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Hydrogen peroxide mediated formation of heteroaryl ethers from pyridotriazol-1-yloxy heterocycles and arylboronic acids

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ABSTRACT

Pyridotriazol-1-yloxypyrimidine **3** reacts with arylboronic acids under palladium-free, Cs_2CO_3, (0.8%) H_2O_2, and DME conditions to produce heteroaryl ethers **4–16** in good yields comparable to the oxidative palladium-catalyzed reaction. The yields of aryl ethers **17–19** from quinazoline **2** with (0.8%) H_2O_2 were modest. Hydrogen peroxide is superior to dioxygen as an oxidant in these reactions.

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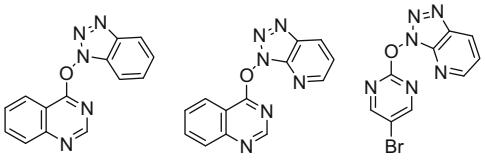
Recently, we have reported on the synthetic versatility of phosphonium-mediated S_NAr reactions of biologically important heterocyles[1,2] using BOP reagents.[3,4] Mechanistic studies regarding the nature of the intermediates in these reactions using ^{31}P NMR and ESI MS techniques are consistent with a pathway involving stepwise formation of heterocyclic benzotriazol-yloxy adducts from the phosphonium intermediates.[5] In this regard, benzotriazol-yloxy quinazoline **1** and other thienopyrimidine heterocycles readily reacted with various nucleophiles in S_NAr fashion.[5] Moreover, since the benzotriazol-yloxy and pyridotriazol-1-yloxy (*O*Pt) adducts are more stable than the corresponding phosphonium intermediates, further investigations of the reactions of **2** and **3** (Eq. 1) under oxidative palladium-catalyzed conditions ($Pd(PPh_3)_4$, O_2, Cs_2CO_3, and DME–H_2O) with arylboronic acids led to the unexpected formation of heteroaryl ethers.[6,7] This transformation is synthetically valuable especially in cases where phenols are not readily available for S_NAr type reactions and is unique compared to the homocoupling reactions in metal-catalyzed reactions in that unsymmetrical ether compounds are obtained instead of biaryls.[8,9]

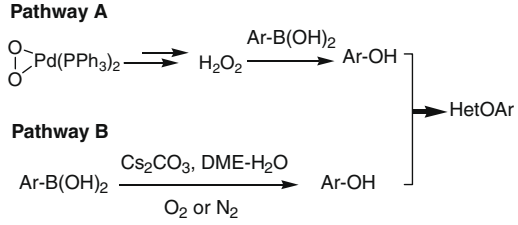


1 2 3 (1)

Mechanistic studies on the oxidative palladium-catalyzed reaction of **2** using labeled dioxygen ($^{18}O_2$) led to the conclusion that the ether oxygen is derived from phenols which are generated from two sources: oxidative Pd catalyzed pathway A (H_2O_2 via O_2) and a non-palladium-mediated pathway B involving Cs_2CO_3 and arylboronic acid (Scheme 1). While the contribution of each pathway to the formation of phenols and eventually heteroaryl ethers was not explored, the latter pathway was unexpected and does not seem to depend solely on dioxygen.

The roles of the Pd(0) catalyst and dioxygen in pathway A were conceived to provide a source of H_2O_2 in situ, which in turn forms phenols in situ. Assuming that quinazolines[6] and pyrimidines[7] *O*Pt adducts react similarly in the oxidative palladium reaction, we explored further the transformation of *O*Pt adducts **2** and **3** to heteroaryl ethers using arylboronic acids and (0.6–1%) H_2O_2 as an oxidant without Pd(0) catalyst. Conceptually, this seemed as an attractive strategy to probe further the synthetic utility of this transformation and its possible mechanistic implications. In this Letter, we report our results on the reaction of **2** and **3** with arylboronic acids mediated by H_2O_2 as an oxidant.

The reaction of arylboronic acids with pyrimidine **3** under Cs_2CO_3, (0.8%) H_2O_2, and DME conditions led to aryl ethers in variable yields (Table 1). Aryl ethers generated from arylboronic acids in entries 4, 6, and 11 are formed in substantially lower yields than those from the oxidative palladium-catalyzed reaction[7] while aryl ether **10** was formed in higher yields under the palladium-free conditions. The isolated yields obtained with arylboronic acids in



Scheme 1.

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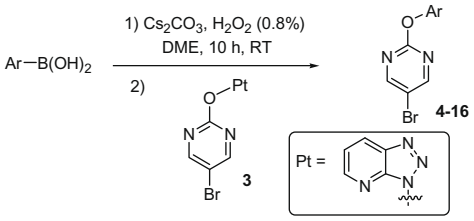
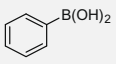
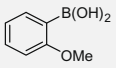
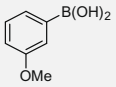
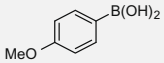
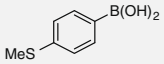
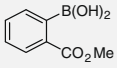
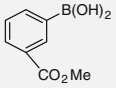
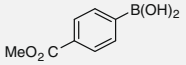
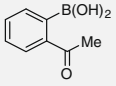
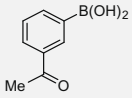
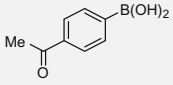
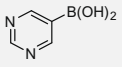
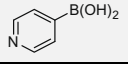
Table 1
Synthesis of aryl ethers **4–16** from **3**



Entry	Boronic acid	Yield[a,b] (%)
1		**4**; 58, 62
2		**5**; 82, 85
3		**6**; 25, 28
4		**7**; 56, 83
5		**8**; 75, 70
6		**9**; 19, 63
7		**10**; 61, 33
8		**11**; 53, 48
9		**12**; 17, 34
10		**13**; 84, 87
11		**14**; 34, 95
12		**15**; 41, 55
13		**16**; 23, 44

[a] Based on isolated products, average of 2–3 experiments Cs_2CO_3, (0.8%) H_2O_2, and DME.
[b] $Pd(PPh_3)_4$, O_2, Cs_2CO_3, and DME–H_2O).

entries 1, 2, 5, 8, 10, and 12 are comparable to those obtained by the oxidative palladium-catalyzed reaction employing the same arylboronic acids[7] and attest to the synthetic potential of this transformation. Although the yields for aryl ethers in entries 3, 9, and 13 are relatively low, they are however, comparable to those obtained by the oxidative palladium conditions.

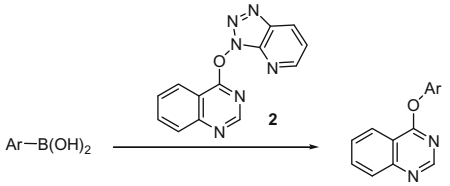
Therefore, in the case of pyrimidine **3** and in reference to the mechanistic proposal outlined in Scheme 1, the formation of aryl ethers under Cs_2CO_3, (0.8%) H_2O_2, and DME conditions in entries 1–3, 5, 7–10, 12, and 13 competes well with the oxidative palladium-catalyzed reaction.[7] This finding suggests an attractive synthesis of heteroaryl ethers under palladium-free conditions.

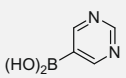
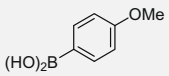
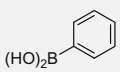
Quinazoline **2** which was previously shown to furnish aryl ethers under Pd(0) conditions, led to the formation of aryl ethers **17–19** with 5-pyrimidinyl, *p*-methoxyphenyl, and phenylboronic acids, respectively under the new H_2O_2 conditions (Table 2). The lower yields of ethers **17–19** compared to those obtained by the oxidative palladium-catalyzed reaction suggest that the latter transformation[6] is a superior method for forming quinazoline heteroaryl ethers compared to the palladium-free H_2O_2 conditions.

Having established a differential in reactivity between **2** and **3** under the palladium-free conditions, it became necessary to evaluate the extent of pathway B (Scheme 1) contributions in the oxidative palladium-catalyzed reaction. To compliment our earlier mechanistic studies,[6] quinazoline **2** was reacted with 5-pyrimidinylboronic acid under Cs_2CO_3, $^{18}O_2$, and DME–H_2O conditions without the Pd(0) catalyst and the ratio of incorporation of ^{18}O into the ether product **17** was monitored with time using ESI/MS techniques. After 24 h, the conversion to the ether product amounted to <10% with a ratio of ^{16}O:^{18}O being 44:56 (Scheme 2). The low conversion is also consistent with that obtained using dioxygen and suggests that pathway B is minor relative to pathway A in the oxidative palladium-catalyzed reaction. Similarly, the preparation of aryl ethers **4**, **7**, and **14** (Table 1 entries 1, 4, and 11) from **3** proceeds in low yields (10–27%) under Cs_2CO_3, O_2, and DME–H_2O conditions.

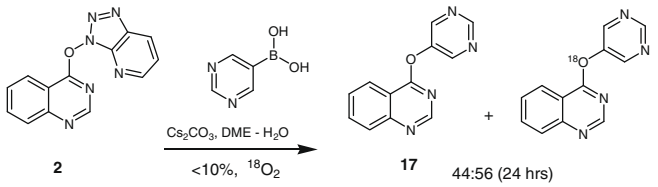
To account for differences between the palladium-free H_2O_2 conditions and oxidative palladium-catalyzed conditions,[6] it would seem plausible to suggest that the choice of arylboronic acid plays a significant role in the formation of phenols from H_2O_2 as in the palladium-free conditions or pathway A in the oxidative palladium reaction[6] since the hydrolysis of $ArPdOB(OH)_2(PPh_3)_2$ produces

Table 2
Synthesis of aryl ethers from **2**



Entry	Boronic acid	Yield[a] (%)	Yield[b] (%)
1		**17**; 20	78
2		**18**; 34	66
3		**19**; 30	80

[a] Based on isolated products, average of 2–3 experiments Cs_2CO_3, (0.8%) H_2O_2, and DME.
[b] $Pd(PPh_3)_4$, O_2, Cs_2CO_3, and DME–H_2O).



Scheme 2.

H_2O_2 and $ArPd(OH)(PPh_3)_2$.[6,10] Excess arylboronic acid can, however, be consumed in the palladium-catalyzed reaction by transmetalation of $ArPd(OH)(PPh_3)_2$ leading to $Ar_2Pd(PPh_3)_2$ and its reductive elimination to the homocoupling product Ar-Ar.[10]

Although the conversion of arylboronic acids to phenols has been previously reported to proceed with 30% H_2O_2[11] or other oxidants such as perborate,[12] hydroxylamine,[13] and oxone, [14,15] limitations of these methods have been reported.[10,16,17] Experimentally, we aimed at using a low concentration of hydrogen peroxide (<1%) for comparative purposes with the oxidative palladium-catalyzed reaction[5–7] since in this case higher concentrations were inhibitory to the formation of heteroaryl ethers.[6,7] The experimental procedure adopted under the palladium-free conditions is a one-pot, two-step sequence involving oxidation of arylboronic acids with (0.8–1%) hydrogen peroxide followed by the addition of the *O*Pt heterocycle **2** or **3**.

In conclusion, the reaction of arylboronic acids with *O*Pt heterocycles **2** and **3** under Cs_2CO_3, (0.8%) H_2O_2, and DME conditions produces heteroaryl ethers in good synthetic yields and is superior to that involving Cs_2CO_3, O_2, and DME–H_2O conditions. Comparative studies between quinazoline **2** and pyrimidine **3** indicate that the palladium-free Cs_2CO_3, (0.8%) H_2O_2, and DME conditions produce heteroaryl ethers **4–16** in yields comparable to that of the palladium-catalyzed conditions ($Pd(PPh_3)_4$, O_2, Cs_2CO_3, and DME–H_2O) in the case of **3**. However, for quinazoline **2** the palladium-catalyzed process is more efficient.

This new transformation complements the direct S_NAr with phenols[5,18,19] and competes well with the oxidative palladium-catalyzed reaction.[6,7] The relative simplicity in eliminating palladium metal and dioxygen and employing H_2O_2 as an oxidant makes it an attractive consideration for the synthesis of heteroaryl ethers. This reaction strongly highlights on the complexity in understanding the reaction pathways in these oxidative transformations.[20]

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.135.

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20. *5-Bromo-2-phenoxypyrimidine* **(4)**: Phenyl boronic acid (50 mg, 0.41 mmol) and Cs_2CO_3 (443 mg, 1.36 mmol) were dissolved in DME (5 mL) at rt. Aqueous H_2O_2 (0.04 mL, 0.8%) was added to the reaction mixture and purged with O_2. The reaction mixture was stirred for 6 h. 3-(5-Bromo-pyrimidin-2-yloxy)-3*H*-[1,2,3] triazolo [4,5-*b*]pyridine (36 mg, 0.12 mmol) was then added at rt and the reaction mixture was stirred for a further 10 h. The crude reaction mixture was then directly purified by flash chromatography to afford a white solid (49 mg, 58%). ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.45 (m, 2H), 7.29 (m, 1H), HRMS (ES-MS) [(M+H)$^+$]: for $C_{10}H_7BrN_2O$ 250.9814, found 250.9817.
5-Bromo-2-(2-methoxyphenoxy)-pyrimidine **(5)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.54 (s, 2H), 7.17 (m, 2H), 7.03 (m, 2H), 3.75 (s, 3 H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{11}H_9BrN_2O_2$ 280.9920, found 280.9918.
5-Bromo-2-(3-methoxyphenoxy)pyrimidine **(6)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.57 (s, 2H), 7.33 (m, 1H), 6.83 (m, 3H), 3.81 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{11}H_9BrN_2O_2$ 280.9926, found 280.9919.
5-Bromo-2-(4-methoxyphenoxy)-pyrimidine **(7)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.12 (d, 2H, *J* = 9.3 Hz), 6.96 (d, 2H, *J* = 9.0 Hz), 3.82 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{11}H_9BrN_2O_2$ 280.9920, found 280.9919.
5-Bromo-2-(4-methylsulfanyl-phenoxy)-pyrimidine **(8)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.57 (s, 2H), 7.33 (d, 2H, *J* = 6.6 Hz), 7.13 (d, 1H, *J* = 6.9 Hz), 2.50 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{11}H_9BrN_2OS$ 296.9692, found 296.9688.
2-(5-Bromo-pyrimidin-2-yloxy)-benzoic acid methyl ester **(9)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.54 (s, 2H), 8.08 (dd, 1H, *J* = 1.6 Hz, *J* = 7.8 Hz), 7.63 (dt, 1H, *J* = 1.5 Hz, *J* = 7.5 Hz), 7.37 (dt, 1H, *J* = 0.9 Hz, *J* = 7.8 Hz), 7.24 (dd, 1H, *J* = 0.9 Hz, *J* = 8.1 Hz), 3.72 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{12}H_9BrN_2O_3$ 308.9869, found 308.9871.
3-(5-Bromo-pyrimidin-2-yloxy)-benzoic acid methyl ester **(10)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.58 (s, 2H), 7.98 (m, 1H), 7.86 (t, 1H, *J* = 2.4 Hz), 7.53 (t, 1H, *J* = 7.8 Hz), 7.39 (m, 1H), 3.92 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{12}H_9BrN_2O_3$ 308.9869, found 308.9875.
4-(5-Bromo-pyrimidin-2-yloxy)-benzoic acid methyl ester **(11)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.59 (s, 2H), 8.14 (d, 2H, *J* = 9.2 Hz), 7.24 (d, 2H, *J* = 8.4 Hz), 3.93 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{12}H_9BrN_2O_3$ 308.9869, found 308.9870.
1-[2-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone **(12)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.55 (s, 2H), 7.89 (dd, 1H, *J* = 1.8 Hz, *J* = 7.8 Hz), 7.60 (td, 1H, *J* = 1.8 Hz, *J* = 7.5 Hz), 7.38 (td, 1H, *J* = 0.9 Hz, *J* = 7.8 Hz), 7.23 (dd, 1H, *J* = 0.9 Hz, *J* = 7.5 Hz), 2.52 (s, 3H).HRMS (ES-MS) [(M+H)$^+$]: for $C_{12}H_9BrN_2O_2$ 292.9920, found 292.9919.
1-[3-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone **(13)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.58 (s, 2H), 7.55 (m, 1H), 7.34 (t, 1H, *J* = 7.8 Hz), 7.13 (m, 1H), 6.79 (s, 1H), 2.62 (s, 3H). HRMS (ES-MS) [(M+Na)$^+$]: for $C_{12}H_9BrN_2O_2$ 314.9740, found 314.9735.
1-[4-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone **(14)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.59 (s, 2H), 8.06 (d, 2H, *J* = 9.2 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 2.62 (s, 3 H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{12}H_9BrN_2O_2$ 292.9919, found 292.9918.
5-Bromo-2-(pyrimidin-5-yloxy)-pyrimidine **(15)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 9.13 (s, 2H), 8.73 (s, 2H), 8.62 (s, 2H). HRMS (ESI-MS) [(M+H)$^+$]: for $C_8H_5BrN_4O$ 252.972, found 252.9719.
5-Bromo-2-(pyrimidin-5-yloxy)-pyrimidine **(16)**: ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.91 (d, 2H, *J* = 5.1 Hz), 8.77 (s, 2H), 6.51 (d, 2H, *J* = 5.1 Hz). MS (ESI-MS) [(M+H)$^+$]: for $C_9H_6BrN_3O$ 252.06, found 252.20.

Aryl ethers **4, 7, 14** from **3,** Cs_2CO_3 and dioxygen in DME:

5-Bromo-2-phenoxypyrimidine **(4)**: This compound was synthesized from 3-(5-bromo-pyrimidin-2-yloxy)-3*H*-[1,2,3] triazolo [4,5-*b*] pyridine (10 mg, 0.03 mmol), phenyl boronic acid (12 mg, 0.10 mmol), and Cs_2CO_3 (44 mg, 0.14 mmol) in DME (1 mL). The reaction mixture was purged with dioxygen and stirred at rt for 10 h. The crude reaction mixture was then directly purified by flash chromatography to afford a white solid (2 mg, 27%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.45 (m, 2H), 7.29 (m, 1H), 7.19 (d, 2H, J = 4.2 Hz). HRMS (ES-MS) [(M+H)$^+$]: for $C_{10}H_7BrN_2O$ 250.9814, found 250.9817.

5-Bromo-2-(4-methoxyphenoxy)-pyrimidine **(7)**: This compound was synthesized from 3-(5-bromo-pyrimidin-2-yloxy)-3*H*-[1,2,3] triazolo [4,5-*b*] pyridine (50 mg, 0.17 mmol), 4-methoxy phenyl boronic acid (78 mg, 0.51 mmol), and Cs_2CO_3 (222 mg, 0.68 mmol) in DME (2.5 mL). The reaction mixture was purged with dioxygen and stirred at rt for 10 h and was purified by flash chromatography as a white solid (10 mg, 21%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.56 (s, 2H), 7.12 (d, 2H, J = 9.3 Hz), 6.96 (d, 2H, J = 9.0 Hz), 3.82 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{11}H_9BrN_2O_2$ 280.9920, found 280.9919.

1-[4-(5-Bromo-pyrimidin-2-yloxy)-phenyl]-ethanone **(14)**: This compound was synthesized from 3-(5-bromo-pyrimidin-2-yloxy)-3*H*-[1,2,3] triazolo [4,5-*b*] pyridine (100 mg, 0.34 mmol), 4-acetyl phenyl boronic acid (220 mg, 1.34 mmol), and Cs_2CO_3 (556 mg, 1.74 mmol) in DME (10 mL). The reaction mixture was purged with dioxygen and stirred at rt for 10 h. The crude reaction mixture was then directly purified by flash chromatography to afford a white solid (10 mg, 10%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 8.59 (s, 2H), 8.06 (d, 2H, J = 9.2 Hz), 7.29 (d, 2H, J = 8.8 Hz), 2.62 (s, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{12}H_9BrN_2O_2$ 292.9919, found 292.9918.

Aryl ethers **17, 18, 19** from **2,** Cs_2CO_3 in DME and aq H_2O_2 (0.8%).

4-(Pyrimidin-5-yloxy)quinazoline **(17)**:: This compound was synthesized from 4-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)quinazoline (90 mg, 0.34 mmol). Pyrimidine boronic acid (186 mg, 1.50 mmol), and Cs_2CO_3 (332 mg, 1.02 mmol) in DME (3 mL) and aq H_2O_2 (0.02 mL, 0.8%) were added to the reaction mixture and stirred for 10 h. The crude reaction mixture was purified by flash chromatography as a white solid (15 mg, 20%).^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 9.06 (s, 1H), 8.41 (s, 2H), 8.77 (s, 1H), 8.39–8.37 (m, 1H), 8.06–7.96 (m, 2H), 7.76–7.73 (m, 1H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{12}H_8N_4O_1$ 225.0771, found 225.0771.

4-(4-Methoxyphenoxy)quinazoline **(18)**: This compound was synthesized from 4-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy)quinazoline (**2**, 64 mg, 0.25 mmol), 4-methoxy phenyl boronic acid (100 mg, 0.82 mmol), and Cs_2CO_3 (346 mg, 1.06 mmol) in DME (10 mL) and aq. H_2O_2 (0.08 mL, 0.8%) and was purified by flash chromatography as a white solid (21 mg, 34%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 8.77(s, 1H), 8.39–8.73 (m, 1H), 8.01(d, J = 2.5 Hz, 1H), 7.94–7.90 (m, 1H), 7.68–7.64 (m, 1H), 7.20–7.17 (m, 2H), 7.01–6.99 (m, 2H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{15}H_{12}N_2O_2$ 253.0971, found 253.0964.

4-Phenoxyquinazoline **(19)**: This compound was synthesized according to substrate 7 from 4-(3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-yloxy) quinazoline (32 mg, 0.12 mmol), phenylboronic acid (50 mg, 0.41 mmol), and Cs_2CO_3 (173 mg, 0.53 mmol) in DME (5 mL) and aq. H_2O_2 (0.04 mL, 0.8%) and was purified by flash chromatography as a white solid (8 mg, 30%).^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.85 (s, 1H), 8.26 (d, J = 8.2 Hz, 1H), 8.05–8.00 (m, 2H), 7.80 (t, J = 6.3 Hz, 1H), 7.68–7.66 (m, 2H), 7.56–7.54 (m, 3H). HRMS (ES-MS) [(M+H)$^+$]: for $C_{14}H_{10}N_2O_1$ 223.0861, found 223.0862.