an efficient directing group in transitional metal-catalyzed C-H functionalization. Its directing property is distinctive from that of pyridine and quinolines, and regioselectivity is observed in mono-arylation on 2-aryl ring of 2,4-diarylquinazolines (Scheme 1a). Recently, amidation (Scheme 1b),¹⁷ alkylation (Scheme 1c),¹⁸ and trifluoromethylthiolation (Scheme 1d)¹⁹ of 2,4-diarylquinazolines were also explored. Similar with our previous results, all those reactions were also regioselective predominately releasing 2-aryl functionalized products.

Meanwhile, allyl acetate as the coupling-partner still remain challenging such as metal-selective insertion and competitive regioselectivity in β -elimination (β -OAc vs β -H). Although, the pioneering work on Pd catalysis has achieved a breakthrough in

selective β -H elimination^{20,21} and some effective reactions under Rh,²² Ru,²³ and other metal catalysis²⁴ have been published in terms of selective β -OAc elimination, methods for allylation of quinolones by regioselective β -elimination have not been reported yet.

Previous Work: Palladium-catalyzed arylation

Previous Work: Rhodium-catalyzed amidation, alkylation, and trifluoromethylthiolation

This Work: Rhodium-catalyzed allylation

Scheme 1 Reaction design

Prompted by the advantages of the allylated *N*-containing compounds and inspired by what mentioned above, we envisioned that rhodium-catalyzed olefination *via* C-H bond activation could provide the desired allylated 2-aryl product, when 2-arylquinazolin and allyl acetate were used as substrates (scheme 1e).

Experimental

General information

Unless otherwise stated, all commercial reagents were used as received. All solvents were dried and distilled according to standard procedures. Flash column chromatography was performed using silica gel (60-Å pore size, 32-63µm, 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 0~20 Torr at 25-35°C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane on the δ scale. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 on a Bruker DRX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. High resolution mass spectrometry (HRMS) spectra were obtained on a microTOF II Instrument.

General experimental procedure for the reaction of 2,4-diarylquinazoline and allyl acetate

A mixture of 2,4-diarylquinazoline **1** (1.0 equiv), allyl acetate **2a** (1.5 equiv),

[RhCp*Cl₂]₂ (5 mol%), AgSbF₆ (20 mol%) and Cu(OAc)₂ (20 mol%), *p*-NO₂-C₆H₄COOH (20 mol%) in PhCl/DCM at 80 °C. The reaction was detected with TLC. After completion, the mixture was filtered. Evaporation of the filtrate under vacuum and column chromatography isolation afforded the corresponding products **3**

Characterization data:

2-(2-allyl-6-methylphenyl)-4-*p*-tolylquinazoline (3a). Yellow oil, 87%; ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 8.6 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 7.91 (t, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.65-7.59 (m, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.29-7.24 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 5.90-5.77 (m, 1H), 4.82-4.74 (m, 2H), 3.31 (d, *J* = 6.8 Hz, 2H), 2.46 (s, 3H), 2.21 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.4, 163.5, 151.3, 140.1, 139.3, 137.9, 137.2, 136.0, 134.3, 133.6, 130.1, 129.2, 128.9, 128.4, 128.3, 127.4, 127.1, 126.9, 121.1, 115.2, 38.2, 21.4, 20.2; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₅H₂₃N₂⁺ 351.1861, found 351.1856.

2-(2-allyl-6-methylphenyl)-4-*m*-tolylquinazoline (3b). Yellow oil, 80%; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (dd, *J* = 13.0, 8.4 Hz, 2H), 7.93 (dd, *J* = 7.0, 1.4 Hz, 1H), 7.65-7.57 (m, 3H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.28-7.25 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 5.91-5.81 (m, 1H), 4.83-4.74 (m, 2H), 3.31 (d, *J* = 6.8 Hz, 2H), 2.46 (s, 3H), 2.21 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.6, 163.6, 151.4, 139.4, 138.4, 137.9, 137.3, 137.2, 136.1, 133.6, 130.6, 130.5, 128.9, 128.5, 128.3, 127.5, 127.2, 127.1, 126.9, 121.2, 115.2, 38.2, 21.5, 20.2; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₅H₂₃N₂⁺ 351.1861, found 351.1856.

2-(2-allyl-6-methylphenyl)-4-o-tolylquinazoline (3c). Yellow oil, 76% ; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, J = 8.4 Hz, 1H), 7.93 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.71 (dd, J = 8.4, 0.8 Hz, 1H), 7.59-7.56 (m, 1H), 7.43-7.39 (m, 1H), 7.36-7.33 (m, 3H), 7.25 (dd, J = 8.4, 6.8 Hz, 1H), 7.16 (d, J = 7.6 Hz, 2H), 5.88-5.78 (m, 1H), 4.83-4.73 (m, 2H), 3.31 (d, J = 6.6 Hz, 2H), 2.19 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 163.6, 150.8, 139.3, 137.7, 137.1, 136.6, 135.9, 135.8, 133.9, 130.5, 129.2, 129.1, 128.8, 128.5, 128.3, 127.6, 127.0, 126.9, 125.6, 122.1, 115.3, 38.1, 20.1, 19.8; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{23}\text{N}_2^+$ 351.1861, found 351.1856.

2-(2-allyl-6-methylphenyl)-4-phenylquinazoline (3d). Yellow oil, 90%; ^1H NMR (400 MHz, CDCl_3) δ 8.17 (t, J = 8.4 Hz, 2H), 7.93 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.82-7.80 (m, 2H), 7.63 (ddd, J = 8.4, 7.0, 1.2 Hz, 1H), 7.59-7.53 (m, 3H), 7.29-7.25 (m, 1H), 7.17 (d, J = 7.6 Hz, 2H), 5.91-5.81 (m, 1H), 4.85-4.72 (m, 2H), 3.32 (d, J = 6.8 Hz, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.4, 163.6, 151.4, 139.3, 137.9, 137.3, 137.2, 136.0, 133.7, 130.0, 129.9, 128.9, 128.5, 128.4, 128.3, 127.5, 127.0, 126.9, 121.1, 115.2, 38.2, 20.2; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{21}\text{N}_2^+$ 337.1705, found 337.1703.

2-(2-allyl-6-methylphenyl)-4-(4-methoxyphenyl)quinazoline (3e). Yellow oil, 82%; ^1H NMR (400 MHz, CDCl_3) δ 8.23 (dd, J = 8.4, 0.8 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 7.91 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.84-7.79 (m, 2H), 7.62 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.29-7.24 (m, 1H), 7.17 (d, J = 7.6 Hz, 2H), 7.09-7.06 (m, 2H), 5.91-5.81 (m, 1H), 4.83-4.74 (m, 2H), 3.89 (s, 3H), 3.31 (d, J = 6.8 Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.8, 163.5, 161.2, 151.5, 139.4, 137.9, 137.3, 136.0, 133.5, 131.8,

129.7, 128.9, 128.4, 128.3, 127.3, 127.0, 126.9, 121.1, 115.2, 114.0, 55.4, 38.2, 20.2 ;

HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{22}N_2O^+$ 367.1810, found 337.1807.

2-(2-allyl-6-methylphenyl)-4-(4-fluorophenyl)quinazoline (3f). Yellow oil, 76% ; 1H NMR (400 MHz, $CDCl_3$) δ 8.19-8.12 (m, 2H), 7.99-7.90 (m, 1H), 7.87-7.79 (m, 2H), 7.69-7.61 (m, 1H), 7.30-7.23 (m, 3H), 7.17 (d, $J = 7.6$ Hz, 2H), 5.89-5.81 (m, 1H), 4.83-4.73 (m, 2H), 3.30 (d, $J = 6.8$ Hz, 2H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 163.9 (d, $^1J_{C-F} = 249$ Hz), 163.5, 151.5, 139.2, 137.9, 137.2, 136.0, 133.8, 133.3, 132.1 (d, $^3J_{C-F} = 9$ Hz), 129.1, 128.5, 128.4, 127.7, 127.0, 126.7, 120.9, 115.7 (d, $^2J_{C-F} = 22$ Hz), 115.2, 38.2, 20.2 ; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{24}H_{20}FN_2^+$ 355.1611, found 355.1610.

2-(2-allyl-6-methylphenyl)-4-(naphthalen-1-yl)quinazoline (3g). Yellow oil, 87% ; 1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, $J = 8.4$ Hz, 1H), 8.05-8.00 (m, 1H), 7.94 (ddd, $J = 8.4, 5.6, 2.0$ Hz, 2H), 7.71-7.66 (m, 1H), 7.65-7.60 (m, 2H), 7.54-7.47 (m, 3H), 7.41-7.35 (m, 1H), 7.25 (t, $J = 7.6$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 2H), 5.91-5.81 (m, 1H), 4.87-4.75 (m, 2H), 3.38 (d, $J = 6.1$ Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.8, 150.9, 139.3, 137.8, 137.2, 136.0, 134.6, 134.1, 133.6, 131.6, 129.7, 128.8, 128.5, 128.4, 128.3, 127.6, 127.3, 127.0, 126.7, 126.2, 125.5, 125.1, 122.8, 115.3, 38.2, 20.2 ; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{23}N_2^+$ 387.1861, found 387.1863.

2-(2-allyl-6-chlorophenyl)-4-*p*-tolylquinazoline (3h). Yellow oil, 82% ; 1H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, $J = 8.4$ Hz, 1H), 8.16 (d, $J = 8.4$ Hz, 1H), 7.93 (ddd, $J = 8.4, 6.8, 1.4$ Hz, 1H), 7.74 (d, $J = 8.2$ Hz, 2H), 7.64 (ddd, $J = 8.2, 7.0, 1.2$ Hz, 1H), 7.37 (d, $J = 6.8$

Hz, 3H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.25 (d, $J = 6.8$ Hz, 1H), 5.89-5.79 (m, 1H), 4.89-4.79 (m, 2H), 3.33 (d, $J = 6.8$ Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.6, 161.3, 151.3, 140.4, 140.2, 138.6, 136.3, 134.3, 133.7, 133.2, 130.1, 129.4, 129.3, 129.0, 127.8, 127.7, 127.6, 127.2, 121.5, 116.1, 38.2, 21.4; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{20}\text{ClN}_2^+$ 371.1315, found 387.1313.

2-(2-allyl-6-chlorophenyl)-4-m-tolylquinazoline (3i). Yellow oil, 80%; ^1H NMR (400 MHz, CDCl_3) δ 8.19 (t, $J = 8.8$, 2H), 7.94 (ddd, $J = 8.4$, 6.8, 1.4 Hz, 1H), 7.67-7.57 (m, 3H), 7.44 (t, $J = 7.6$ Hz, 1H), 7.37 (dd, $J = 10.6$, 4.0 Hz, 2H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.26-7.24 (m, 1H), 5.91-5.80 (m, 1H), 4.92-4.78 (m, 2H), 3.33 (d, $J = 6.8$ Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 161.3, 151.3, 140.4, 138.5, 138.4, 136.9, 136.3, 133.8, 133.2, 130.6, 130.5, 129.5, 128.9, 128.3, 127.8, 127.6, 127.2, 121.5, 116.1, 38.2, 21.5; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{24}\text{H}_{20}\text{ClN}_2^+$ 371.1315, found 387.1313.

2-(2-allyl-6-methylphenyl)-6-chloro-4-p-tolylquinazoline (3j). Yellow oil, 85%; ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 2.2$ Hz, 1H), 8.08 (d, $J = 9.0$ Hz, 1H), 7.85 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.71 (d, $J = 8.1$ Hz, 2H), 7.39 (d, $J = 7.9$ Hz, 2H), 7.30-7.25 (m, 1H), 7.17 (d, $J = 7.6$ Hz, 2H), 5.87-5.77 (m, 1H), 4.82-4.70 (m, 2H), 3.30 (d, $J = 6.8$ Hz, 2H), 2.48 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.6, 163.9, 149.9, 140.6, 139.1, 137.9, 137.2, 136.1, 134.6, 133.9, 133.2, 130.7, 129.9, 129.5, 128.6, 128.4, 127.1, 125.9, 121.7, 115.2, 38.2, 21.4, 20.2; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{25}\text{H}_{22}\text{ClN}_2^+$ 385.1472, found 385.1473.

2-(2-allyl-6-methylphenyl)-6-methoxy-4-m-tolylquinazoline (3k). Yellow oil, 83%; ^1H

NMR (400 MHz, CDCl₃) δ 8.06 (d, J = 9.2 Hz, 1H), 7.63 (s, 1H), 7.62-7.55 (m, 2H), 7.48-7.41 (m, 2H), 7.35 (d, J = 7.6 Hz, 1H), 7.25 (dd, J = 8.4, 6.7 Hz, 1H), 7.16 (d, J = 7.6 Hz, 2H), 5.90-5.80 (m, 1H), 4.87-4.70 (m, 2H), 3.87 (s, 3H), 3.30 (d, J = 6.8 Hz, 2H), 2.46 (s, 3H), 2.20 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 161.6, 158.4, 147.6, 139.4, 138.5, 138.0, 137.5, 137.4, 136.2, 130.5, 130.4, 130.3, 128.4, 128.3, 128.2, 126.9, 126.8, 126.3, 121.9, 115.1, 104.4, 55.6, 38.2, 21.5, 20.2; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₆H₂₅N₂O⁺ 381.1967, found 381.1963.

2-(2-allyl-6-methylphenyl)-6-methoxy-4-p-tolylquinazoline (3l). Yellow oil, 88%; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, J = 9.2 Hz, 1H), 7.73 (d, J = 8.2 Hz, 2H), 7.57 (dd, J = 9.2, 2.8 Hz, 1H), 7.46 (d, J = 2.8 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.27-7.22 (m, 1H), 7.15 (d, J = 7.6 Hz, 2H), 5.91- 5.81 (m, 1H), 4.82- 4.73 (m, 2H), 3.87 (s, 3H), 3.30 (d, J = 6.8 Hz, 2H), 2.46 (s, 3H), 2.20 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.7, 161.6, 158.4, 147.6, 139.9, 139.4, 138.0, 137.4, 136.2, 134.8, 130.4, 129.7, 129.3, 128.3, 128.2, 126.9, 126.3, 121.9, 115.1, 104.4, 55.6, 38.2, 21.4, 20.2; HRMS (ESI) m/z [M + H]⁺ calcd for C₂₆H₂₅N₂O⁺ 381.1967, found 381.1963.

2-(2-allyl-5-methylphenyl)-4-phenylquinazoline (3m). Yellow oil, 89%; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (dd, J = 8.2, 4.4 Hz, 2H), 7.90 (t, J = 7.7 Hz, 1H), 7.84 (dd, J = 6.1, 2.6 Hz, 2H), 7.77 (s, 1H), 7.61-7.52 (m, 4H), 7.27-7.18 (m, 2H), 5.91-5.81 (m, 1H), 4.93-4.85 (m, 2H), 3.82 (d, J = 6.5 Hz, 2H), 2.40 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 168.0, 163.3, 151.6, 138.5, 138.3, 137.5, 136.3, 135.9, 133.5, 131.4, 130.4, 130.2, 130.1, 129.8, 129.1, 128.5, 127.2, 126.9, 121.0, 114.8, 37.9, 20.9; HRMS (ESI) m/z [M + H]⁺

calcd for $C_{24}H_{21}N_2^+$ 337.1705, found 337.1708.

2-(2,6-diallyl-4-methoxyphenyl)-4-*p*-tolylquinazoline (3n). Yellow oil, 84%; 1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, $J = 8.4$ Hz, 1H), 8.12 (d, $J = 8.4$ Hz, 1H), 7.91 (dd, $J = 11.2$, 4.1 Hz, 1H), 7.71 (d, $J = 8.0$ Hz, 2H), 7.61 (t, $J = 7.6$ Hz, 1H), 7.37 (d, $J = 7.8$ Hz, 2H), 6.75 (s, 2H), 5.84 (ddt, $J = 16.9$, 10.0, 6.8 Hz, 2H), 4.89-4.72 (m, 4H), 3.83 (s, 3H), 3.32 (d, $J = 6.8$ Hz, 4H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 151.4, 140.1, 137.1, 133.6, 130.1, 129.2, 128.9, 127.4, 127.1, 121.1, 115.5, 112.9, 55.3, 38.4, 21.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{28}H_{27}N_2O^+$ 407.2127, found 407.2129.

2-(2,6-diallyl-4-methylphenyl)-4-phenylquinazoline (3o). Yellow oil, 86%; 1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J = 8.6$ Hz, 1H), 7.92 (s, 1H), 7.82-7.75 (m, 2H), 7.59-7.52 (m, 3H), 7.46 (dd, $J = 8.6$, 1.5 Hz, 1H), 7.31 (dd, $J = 8.0$, 7.2 Hz, 1H), 7.20 (d, $J = 7.6$ Hz, 2H), 5.90-5.80 (m, 2H), 4.86-4.73 (m, 4H), 3.32 (d, $J = 6.8$ Hz, 4H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 163.3, 151.6, 144.8, 139.3, 138.2, 137.4, 137.2, 130.0, 129.8, 129.7, 128.6, 128.5, 127.9, 127.5, 126.7, 119.3, 115.3, 38.3, 22.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{25}N_2^+$ 377.2018, found 377.2018.

2-(2-(*but-3-en-2-yl*)-6-methylphenyl)-4-*p*-tolylquinazoline (3p). Yellow oil, 80%; 1H NMR (400 MHz, $CDCl_3$) δ 8.22 (dd, $J = 8.4$, 0.8 Hz, 1H), 8.15 (d, $J = 8.2$ Hz, 1H), 7.92 (ddd, $J = 8.4$, 6.8, 1.4 Hz, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.62 (ddd, $J = 8.2$, 6.8, 1.2 Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 2H), 7.29 (t, $J = 7.6$ Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.15 (d, $J = 7.4$ Hz, 1H), 6.06-5.98 (m, 1H), 4.93-4.82 (m, 2H), 3.39-3.29 (m, 1H), 2.46 (s, 3H), 2.17 (s, 3H), 1.30 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 163.8, 151.4,

143.3, 143.0, 140.1, 139.1, 135.9, 134.4, 133.6, 130.1, 129.2, 128.9, 128.5, 128.1, 127.4, 127.1, 124.4, 121.2, 112.5, 39.3, 21.4, 20.3 ; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{27}N_2^+$ 379.2174, found 379.2174.

2-(2-(but-2-enyl)-6-methylphenyl)-4-p-tolylquinazoline (3q). Yellow oil, 79% ; 1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, $J = 8.4$ Hz, 1H), 8.15 (d, $J = 8.4$ Hz, 1H), 7.94-7.88 (m, 1H), 7.76-7.70 (m, 2H), 7.61 (t, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.25 (t, $J = 7.6$ Hz, 1H), 7.16 (t, $J = 6.8$ Hz, 2H), 5.51-4.98 (m, 2H), 3.28 (dd, $J = 24.8, 7.0$ Hz, 2H), 2.46 (s, 3H), 2.20 (d, $J = 7.6$ Hz, 3H), 1.36 (ddd, $J = 29.8, 6.4, 1.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 163.8, 151.6, 140.2, 139.5, 138.9, 136.0, 134.5, 133.6, 130.1, 129.3, 129.1, 128.9, 128.5, 128.1, 127.1, 126.8, 125.6, 124.1, 121.2, 37.2, 21.5, 20.2, 17.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{27}N_2^+$ 379.2174, found 379.2174.

1,6-dimethyl-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one (3r). Yellow oil, 80% ; 1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, $J = 7.8$ Hz, 1H), 7.76-7.67 (m, 2H), 7.45 (dt, $J = 8.2, 4.2$ Hz, 1H), 7.31 (t, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 7.4$ Hz, 1H), 7.10 (d, $J = 7.2$ Hz, 1H), 5.53-5.47 (m, 1H), 3.28 (dd, $J = 15.8, 5.4$ Hz, 1H), 2.87 (s, 3H), 2.82 (dd, $J = 15.8, 1.6$ Hz, 1H), 1.19 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 148.9, 147.2, 140.3, 136.4, 133.9, 131.6, 130.6, 127.8, 127.5, 126.6, 126.5, 120.5, 45.2, 34.9, 23.7, 17.0; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{18}H_{17}N_2O^+$ 277.1341, found 277.1340.

10-chloro-1,6-dimethyl-5H-isoquinolino[1,2-b]quinazolin-8(6H)-one(3s). Yellow oil, 83%; 1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, $J = 1.4$ Hz, 1H), 7.66 (d, $J = 1.4$ Hz, 2H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.27-7.24 (m, 1H), 7.11 (d, $J = 7.4$ Hz, 1H), 5.53-5.41 (m, 1H),

3.29 (dd, $J = 15.8, 5.4$ Hz, 1H), 2.84 (s, 3H), 2.81 (d, $J = 1.8$ Hz, 1H), 1.19 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.3, 149.2, 145.7, 140.4, 136.4, 134.4, 132.2, 131.7, 130.9, 129.2, 127.5, 126.6, 126.0, 121.5, 45.5, 34.9, 23.8, 17.0; HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{18}\text{H}_{16}\text{ClN}_2\text{O}^+$ 311.0951, found 311.0951.

Results and discussions

To verify the possibility of this projected transformation, we firstly optimize the reaction condition. The reaction of 2-*o*-tolyl-4-*p*-tolylquinazoline **1a** with allyl acetate **2a** was selected as the model reaction. In order to abstract chloride from Rh, AgSbF_6 and $\text{Cu}(\text{OAc})_2$ were selected as additives. To our delight, the preliminary experiment showed that the transformation seemed reliable under rhodium catalysis. When 5 mol% $[\text{Cp}^*\text{RhCl}_2]_2$ was used as the catalyst, 20 mol% AgSbF_6 and 20 mol% $\text{Cu}(\text{OAc})_2$ as the additives at 60 °C in DCE, the desired 2-(2-allyl-6-methylphenyl)-4-*p*-tolylquinazoline **3a** was observed although this transformation was still not completed after 12h (Table 1, entry 1). The allylated product on the 4-aryl group of **1a** was not detected. The structure identification of the product indicated that no ester group was found, and the reaction may go through β -OAc elimination pathway. Encouraged by this regioselective transformation, representative rhodium catalysts such as $\text{RhCl}_2(p\text{-cymene})$, $\text{Rh}(\text{acac})(1,5\text{-cyclooctadiene})$, RhClPPh_3 , and $\text{Rh}(\text{OAc})_2$ were screened and found to be less active catalysts (Table 1, entries 2-5). Next, we evaluated the result-affecting factors such as solvent, additive, temperature, and the results are also summarized in Table 1.

A variety of solvents such as $\text{C}_2\text{H}_5\text{OH}$, MeCN, CH_3OH , DMF, THF, DCM, PhCl were investigated and the results implied that all these solvents could not make marked improvement on the reaction (not list in Table 1, see in Support information). Surprisingly, remarkable increased efficiency of the reaction was observed by switching to PhCl/DCM, affording the desired product **3a** in 80% (Table 1, entry 6). This is probably because of the dissolution and stabilizing effect of PhCl/DCM to substrates and rhodium catalyst. Then the copper salts were screened, and found that $\text{Cu}(\text{NO}_3)_2$ and $\text{Cu}(\text{OCOCF}_3)_2$ also promoted this reaction with respectively less yields 78% and 60% (Table 1, entries 7-8), whereas CuCl_2 and CuBr_2 were totally ineffective (Table 1, entries 9-10). Thus, $\text{Cu}(\text{OAc})_2$ was the best choice. Elevating temperature was favorable for the reaction, giving the desired product **3a** in 87% (Table 1, entry 11). Reducing the amount of rhodium-catalyst or AgSbF_6 led to lower yield (Table 1, entries 12-13). Control experiments revealed that the use of AgSbF_6 seems necessary because no desired product **3a** was observed in the absence of this additive (Table 1, entry 14). Similarly, the reactions without $p\text{-NO}_2\text{-C}_6\text{H}_4\text{COOH}$ did not give the desired product **3a**, probably attributing to the additive facilitating β -acetate elimination step (Table 1, entry 15). Different amounts of allyl acetate **2a** were studied (Table 1, entries 16-17). It was noteworthy that similar yield was observed when **1a** was treated with 1.5 equivalent of allyl acetate **2a**, resulting in the desired product **3a** in 86% yield (Table 1, entry 16). However, further reduction of equivalent of **2a** low the yield to 67% (Table 1, entry 17). Based on the investigations above, the combination of

$[\text{RhCp}^*\text{Cl}_2]_2$ (5 mol%), AgSbF_6 (20 mol%) and $\text{Cu}(\text{OAc})_2$ (20 mol%), $p\text{-NO}_2\text{-C}_6\text{H}_4\text{COOH}$ (20 mol%) in PhCl/DCM at $80\text{ }^\circ\text{C}$ under air was defined as the optimal conditions for this reaction.

Table 1. Optimization of the Reaction Conditions ^a

$\text{1a} + \text{2a} \xrightarrow[\text{[Cu], Solvent, Temp.}]{\text{[Rh], AgSbF}_6, p\text{-NO}_2\text{-C}_6\text{H}_4\text{COOH}}$ 3a

Entry	[Rh]	[Cu]	Solvent	Yield (%) ^b
1	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{OAc})_2$	DCE	9
2	$\text{RhCl}_2(p\text{-cymene})$	$\text{Cu}(\text{OAc})_2$	DCE	trace
3	$\text{Rh}(\text{acac})(1,5\text{-cyclooctadiene})$	$\text{Cu}(\text{OAc})_2$	DCE	trace
4	RhClPPh_3	$\text{Cu}(\text{OAc})_2$	DCE	trace
5	$\text{Rh}(\text{OAc})_2$	$\text{Cu}(\text{OAc})_2$	DCE	trace
6	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{OAc})_2$	PhCl/DCM	80
7	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{NO}_3)_2$	PhCl/DCM	78
8	$[\text{Cp}^*\text{RhCl}_2]_2$	$\text{Cu}(\text{OCOCF}_3)_2$	PhCl/DCM	60
9	$[\text{Cp}^*\text{RhCl}_2]_2$	CuCl_2	PhCl/DCM	trace
10	$[\text{Cp}^*\text{RhCl}_2]_2$	CuBr_2	PhCl/DCM	21

11 ^c	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	PhCl/DCM	87
12 ^d	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	PhCl/DCM	67
13 ^e	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	PhCl/DCM	60
14 ^f	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	PhCl/DCM	NR
15 ^g	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	PhCl/DCM	NR
16 ^h	[Cp*RhCl₂]₂	Cu(OAc)₂	PhCl/DCM	86
17 ⁱ	[Cp*RhCl ₂] ₂	Cu(OAc) ₂	PhCl/DCM	67

^aReaction conditions: 1a (0.2 mmol), 2a (0.4 mmol), [Rh]-catalyst (5 mol %), [Cu] (20 mol%), AgSbF₆ (20 mol%), 60 °C, 24 hrs.

^bYields based on isolation.

^cThe reaction was carried out at 80 °C.

^d2 mol% [Cp*RhCl₂]₂ was used.

^e8 mol% AgSbF₆ was used.

^fThe reaction was performed in absence of AgSbF₆.

^gThe reaction was performed in absence of *p*-NO₂-C₆H₄COOH.

^h1.5 equiv methyl acrylate **2a** was used.

ⁱ1.0 equiv methyl acrylate **2a** was used.

With these optimized conditions in hand, we started to explore the generality of the reaction for the synthesis of allylated 2,4-diarylquinazolines, and the results are summarized in Table 2. Thus, a series of 2,4-diarylquinazolines were examined. As

expected, a variety of allylated products were constructed with high efficiency. The effect of substituted on the 4-phenyl ring was first studied, and the position of methyl group on 4-phenyl ring was found have great impact on the yield. For example, with the methyl in the *para* position, the reaction provided the desired product **3a** in 86% yield. A lower yield of 80% was delivered (Table 2, **3b**) when the substrate with *meta*-methyl on 4-phenyl group was used, whereas the substrate with *ortho*-methyl was less favourable for the reaction, regioselectively providing the desired product only in 76% yield (Table 2, **3c**). It should be noted that higher yield of 90% of the corresponding products with excellent regioselectivity was obtained, in case of 4-phenyl ring without any substituent (Table 2, **3d**). Other functional groups such as methoxyl group, fluoro on 4-phenyl ring were compatible, leading to the corresponding products in 82% and 76% yields (Table 2, **3e-3f**). The substrate with 4-naphthalene substituted was also tolerant with 87% yield (Table 2, **3g**).

The substituent effect on 2-phenyl of quinazoline were then studied. It is noteworthy that quinazolines with *ortho*-Cl-substituted on 2-phenyl ring worked smoothly and furnished the corresponding products in about 80% yield (Table 2, **3h-3i**). During the subsequent attempts, substituents attached on quinazoline core have no significant impact on the reactions. For instance, the reaction of **1j-1l** with **2a** gave rise to the desired corresponding products **3j-3l** in 83-88% yield (Table 2, **3j-3l**). Interestingly, regioselective allylated product was observed at the less sterically hindered site when the 2-position phenyl ring of the quinazoline possessed a methyl group at its *meta* position

(Table 2, **3m**). In the case of the *para*-substituted substrates, **1n** and **1o** only gave bisallylated product **3n** and **3o** in excellent corresponding yield with 84% and 86% in the presence of allyl acetate **2a** with 3 equiv (Table 2, **3n-3o**).

Table 2. Substrate exploration^a

Substrate	R ¹	R ²	R ³	R ⁴	R ⁵	3 (% yield) ^a
1a	H	4-methylphenyl	2-methyl	H	H	3a (86)
1b	H	3-methylphenyl	2-methyl	H	H	3b (80)
1c	H	2-methylphenyl	2-methyl	H	H	3c (76)
1d	H	phenyl	2-methyl	H	H	3d (90)
1e	H	4-methoxyphenyl	2-methyl	H	H	3e (82)
1f	H	4-fluorophenyl	2-methyl	H	H	3f (76)
1g	H	naphthalen-1-yl	2-methyl	H	H	3g (87)
1h	H	4-methylphenyl	2-chloro	H	H	3h (82)
1i	H	3-methylphenyl	2-chloro	H	H	3i (80)
1j	chloro	4-methylphenyl	2-methyl	H	H	3j (85)
1k	methoxy	3-methylphenyl	2-methyl	H	H	3k (83)
1l	methoxy	4-methylphenyl	2-methyl	H	H	3l (88)

1m	H	phenyl	3-methyl	H	H	3m (89)
1n	H	4-methylphenyl	H	H	H	3n (84)
1o	H	phenyl	H	H	H	3o (86)
1p	H	4-methylphenyl	2-methyl	methyl	H	3p (80)
1q	H	4-methylphenyl	2-methyl	H	methyl	3q (79)

^a Yields based on isolation.

Next, to further illustrate the generality of this olefinic allylation reaction, several allyl resources were detected under the optimal reaction condition (Table 3). With respect to substituted allyl acetates examined, synthetically useful chemical yields and high stereoselectivity along with excellent γ -selectivity were obtained. For example when but-2-enyl acetate **2b** and but-3-en-2-yl acetate **2c** were subjected to the optimized reaction condition with **1a**, the transformation proceed smoothly to afford the desired product **3p** and **3q** in 80% and 79% yields, respectively (Table 2, **3p** and **3q**). Other activated olefins such as allyl methyl carbonate **2d**, allyl 2,2,2-trifluoroacetate **2e**, allyl trifluoromethanesulfonate **2f**, allyl benzoate **2g** were screened as well. To our surprise, only **2d** was the only suitable candidate, affording **3a** in 69% yield. Others were not suitable for the reaction, and no corresponding product was observed.

Table 3 Allyl sources

Other azine substrates such as 2-phenylquinoxalin and 4-arylquinazoline were investigated under the standard conditions. However, the results indicated that this substrate did not tolerate the reaction conditions. It is intriguing that when 2-*o*-tolylquinazolin-4(3*H*)-one **1r** and 6-chloro-2-*o*-tolylquinazolin-4(3*H*)-one **1s** were used as the substrates, tandem rhodium-catalyzed olefination of C-H bond and aza-michael addition were generated, providing 1,6-dimethyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **3r** and 10-chloro-1,6-dimethyl-5*H*-isoquinolino[1,2-*b*]quinazolin-8(6*H*)-one **3s** in 80% and 83% yield, respectively (Scheme 2).

Scheme 2. Reactions of different quinazolones with allyl acetate

In light of these experimental results and previous reported,^{22a, 23} a possible mechanism for the allylation of quinazoline was proposed in Scheme 3. The catalytic cycle is initiated by the additive activated rhodium catalyst, facilitating a C-H activation step to form intermediate **I**. The ensuing migratory insertion of the allyl acetate **2a** occurred to

generated intermediate **II**, which was induced by coordination carbonyl of acetoxyl to the metal center to afford the desired allylated product **3a** by β -acetate elimination and regenerates the rhodium (III) catalyst.

Scheme 3. Proposed catalytic pathway

Conclusion

In conclusion, we have disclosed a novel rhodium-catalyzed direct C-H olefinic allylation of quinazoline with easily available allyl acetates as electrophiles. A broad range of functionalities and substitution patterns with respect to quinazoline and allyl acetate were tolerated. With the assistance of the quinazoline as directing group, this protocol provides a straightforward and efficient method for the preparation of synthetically useful functionalized quinazolines which were potential biological compounds. Exploring application of these allylated compounds in other coupling

reactions is under investigation in our laboratory, and the results will be reported in due course.

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Supplementary data

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

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