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Palladium-catalyzed one pot 2-arylquinazoline formation *via* hydrogen-transfer strategy†

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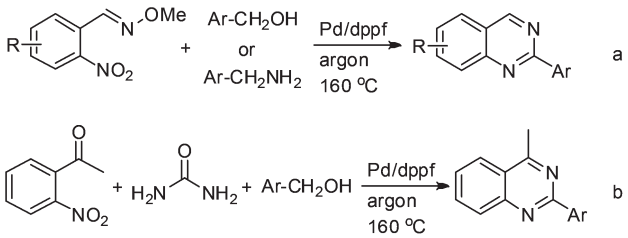
The palladium catalytic system was first applied to 2-arylquinazoline synthesis *via* hydrogen transfer methodology. Various (*E*)-2-nitrobenzaldehyde *O*-methyl oximes reacted easily with alcohols or benzyl amines to provide N-heterocyclic compounds in good to high yields. Similarly, the heterocyclic products could be prepared by the reaction of 1-(2-nitrophenyl)ethanone, urea and benzyl alcohols. In these reactions, the nitro group was reduced *in situ* by hydrogen generated from the alcohol dehydrogenation step.

Introduction

Quinazolines represent a class of annulated N-heterocycles and are widespread in natural products and pharmaceuticals.[1] These nitrogen-containing chemicals have been widely investigated for their physiological and biological properties, such as their antibacterial, antitubercular, antiviral and anticancer activities. Therefore, a variety of methods have been developed to synthesize quinazoline and its derivatives, especially 2-substituted quinazolines.[2] Conventional synthetic methods for the synthesis of quinazolines mainly rely on the condensation and subsequent cyclization of amino group with carbonyl compounds.[3] The oxidative reaction of 2-aminobenzylamines with aldehydes,[4] amidines with *o*-halogen benzyl amines or other bi-functional substrates,[5] amides with *o*-halogen benzyl amines,[6] and other novel approaches[7] have successfully been employed for quinazoline preparation. The dehydrogenation of unsaturated N-heterocycles also serves as a useful alternative approach for preparing quinazolines.[8] Recently, the arylation of quinazoline or its halogenated derivatives provided an efficient route for 2-arylquinazolines.[9] Ellman and co-workers found that a combination of cross-coupling and dehydrogenation of dihydroquinazoline with phenyl halides could provide 2-phenylquinazoline in one pot.[10]

Despite the progress that has been made in substituted quinazoline syntheses, most of the methods rely on using amines (direct or indirect) as starting materials under oxidative conditions. The preparation of N-heterocycles from other stable functionalized substrates, rather than from an active and less stable amino group, would be highly desirable. Recently, there has been significant interest in the transition-metal-catalyzed C–N bond-forming reactions from amines and alcohols (or benzyl amines) *via* hydrogen transfer methodology.[11] This methodology provides an efficient and environmentally benign approach for amine preparation. We and other groups have successfully developed various methods for amine and amide formation directly from aromatic nitro compounds and alcohols *via* hydrogen transfer strategy.[12] We also synthesized various diaryl amines from nitroarenes using cyclohexanones as hydrogen and aryl sources.[13] In this kind of reaction, the nitro group was reduced *in situ* by hydrogen produced from alcohol or cyclohexanone oxidation. Very recently, oximes have emerged as very promising substrates for the construction of heterocycles.[14] Various N-heterocycles could easily be synthesized from oximes *via* transition-metal-catalyzed N–O bond cleavage and subsequent C–N bond formation.[15] Because of the importance of substituted quinazolines in natural products and pharmaceuticals, herein, we report new approaches for synthesizing 2-arylquinazolines from (*E*)-2-nitrobenzaldehyde *O*-methyl oximes and alcohols or benzyl amines (Scheme 1, a) or from 1-(2-nitrophenyl)ethanone, urea and benzyl alcohols *via* hydrogen transfer methodology (Scheme 1, b).



Scheme 1 2-Arylquinazoline formation from nitroarenes.

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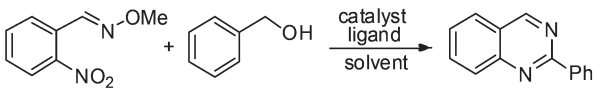
Results and discussion

We initiated the study with the reaction of (*E*)-2-nitrobenzaldehyde *O*-methyl oxime (**1a**) and benzyl alcohol (**2a**) in toluene to optimize the reaction conditions. The iron catalyst, dppf, was first investigated for this kind of reaction because it showed good efficiency in N-heterocycle preparation using nitroarenes as starting materials.[12h,i] As shown in Table 1, when a mixture of **1a** (0.2 mmol) and **2a** (0.6 mmol) was heated in a sealed tube under argon at 160 °C using dppf as the sole catalyst, the desired product 2-phenylquinazoline (**3a**) was obtained in 19% yield as determined by GC-MS and GC analysis (entry 1). Repeating the reaction with $Pd(OAc)_2$ as a co-catalyst significantly improved the reaction yield to 72% (entry 2). Other palladium salts such as $PdCl_2$, $Pd(acac)_2$, $Pd(COD)Cl_2$ and $Pd(TFA)_2$ were also screened in the presence of dppf, and they showed lower catalytic activity compared to $Pd(OAc)_2$ (entries 3–6). Replacement of dppf with other phosphine ligands significantly decreased the reaction yield, and no desired product was determined when nitrogen containing ligand 1,10-phenanthroline was used (entries 7–13). The impact of solvent on the reaction yield was also investigated. Slightly lower yield was obtained when the reaction was carried out in other organic solvents such as NMP, diglyme, DMF and DMA (entries 14–17). Anisole was proved to be a suitable reaction media for this kind of transformation, and its use afforded the product in 90% yield (entry 18). Decreasing the reaction temperature to 140 °C or performing the reaction under an air atmosphere led to significant decrease in the catalytic activity of the $Pd(OAc)_2$/dppf system (entries 19–20).

Based on the optimized reaction conditions, the substrate scope with respect to (*E*)-2-nitrobenzaldehyde *O*-methyl oxime (**1a**) and benzylic substrates (**2**) was studied (Table 2). Substituted benzylic alcohols with electron-donating groups on the aromatic ring such as methyl and methoxy could be smoothly transformed into the quinazoline products with high yields (entries 2 and 3). Halogen substituents such as chloro and fluoro were compatible (entries 4 and 5). However, a bromo substituent at the *para* position of benzyl alcohol significantly decreased the reaction yield to 30% because of the cleavage of C–Br bond (entry 6). The position of the substituent profoundly affected the reaction yield. When 2-methylbenzyl alcohol (**2g**) was employed, the corresponding product **3g** was obtained in only 38% yield, which was much lower than that of **3b** and **3h** (entries 2, 7 and 8). The hindered substrate 1-naphthalenemethanol (**2i**) could easily react with **1a** and afforded product

Table 1 Screening for the optimal conditions[a]

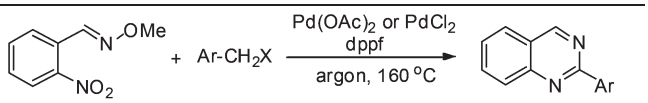


1a **2a** **3a**

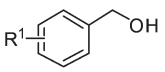
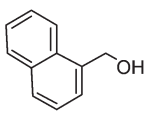
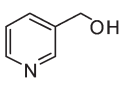
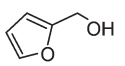
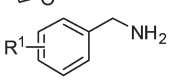
Entry	Catalyst	Ligand	Solvent	Yield[b] (%)
1		dppf	Toluene	19
2	$Pd(OAc)_2$	dppf	Toluene	72
3	$PdCl_2$	dppf	Toluene	24
4	$Pd(acac)_2$	dppf	Toluene	20
5	$Pd(COD)Cl_2$	dppf	Toluene	24
6	$Pd(TFA)_2$	dppf	Toluene	62
7	$Pd(OAc)_2$	PCy_3HBF_4	Toluene	16
8	$Pd(OAc)_2$	PPh_3	Toluene	7
9	$Pd(OAc)_2$	Xantphos	Toluene	20
10	$Pd(OAc)_2$	DPEphos	Toluene	8
11	$Pd(OAc)_2$	dppe	Toluene	16
12	$Pd(OAc)_2$	dppe	Toluene	11
13	$Pd(OAc)_2$	1,10-Phen	Toluene	Trace
14	$Pd(OAc)_2$	dppf	NMP	70
15	$Pd(OAc)_2$	dppf	Diglyme	48
16	$Pd(OAc)_2$	dppf	DMF	64
17	$Pd(OAc)_2$	dppf	DMA	47
18	**$Pd(OAc)_2$**	**dppf**	**Anisole**	**90**
19[c]	$Pd(OAc)_2$	dppf	Anisole	22
20[d]	$Pd(OAc)_2$	dppf	Anisole	43

[a] Conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), catalyst (5 mol%), ligand (10 mol%), solvent (0.5 mL), 48 h, 160 °C under argon. [b] GC yield. [c] At 140 °C. [d] Under air.

Table 2 Reactions of **1a** with benzylic alcohols and amines[a]



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

Entry	Alcohol or amine		Product	Yield[b] (%)
				
1	R^1 = H	**2a**	**3a**	85
2	R^1 = 4-Me	**2b**	**3b**	88
3	R^1 = 4-OMe	**2c**	**3c**	85
4[c]	R^1 = 4-F	**2d**	**3d**	79
5[c]	R^1 = 4-Cl	**2e**	**3e**	73
6[c]	R^1 = 4-Br	**2f**	**3f**	30
7	R^1 = 2-Me	**2g**	**3g**	38
8	R^1 = 3-Me	**2h**	**3h**	68
9[c]		**2i**	**3i**	70
10[c]		**2j**	**3j**	48
11[c]		**2k**	**3k**	43
				
12	R^1 = H	**2l**	**3a**	84
13	R^1 = 4-Me	**2m**	**3b**	88
14	R^1 = 4-OMe	**2n**	**3c**	85
15	R^1 = 4-F	**2o**	**3d**	82
16	R^1 = 4-Cl	**2p**	**3e**	80

[a] Conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), dppf (10 mol%), anisole (0.5 mL), 160 °C, 48 h under argon. For entries 12–16, $PdCl_2$ (5 mol%) was used. [b] Isolated yields based on **1a**. [c] $Pd(OAc)_2$ (7.5 mol%) and dppf (15 mol%) were used.

3i in fair yield (entry 9). Hetero benzylic alcohols, *i.e.* pyridin-3-ylmethanol (**2j**) and furan-2-ylmethanol (**2k**), also participated in the reaction to provide the corresponding quinazolines **3j** and **3k** in moderate yields (entries 10 and 11).

Unfortunately, simple aliphatic alcohols, such as cyclohexanol and 1-butanol, were not active under the current reaction conditions. To our delight, benzyl amines also could be smoothly condensed with **1a** under the modified reaction conditions using $PdCl_2$ as the catalyst precursor to afford 2-arylquinazolines in high yields (entries 12–16). The pattern of the substituents did not make considerable difference to the reaction yields.

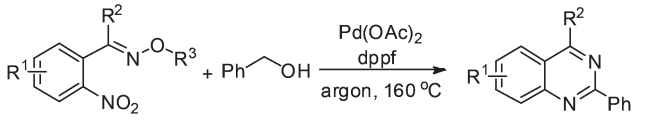
To further examine the scope and the limitations of the reaction, substituted (*E*)-2-nitrobenzaldehyde *O*-methyl oximes (**1**) were treated with **2a** under the standard conditions (Table 3). When (*E*)-5-methoxy-2-nitrobenzaldehyde *O*-methyl oxime (**1b**) reacted with benzyl alcohol, the desired product **3l** was obtained in 88% yield (entry 1). Halogen substituents such as fluoro and chloro were tolerated and afforded the substituted quinazolines **3m** and **3n** in 82% and 72% yields, respectively (entries 2 and 3). Again, a bromo substituent significantly decreased the reaction yield (entry 4). The reaction resulted in poor activity when a methyl substituent was located in the C=N bond (entry 5). In addition to methoxy group, a benzoxy group also could serve as an efficient leaving group to afford product **3a** in good yield (entry 6). Very low yield was observed when (*E*)-2-nitrobenzaldehyde oxime (**1h**) reacted with benzyl alcohol (entry 7).

To our surprise, the three-component reaction of 1-(2-nitrophenyl)ethanone (**1i**), urea and benzyl alcohol (**2a**) in the presence of $Pd(OAc)_2$/dppf also could provide 4-methyl-2-phenylquinazoline (**3p**) in 86% yield (Table 4, entry 1). Various benzylic alcohols with electron-donating substituents could efficiently involve the reaction to provide the corresponding products in good yields (entries 2–4). Lower yields were observed when halogen substituents were presented at the *para* position of benzyl alcohols (entries 5–7). The position of the substituent significantly affected the reaction and only 35% yield was obtained when the methyl group was located at the *ortho* position of benzyl alcohol (entry 8). Similarly, the hindered substrate 1-naphthalenemethanol (**2i**) reacted with **1i** and afforded the corresponding product **3y** in low yield (entry 10).

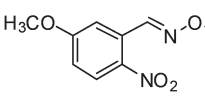
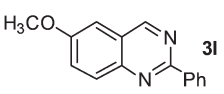
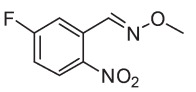
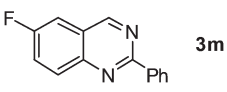
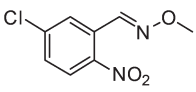
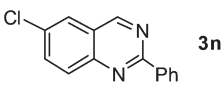
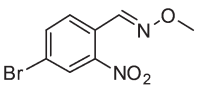
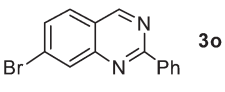
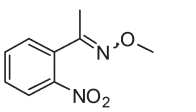
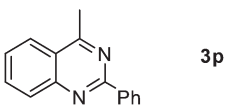
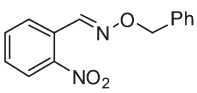
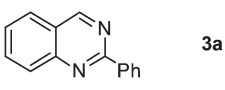
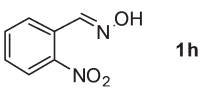
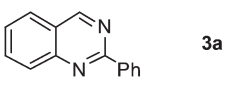
Moreover, 2-phenylquinazolin-4(3*H*)-one (**3z**) was obtained in 75% isolated yield when 2-nitrobenzonitrile (**1j**) was treated with **2a** (Scheme 2).

To gather more information about the possible reaction mechanism, some control experiments were carried out under

Table 3 Reactions of **2a** with various oximes[a]

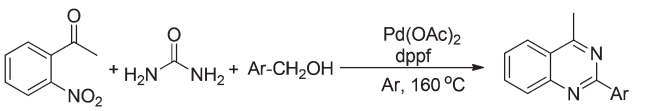


1 **2a** **3**

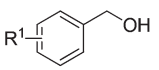
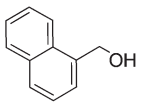
Entry	Oxime	Product	Yield[b] (%)
1	 **1b**	 **3l**	88
2	 **1c**	 **3m**	82
3	 **1d**	 **3n**	72
4	 **1e**	 **3o**	43
5	 **1f**	 **3p**	61
6	 **1g**	 **3a**	77
7	 **1h**	 **3a**	8[c]

[a] Conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), dppf (10 mol%), anisole (0.5 mL), 160 °C, 48 h under argon. [b] Isolated yields based on **1**. [c] GC yield.

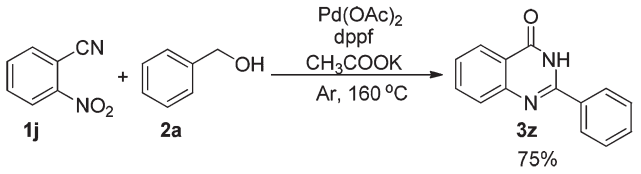
Table 4 Reactions of **1i** with various benzylic alcohols[a]



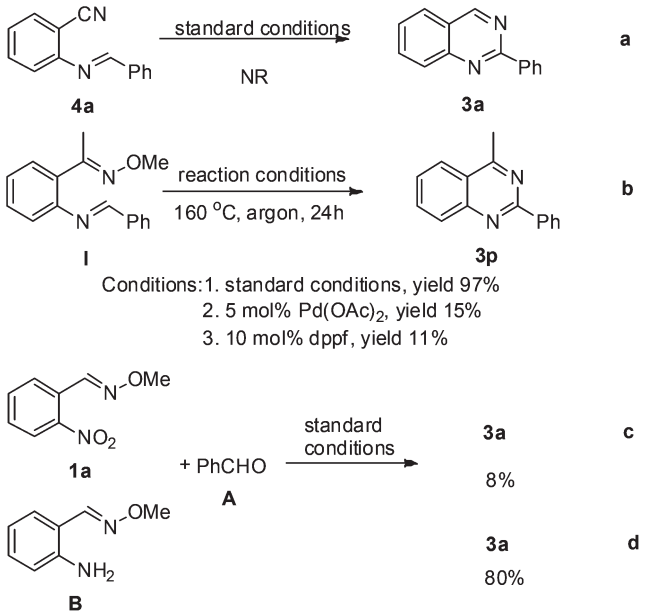
1i **2** **3**

Entry	Alcohol		Product	Yield[b] (%)
				
1	R^1 = H	**2a**	**3p**	86
2	R^1 = 4-Me	**2b**	**3q**	88
3	R^1 = 4-OMe	**2c**	**3r**	90
4	R^1 = 4-$CH(CH_3)_2$	**2q**	**3s**	89
5	R^1 = 4-F	**2d**	**3t**	48
6	R^1 = 4-Cl	**2e**	**3u**	42
7	R^1 = 4-Br	**2f**	**3v**	21
8	R^1 = 2-Me	**2g**	**3w**	35
9	R^1 = 3-Me	**2h**	**3x**	75
10		**2i**	**3y**	30

[a] Conditions: **1i** (0.2 mmol), **2** (0.6 mmol), urea (0.3 mmol), $Pd(OAc)_2$ (7.5 mol%), dppf (5 mol%), diglyme (0.5 mL), 160 °C, 24 h under argon. [b] Isolated yields based on **1i**.



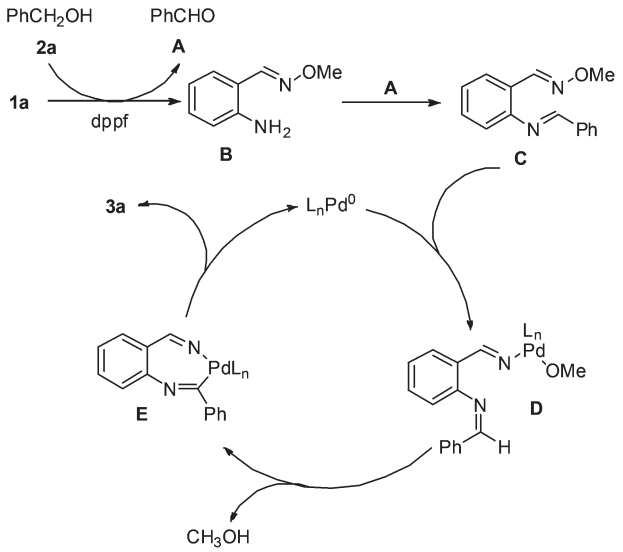
Scheme 2 2-Phenylquinazolin-4(3*H*)-one formation from 2-nitrobenzonitrile.



Scheme 3 Investigation of the reaction mechanism under various conditions (a–d).

various conditions (Scheme 3). During the optimization process of the reaction conditions, we observed a small amount of nitrile intermediate **4a**.[16] Further treatment of **4a** under the standard reaction conditions did not afford the corresponding product **3a** (Scheme 3, a). This indicates that the cyclization reaction did not involve a cyano intermediate pathway, which is identical with the reaction result of 2-nitrobenzonitrile (**1j**) and **2a** (Scheme 2). An imine compound **I** was prepared and treated under the standard reaction conditions to afford the corresponding product **3p** in 97% yield, as determined by GC analysis. Considerably lower yields were observed when the same compound was treated with $Pd(OAc)_2$ or dppf separately (Scheme 3, b). Treatment of **1a** with benzaldehyde only gave the product in 8% yield, whereas the reaction of compound **B** with benzaldehyde provided the product in 80% yield (Scheme 3, c and d). This indicates that the alcohol acted as the hydrogen donor to reduce the nitro group as we expected.

Based on these results, a plausible mechanism for 2-arylquinazolines is proposed in Scheme 4. The dehydrogenation of benzyl alcohol (**2a**) generates benzaldehyde **A** and reduces **1a** to intermediate **B**. The condensation of benzaldehyde with intermediate **B** affords an imine intermediate **C**. The oxidative addition of **C** to Pd(0) affords complex **D**.[17] The palladation of



Scheme 4 Possible mechanism.

the imidoyl C–H bond of **D** forms the cyclized intermediate **E** and generates methanol as a by-product. Finally, reductive elimination of **E** yields the desired product **3a** and releases the active Pd(0) catalyst to complete the catalytic cycle.

Conclusions

In conclusion, we have demonstrated a Pd/Fe-catalyzed 2-arylquinazoline formation from (*E*)-2-nitrobenzaldehyde *O*-methyl oximes or 1-(2-nitrophenyl)ethanone and alcohols or amines *via* the hydrogen transfer strategy. In this transformation, the alcohol (or amine) dehydrogenation, nitro reduction, and cyclization were realized in one pot. Because nitroarenes and benzyl alcohols or amines are readily available and stable chemicals, this method can afford an efficient approach for the preparation of 2-arylquinazolines. The scope and mechanism of this reaction is under investigation in our laboratory.

Experimental section

General methods

All experiments were carried out under an atmosphere of argon. Flash column chromatography was performed over silica gel 48–75 μm. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-AV (400 and 100 MHz, respectively) instrument, which was internally referenced to $SiMe_4$ or chloroform signals. MS analyses were performed on an Agilent 5975 GC-MS instrument (EI). The new compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS and HRMS. The structures of known compounds were further corroborated by comparing their ^{1}H NMR, ^{13}C NMR data and MS data with those found in the literature. All reagents were used as received from commercial sources without further purification. Solvents were used as received without further purification.

General procedure for the preparation of substrates (1a–1g)[18]

To a 250 mL round bottom flask, 2-nitrobenzaldehyde (5.0 g, 33.1 mmol), methoxylamine hydrochloride (3.0 g, 35.9 mmol) and ethanol (50 mL) were added. The reaction mixture was refluxed with stirring under a nitrogen atmosphere for 3 h and then allowed to stand at room temperature overnight. The reaction mixture was concentrated *in vacuo* to obtain a yellow solid. The crude product was partitioned between dichloromethane and water. The layers were separated and the organic phase was washed with water, followed by saturated sodium chloride. The organic phase was dried over magnesium sulfate, filtered and the filtrate was concentrated *in vacuo* to obtain 5.46 g of (*E*)-*O*-methyloxime-2-nitrobenzaldehyde (**1a**) (CAS: 135436-97-4). Other substrates were synthesized similarly. (*E*)-2-Nitrobenzaldehyde oxime (**1h**) was purchased from Alfa-Aesar and used as received without further purification.

General procedure: 2-phenylquinazoline (3a)

A 10 mL oven-dried reaction vessel was charged with Pd $(OAc)_2$ (2.2 mg, 0.01 mmol), dppf (11.0 mg, 0.02 mmol), (*E*)-2-nitrobenzaldehyde *O*-methyl oxime (**1a**, 36.0 mg, 0.2 mmol) and benzyl alcohol (**2a**, 62.0 μL, 0.6 mmol). The reaction vessel was purged three times with argon, and anisole (0.5 mL) was added to the sealed reaction vessel by a syringe. The resulting solution was stirred for 48 h at 160 °C. After cooling to room temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography (neutral aluminum oxide, petroleum ether–ethyl acetate = 30 : 1) to obtain **3a** as pale yellow solid; yield: 35.1 mg (85%).

2-Phenylquinazoline (3a, CAS: 25855-20-3).[19] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.48 (s, 1H), 8.63–8.62 (m, 2H), 8.11–8.09 (m, 1H), 7.95–7.90 (m, 2H), 7.64–7.61 (m, 1H), 7.55–7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.0, 160.4, 150.7, 138.0, 134.0, 130.6, 128.6, 128.5, 127.2, 127.2, 127.1, 123.5; MS (EI) *m*/*z* (%) 206 (100), 179, 152, 103, 76.

2-(*p*-Tolyl)quinazoline (3b).[19] A pale yellow solid; yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.45 (s, 1H), 8.51 (d, J = 8.0 Hz, 2H), 8.08–8.06 (m, 1H), 7.93–7.88 (m, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.36–7.34 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.2, 160.4, 150.9, 140.8, 135.4, 134.0, 129.4, 128.6, 128.6, 127.1, 127.0, 123.6, 21.5; MS (EI) *m*/*z* (%) 220 (100), 193, 165, 110, 76.

2-(4-Methoxyphenyl)quinazoline (3c, CAS: 67205-04-3).[19] A pale yellow solid; yield 85%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.43 (s, 1H), 8.58 (d, J = 8.0 Hz, 2H), 8.06–8.04 (m, 1H), 7.91–7.87 (m, 2H), 7.58 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 8.0 Hz, 2 H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.9, 160.9, 150.9, 147.7, 134.0, 130.9, 130.3, 128.5, 127.1, 126.8, 123.4, 114.0, 55.4; MS (EI) *m*/*z* (%) 236 (100), 221, 193, 166, 76.

2-(4-Fluorophenyl)quinazoline (3d, CAS: 1208259-07-7).[20] A pale yellow solid; yield 79%; ^{1}H NMR (400 MHz, CDCl3, ppm) δ 9.45 (s, 1H), 8.65–8.61 (m, 2H), 8.08–8.06 (m, 1H), 7.94–7.90 (m, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7 (d, J = 249.0 Hz), 159.5, 159.2, 149.8, 133.1, 129.7 (d, J = 9.0 Hz), 127.6, 126.2, 126.1, 125.1, 122.5, 114.5 (d, J = 21.0 Hz); MS (EI) *m*/*z* (%) 315 (100), 223, 196, 120, 77; MS (EI) *m*/*z* (%) 224 (100), 197, 170, 112, 76.

2-(4-Chlorophenyl)quinazoline (3e).[19] A pale yellow solid; yield 73%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.46 (s, 1H), 8.58 (d, J = 8.0 Hz, 2H), 8.09–8.07 (m, 1H), 7.95–7.91 (m, 2H), 7.65–7.62 (m, 1H), 7.52–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.5, 160.1, 150.8, 136.9, 136.6, 134.2, 130.0, 128.8, 128.7, 127.4, 127.1, 123.7; MS (EI) *m*/*z* (%) 240 (100), 213, 178, 151, 120.

2-(4-Bromophenyl)quinazoline (3f, CAS: 1222094-28-1).[20] A pale yellow solid; yield 30%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.46 (s, 1H), 8.51 (d, J = 8.0 Hz, 2H), 8.08 (d, J = 8.0 Hz, 1H), 7.95–7.91 (m, 2H), 7.68–7.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.5, 160.2, 150.8, 137.1, 134.2, 131.8, 130.2, 128.7, 127.5, 127.2, 125.4, 123.7; MS (EI) *m*/*z* (%) 284 (100), 257, 205, 178, 76.

2-(*o*-Tolyl)quinazoline (3g, CAS: 1208259-15-7).[21] A brown solid; yield 38%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.51 (s, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.99–7.89 (m, 3H), 7.67 (t, J = 8.0 Hz, 1H), 7.38–7.33 (m, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.1, 160.0, 150.5, 138.6, 137.5, 134.1, 131.3, 130.7, 129.3, 128.6, 127.5, 127.1, 126.0, 123.0, 21.1; MS (EI) *m*/*z* (%) 219 (100), 190, 165, 110, 77.

2-(*m*-Tolyl)-3,4-dihydroquinazoline (3h).[22] A pale yellow solid; yield 68%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.47 (s, 1H), 8.43–8.40 (m, 2H), 8.10 (d, J = 8.0 Hz, 1H), 7.95–7.90 (m, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.44 (t, J = 8.0 Hz, 1H), 7.34–7.32 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.3, 160.4, 150.9, 138.3, 138.1, 134.0, 131.4, 129.2, 128.7, 128.6, 127.2, 127.1, 125.9, 123.6, 21.5; MS (EI) *m*/*z* (%) 220 (100), 193, 165, 110, 76.

2-(Naphthalen-1-yl)quinazoline (3i, CAS: 93656-11-2).[20] A brown solid; yield 70%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.60 (s, 1H), 8.70 (d, J = 8.0 Hz, 1H), 8.19–8.17 (m, 2H), 8.04–7.93 (m, 4H), 7.71 (t, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.57–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.2, 161.0, 151.3, 137.0, 134.9, 132.0, 131.5, 131.1, 130.4, 129.4, 129.2, 128.4, 127.8, 127.5, 126.7, 126.6, 126.0, 123.9; MS (EI) *m*/*z* (%) 311 (100), 221, 192, 120, 77; MS (EI) *m*/*z* (%) 255 (100), 228, 153, 128, 77.

2-(Pyridin-3-yl)quinazoline (3j).[20] A pale yellow solid; yield 48%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.86 (s, 1H), 9.54 (s, 1H), 8.92 (d, J = 8.0 Hz, 1H), 8.79–8.78 (m, 1H), 8.17–8.15 (m, 1H), 8.02–7.98 (m, 2H), 7.73–7.70 (m, 1H), 7.53–7.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.3, 159.9, 151.9, 151.4, 151.0, 136.5, 135.0, 134.3, 129.4, 128.4, 127.8, 124.5, 124.0; MS (EI) *m*/*z* (%) 207 (100), 179, 153, 103, 76.

2-(Furan-2-yl)quinazoline (3k).[20] A pale green solid; yield 43%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.40 (s, 1H), 8.12–8.10 (m, 1H), 7.92–7.90 (m, 2H), 7.70 (s, 1H), 7.63–7.60 (m, 1H), 7.47 (s, 1H), 6.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.4, 154.9, 153.3, 151.2, 146.0, 135.1, 129.5, 129.1, 127.9, 124.1, 114.8, 113.0; MS (EI) *m*/*z* (%) 196 (100), 168, 140, 114, 76.

General procedure for benzyl amine substrates (3a)

A 10 mL oven-dried reaction vessel was charged with $PdCl_2$ (1.8 mg, 0.01 mmol), dppf (11.0 mg, 0.02 mmol), (*E*)-2-nitrobenzaldehyde *O*-methyl oxime (**1a**, 36.0 mg, 0.2 mmol) and benzylamine (**2l**, 65.6 μL, 0.6 mmol). The reaction vessel was purged with argon three times, and anisole (0.5 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred for 48 h at 160 °C. After cooling to room temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography (neutral aluminum oxide, petroleum ether–ethyl acetate = 30 : 1) to obtain **3a** as pale yellow solid; yield: 34.6 mg (84%).

6-Methoxy-2-phenylquinazoline (3l, CAS: 34637-66-6).[19] A pale yellow solid; yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.38 (s, 1H), 8.57 (d, J = 8.0 Hz, 2H), 8.02–7.99 (m, 1H), 7.58–7.52 (m, 4H), 7.17 (s, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 158.5, 157.8, 157.3, 146.1, 137.3, 129.2, 129.2, 127.6, 127.2, 126.1, 123.5, 103.0, 54.7; MS (EI) m/z (%) 236 (100), 221, 193, 106, 63.

6-Fluoro-2-phenylquinazoline (3m, CAS: 1399327-71-9).[19] A pale yellow solid; yield 82%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.44 (s, 1H), 8.61–8.59 (m, 2H), 8.13–8.09 (m, 1H), 7.71–7.66 (m, 1H), 7.56–7.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.4 (J = 250.0 Hz), 160.7, 159.8 (J = 6.0 Hz), 148.0, 137.8, 131.4 (J = 8.0 Hz), 130.7, 128.7, 128.5, 124.4 (J = 26.0 Hz), 123.9 (J = 8.0 Hz), 110.1 (J = 22.0 Hz); MS (EI) m/z (%) 224 (100), 197, 170, 112, 77.

6-Chloro-2-phenylquinazoline (3n, CAS: 58058-53-0).[23] A pale yellow solid; yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.41 (s, 1H), 8.61–8.60 (m, 2H), 8.05–8.03 (m, 1H), 7.92 (s, 1H), 7.85–7.83 (m, 1H), 7.55–7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.1, 160.2, 150.0, 138.4, 135.7, 133.5, 131.5, 131.1, 129.4, 129.3, 126.5, 124.7; MS (EI) m/z (%) 240 (100), 213, 178, 120, 75.

7-Bromo-2-phenylquinazoline (3o). A pale yellow solid; yield 43%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.45 (s, 1H), 8.61 (s, 2H), 8.30 (s, 1H), 7.82–7.80 (m, 1H), 7.73–7.70 (m, 1H), 7.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.9, 160.3, 151.5, 137.7, 131.2, 131.0, 131.0, 128.9, 128.8, 128.7, 128.3, 122.2; MS (EI) m/z (%) 284 (100), 257, 178, 151, 75; HRMS calcd for: $C_{14}H_9BrN_2$ $[M + H]^+$ = 285.0022, found = 285.0020.

4-Methyl-2-phenylquinazoline (3p, CAS: 1806-66-2).[24] A pale yellow solid; yield 61%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.62 (d, J = 8.0 Hz, 2H), 8.09 (t, J = 8.0 Hz, 2H), 7.88–7.85 (m, 1H), 7.60–7.51 (m, 4H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.2, 160.3, 150.5, 138.4, 133.5, 130.4, 129.4, 128.6, 128.5, 126.8, 125.0, 123.1, 22.0; MS (EI) m/z (%) 220 (100), 205, 179, 110, 76.

General procedure for Table 4 (3p) substrates

A 10 mL oven-dried reaction vessel was charged with $Pd(OAc)_2$ (3.4 mg, 0.075 mmol), dppf (5.5 mg, 0.05 mmol), 1-(2-nitrophenyl)ethanone (**1i**, 27.0 μL, 0.2 mmol), urea (18.0 mg, 0.3 mmol) and benzyl alcohol (**2a**, 62.0 μL, 0.6 mmol). The reaction vessel was purged with argon three times, and diglyme (0.5 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred for 24 h at 160 °C. After cooling to room temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography (neutral aluminum oxide, petroleum ether–ethyl acetate = 100 : 1) to obtain **3p** as pale yellow solid; yield: 37.8 mg (86%).

4-Methyl-2-(*p*-tolyl)quinazoline (3q, CAS: 1400697-35-9).[25] A pale yellow solid; yield 88%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, J = 4.0 Hz, 2H), 8.09–8.04 (m, 2H), 7.85 (t, J = 8.0 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.34–7.32 (m, 2H), 3.01 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.1, 160.2, 150.5, 140.6, 135.6, 133.4, 129.3, 129.2, 128.6, 126.6, 125.0, 123.0, 22.0, 21.5; MS (EI) m/z (%) 234(100), 219, 193, 117, 89.

2-(4-Methoxyphenyl)-4-methylquinazoline (3r, CAS: 84570-78-5).[25] A pale yellow solid; yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.59 (d, J = 12.0 Hz, 2H), 8.06–8.01 (m, 2H), 7.83 (t, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.0, 161.7, 156.8, 150.5, 133.4, 131.1, 130.2, 129.1, 126.4, 125.0, 122.8, 113.9, 55.4, 22.0; MS (EI) m/z (%) 250 (100), 235, 209, 192, 103.

2-(4-Isopropylphenyl)-4-methylquinazoline (3s).[26] A pale yellow solid; yield 89%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.52 (d, J = 8.0 Hz, 2H), 8.07 (t, J = 8.0 Hz, 2H), 7.85 (t, J = 8.0 Hz, 1H), 7.58–7.55 (m, 1H), 7.38 (d, J = 8.0 Hz, 2H), 3.01 (s, 3H), 1.31 (d, J = 8.0 Hz, 6H), 1.26 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.0, 160.4, 151.4, 150.6, 136.1, 133.3, 129.3, 128.7, 126.6, 126.5, 124.9, 123.0, 34.1, 23.9, 21.9; MS (EI) m/z (%) 262 (100), 247, 232, 117, 77.

2-(4-Fluorophenyl)-4-methylquinazoline (3t, CAS: 1315314-55-6).[25] A pale yellow solid; yield 48%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.65–8.62 (m, 2H), 8.07 (q, J = 8.0 Hz, 2H), 7.88–7.85 (m, 1H), 7.60–7.57 (m, 1H), 7.22–7.18 (m, 2H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.2, 164.6 (d, J = 248.0 Hz), 159.3, 150.5, 134.5 (d, J = 3.0 Hz), 133.5, 130.7 (d, J = 9.0 Hz), 129.2, 126.8, 125.0, 122.9, 115.4 (d, J = 21 Hz), 21.9; MS (EI) m/z (%) 315 (100), 223, 196, 120, 77; MS (EI) m/z (%) 238 (100), 223, 197, 119, 76.

2-(4-Chlorophenyl)-4-methylquinazoline (3u, CAS: 1315314-54-5).[25] A pale yellow solid; yield 42%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58 (d, J = 8.0 Hz, 1H), 8.08 (q, J = 8.0 Hz, 2H), 7.89–7.86 (m, 1H), 7.60 (t, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.33–7.30 (m, 1H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.3, 150.4, 136.9, 136.6, 133.6, 129.9, 129.3, 128.7, 128.7, 127.0, 125.0, 123.1, 21.9; MS (EI) m/z (%) 254 (100), 239, 213, 178, 102.

2-(4-Bromophenyl)-4-methylquinazoline (3v, CAS: 1054478-98-6).[26] A pale white solid; yield 21%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.51 (d, J = 8.0 Hz, 2H), 8.07 (q, J = 8.0 Hz, 2H), 7.87 (t, J = 8.0 Hz, 1H), 7.66–7.58 (m, 3H), 3.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.3, 159.3, 150.4, 137.3, 133.6, 131.7, 130.2, 129.3, 127.0, 125.1, 125.0, 123.1, 21.9; MS (EI) m/z (%) 298 (100), 283, 257, 178, 102.

4-Methyl-2-(*o*-tolyl)quinazoline (3w). A pale yellow solid; yield 35%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14 (d, J = 8.0 Hz,

1H), 8.08 (d, J = 8.0 Hz, 1H), 7.91–7.84 (m, 2H), 7.65–7.64 (m, 1H), 7.32 (s, 3H), 3.02 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.8, 163.4, 150.2, 139.0, 137.3, 133.5, 131.2, 130.5, 129.3, 129.1, 127.1, 125.9, 124.9, 122.4, 21.8, 20.9; MS (EI) m/z (%) 233 (100), 218, 165, 116, 89; HRMS calcd for: $C_{16}H_{15}N_2$ $[M + H]^+$ = 235.12298, found = 235.12313.

4-Methyl-2-(*m*-tolyl)quinazoline (3x). A pale yellow solid; yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.43–8.41 (m, 2H), 8.10–8.07 (m, 2H), 7.86 (t, J = 8.0 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.32–7.30 (m, 1H), 3.03 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.1, 160.4, 150.5, 138.3, 138.1, 133.4, 131.2, 129.3, 129.1, 128.5, 126.8, 125.8, 125.0, 123.0, 22.0, 21.5; MS (EI) m/z (%) 234 (100), 219, 193, 116, 91; HRMS calcd for: $C_{16}H_{15}N_2$ $[M + H]^+$ = 235.12298, found = 235.12312.

4-Methyl-2-(naphthalen-1-yl)quinazoline (3y). A pale yellow solid; yield 30%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.64–8.61 (m, 1H), 8.20–8.12 (m, 3H), 7.98–7.91 (m, 3H), 7.69–7.60 (m, 2H), 7.53–7.51 (m, 2H), 3.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.2, 162.8, 150.3, 136.7, 134.3, 133.7, 131.4, 130.1, 129.4, 129.3, 128.4, 127.3, 126.6, 126.2, 125.8, 125.3, 125.0, 122.6, 21.9; MS (EI) m/z (%) 270 (100), 255, 228, 153, 127; HRMS calcd for: $C_{19}H_{15}N_2$ $[M + H]^+$ = 271.12298, found = 271.12316.

Procedure for 3z formation

A 10 mL oven-dried reaction vessel was charged with $Pd(OAc)_2$ (2.2 mg, 0.05 mmol), dppf (11.0 mg, 0.1 mmol), anhydrous potassium acetate (19.6 mg, 0.2 mmol), 2-nitrobenzonitrile (**1j**, 29.6 mg, 0.2 mmol) and benzyl alcohol (**2a**, 62.0 μL, 0.6 mmol). The reaction vessel was purged three times with argon, and anisole (0.5 mL) was added to the sealed reaction vessel by syringe. The resulting solution was stirred at for 40 h 160 °C. After cooling to room temperature, the volatiles were removed under vacuum and the residue was purified by column chromatography (neutral aluminum oxide, petroleum ether–ethyl acetate = 5 : 1) to give **3z** as pale yellow solid; yield: 33.3 mg (75%).

2-Phenylquinazolin-4(3*H*)-one (3z, CAS: 1022-45-3).[27] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.02 (s, 1H), 8.34 (d, J = 8.0 Hz, 1H), 8.21–8.20 (m, 2H), 7.86–7.80 (m, 2H), 7.60 (s, 3H), 7.52 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.5, 152.4, 150.3, 135.5, 133.6, 132.3, 129.7, 128.7, 128.1, 127.5, 127.1, 121.6; MS (EI) m/z (%) 206 (100), 179, 152, 103, 76.

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