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Copper-Catalyzed C–H Arylation of Fused-Pyrimidinone Derivatives Using Diaryliodonium Salts

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Abstract: Copper-catalyzed Csp2–Csp2 bond forming reactions through C–H activation are still one of the most useful strategies for the diversification of heterocyclic moieties using various coupling partners. A catalytic protocol for the C–H (hetero)arylation of thiazolo[5,4-*f*]quinazolin-9(8*H*)-ones and more generally fused-pyrimidinones using catalyst loading of CuI with diaryliodonium triflates as aryl source under microwave irradiation has been disclosed. The selectivity of the transfer of the aryl group was also disclosed in the case of unsymmetrical diaryliodonium salts. Specific phenylation of valuable fused-pyrimidinones including quinazolinone are provided. This strategy enables a rapid access to an array of various (hetero)arylated *N*-containing polyheteroaromatics as new potential bioactive compounds.

Keywords: copper catalysis; C–H arylation; fused-pyrimidinone; diaryliodonium salts; microwave irradiation; kinase inhibitors

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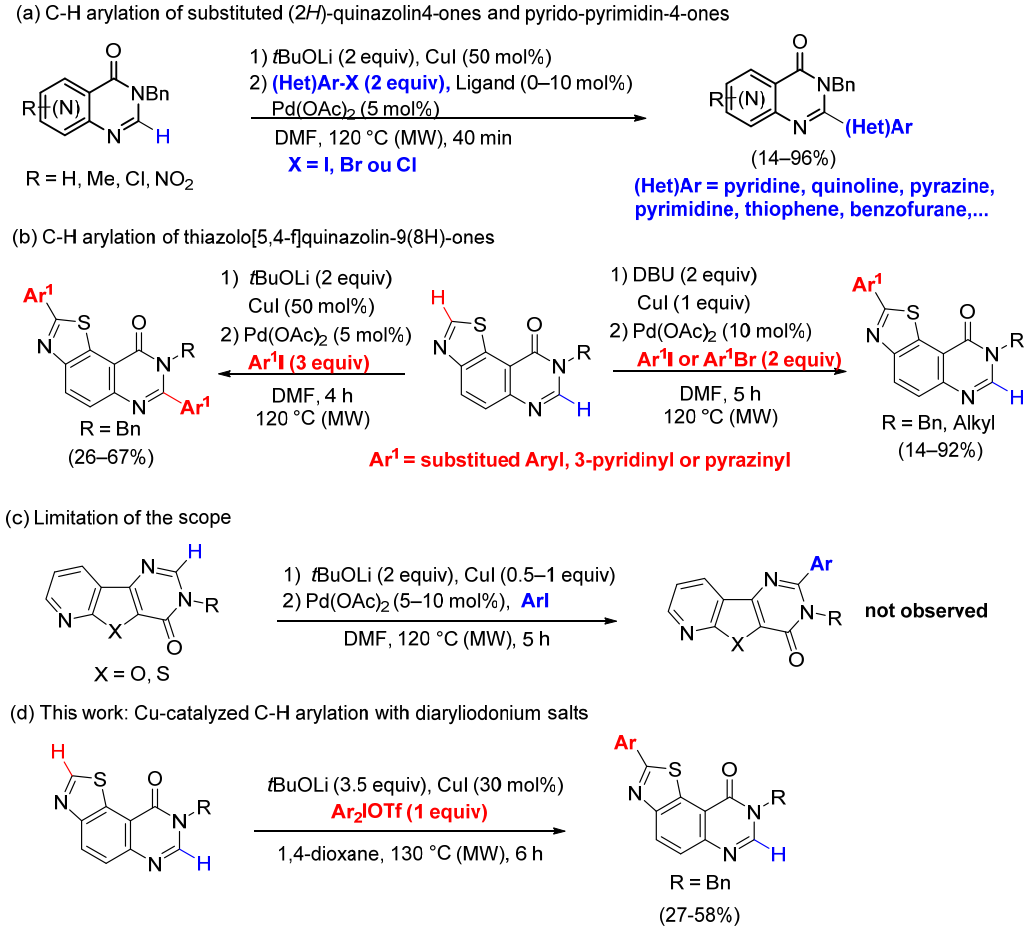
1. Introduction

Bi-heterocylic structures are found in many bioactive compounds and fused pyrimidinones represent a relevant substructure in medical chemistry, exhibiting a broad range of pharmacological activities. Although the synthesis of functionalized polyaromatic heterocycles is commonly realized through cyclization pathways including condensation and multicomponent reactions, the heterocycles derivatization from the preformed cycles is fairly appealing. For this reason, late-stage C–H arylation of heteroarenes appeared as a tailored tool for incorporating diversifications into high valuable scaffolds, notably in drug discovery [1–3]. It is now recognized that a slight modification of the core motif triggered by the incorporation of an aryl moiety or a functional group onto the skeleton could have a huge impact on the pharmacological profile compared to the parent compound. This expanding methodology's main feature is the introduction of structural diversity into complex molecules having multiple Csp2–H bonds [4–8]. Our group has previously reported the selective palladium-catalyzed and copper assisted C2–H arylation of quinazolin-4-ones, pyrido-pyrimidin-4-ones (see (a) in Scheme 1a) and thiazolo[5,4-*f*]quinazolin-9(8*H*)-one under microwave irradiation (Scheme 1b) [9–14]. This aforementioned heterocycle was used as a versatile scaffold for Structure Activity Relationship (SAR) studies in DYRK1A kinase inhibition involved in the field of neurodegenerative diseases [15–17] and cancer therapy [18–20]. Nevertheless, the developed synergistic Pd/Cu catalysis suffers from some limitations, including the use of a large amount of transition-metal catalysts and poor reactivity of certain classes of substrates. For example, this strategy was proved to be inefficient in some fused-pyrimidinone series (Scheme 1c). We then hypothesized that a similar strategy could be used to synthesize various arylated polycyclic *N*-containing

heteroarenes using an eco-friendlier C–H arylation reaction. Since diaryliodonium salts have gained extensive attention as smooth and selective electrophilic arylation reagents under both metal-catalyzed and metal-free conditions [21–29], we envisioned the use of this non-toxic and easy to handle class of hypervalent iodine compounds as coupling partner [30–40] (Scheme 1d). As part of our ongoing effort to develop direct C–H arylation procedures on heteroarenes, herein we report a copper-catalyzed complementary arylation of thiazoloquinazolinones and fused-quinazolinone analogues with diaryliodonium triflates.



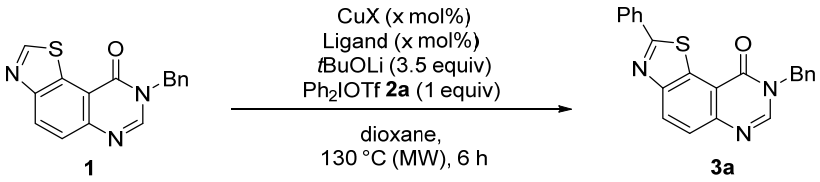
Scheme 1. C–H arylation of fused-pyrimidinone derivatives. (**a**) C-H arylation of substituted (2H)-quinazolin4-ones and pyrido-pyrimidin-4-ones; (**b**) C-H arylation of thiazolo[5,4-f]quinazolin-9(8H)-ones; (**c**) Limitation of the scope; (**d**) This work: Cu-catalyzed C-H arylation with diaryliodonium salts.

2. Results

Inspired by seminal works on C–H arylation of azaheteroarenes [29,41–46], the reaction of the N^8-benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1 with diphenyliodonium triflate 2a as model substrates was first explored under metal-catalyzed (palladium or copper) and metal-free C–H arylation conditions (See Table S1, Supplementary Material). Under palladium or metal-free catalysis, less than 10% of the phenylated product 3a was observed and the reaction took place selectively at the most acidic position. The expected product 2-phenyl-N^8-benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 3a was obtained in 59% NMR yield along with 21% of starting material 1 in the presence of *t*BuOLi as a base, copper iodide (30 mol%) as catalyst and dioxane as solvent under reflux for 24 h. Driven by Kumar's results reported on benzoxazoles in 2014 [45], microwave (MW) irradiation was then applied to the reaction. Interesting results were obtained after 6 h at 130 °C under MW irradiation (See Table S2, Supplementary Material) leading to 2-phenyl-N^8-

benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 3a in 64% NMR yield along with 21% of starting material 1. Encouraged by these results, we explored whether this copper-catalyzed arylation reaction could be done to construct the desired 2-aryl-N^8-benzylthiazoloquinazolinone derivatives. Initial experiments were aimed at screening the copper source and the ligand [47]. The results of the experiments to optimize the reaction conditions are shown in Table 1.

Table 1. Optimization of the catalytic system.



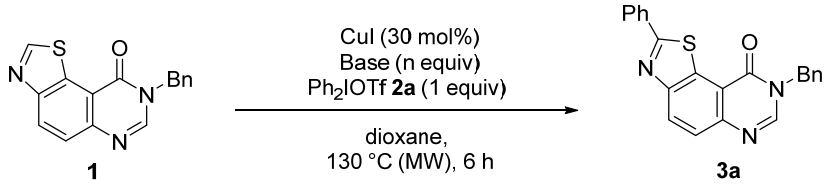
Entries [1]	Copper Source	mol%	Ligand	NMR Yield [2] of 3a (%)
1	CuI	30	-	64 (21) [3]
2	CuBr	30	-	36 (23)
3	CuCl	30	-	48 (28)
4	CuOAc	30	-	59 (31)
5	CuSCN	30	-	61 (24)
6	CuTC	30	-	42 (33)
7	$CuCl_2$	30	-	27 (49)
8	$Cu(OAc)_2$	30	-	50 (38)
9	$Cu(OTf)_2$	30	-	41 (35)
10	Cu_2O	30	-	7 (49)
11	Cu_2O	30	-	NR [4]
12	CuI	15	-	36 (45)
13	CuI	50	-	63 (23)
14	CuI	100	-	66 (10)
15	CuI	30	1,10-Phen	54 (40)
16	CuI	30	XantPhos	55 (43)
17	CuI	30	Bipy	36 (35)
18	CuI	30	1,10-Phen	60 (18) [5]
19	CuI	30	Bipy	49 (48) [5]
20	CuI	100	1,10-Phen	59 (33) [5]

[1] Reaction conditions: 1 (1 equiv), 2a (1 equiv), CuX (x mol%), Ligand (30 mol%), *t*BuOLi (3.5 equiv) was stirred in dioxane (0.37 M) under microwave irradiation at 130 °C for 6 h. [2] NMR yields are calculated using 1,3,5-trimethoxybenzene as internal standard. [3] % of recovered starting material 1. [4] Without base, NR: no reaction. [5] Reaction conditions: CuI (30 mol% or 1 equiv) and ligand (30 mol% or 1 equiv) were first stirred at RT for 90 min. Then **2a** (1 equiv) was added and the reaction mixture was stirred at RT for 30 min, before adding *t*BuOLi (3.5 equiv) and 1 (1 equiv). The resulting reaction mixture was stirred in dioxane (0.37 M) under microwave irradiation at 130 °C for 6 h.

As shown in Table 1, CuI was found to be the most effective catalyst (entry 1). Remarkably, when the reaction was carried out with Cu(II) catalysts, the yields of the phenylated product 3a drop (Table 1, entries 6–9). The absence of base resulted in no detectable product formation (Table 1, entry 11). Decreasing the amount of copper iodide resulted in lower yields and when the catalyst loading is increased, no striking improvement of the yield of the desired product was observed (Table 1, entries 12–14). The addition of common *N*-heteroarene ligands such as 1,10-phenanthroline (1,10-Phen) and bipyridine (Bipy) or a phosphorous ligand (Xantphos) did not improve the yield (Table 1, entries 15–20). Although additional ligand and copper source screening gave no further improvement, phenylated product was obtained in 64% NMR yield (58% isolated yield) by using a catalytic amount of CuI (30 mol%). In an attempt to verify the utility of the copper(I) catalysis, we noticed that no reaction took place when CuI was removed, pointing out the pivotal role of metallic ions. To optimize the reaction conditions further, various bases and greener or biomass-derived solvents were screened [48,49]. Evaluation of solvent and base revealed that the choice of the solvent drastically affected the yields of desired product. No reaction was observed using Cyrene, PEG-400 and γ-valerolactone

(GVL) as solvent, whereas eucalyptol and 2-methyl-THF gave the desired product in 10% and 41%, respectively (See Table S3, Supplementary Material). The screening of the bases revealed that no reaction occurred using common bases including *t*BuOK, K_3PO_4, NaOAc and 4,4′-di-tert-butyl-2,2′-bipyridine (dtbpy) (Table 2, entries 2, 5–6, 10) whereas the expected phenylated product 3a was detected at less than 10% yield with Cs_2CO_3 or nitrogen containing bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Hünig's base and 1,4-diazabicyclo[2.2.2]octane (DABCO) (Table 2, entries 3, 7–9).

Table 2. Screening of the base.

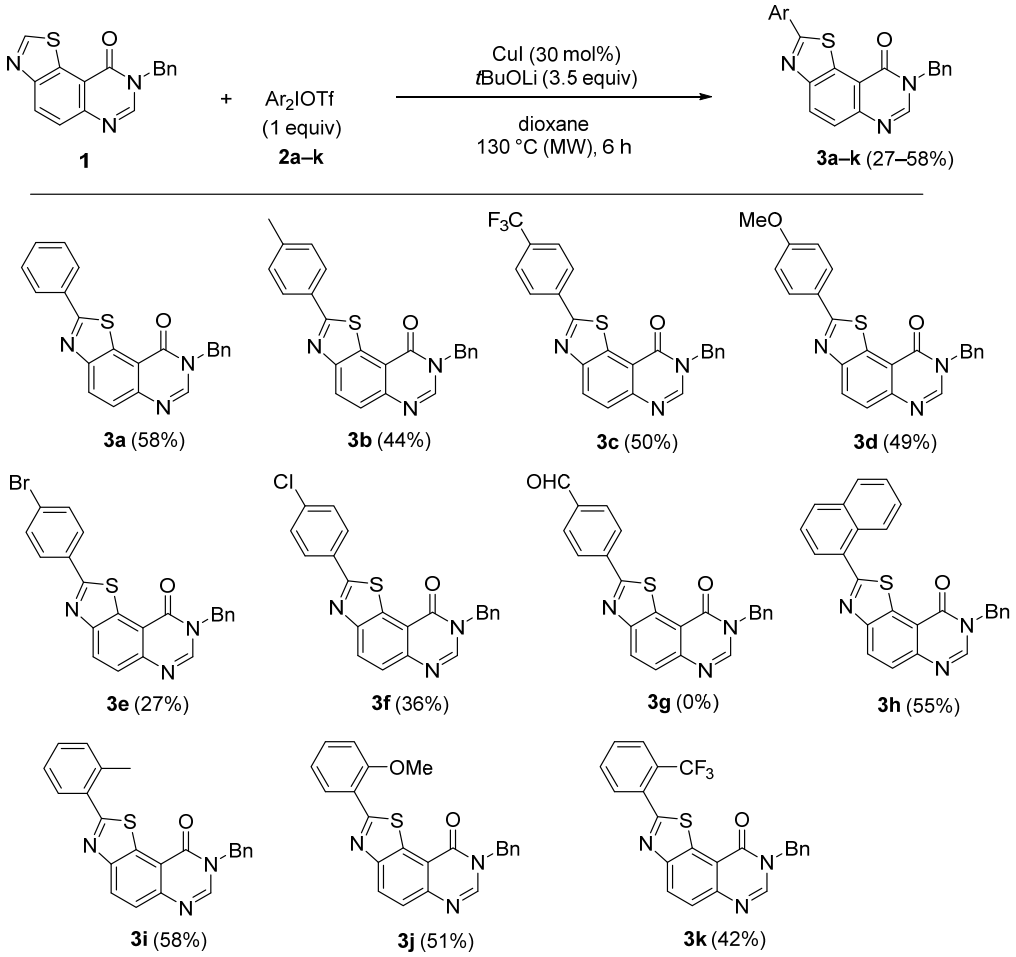


Entries [1]	Base	N Equiv	NMR Yield [2] of 3a (%)
1	*t*BuOLi	3.5	64 (21) [3]
2	*t*BuOK	3.5	NR
3	Cs_2CO_3	3.5	7 (85)
4	Li_2CO_3	3.5	0 (65) [4]
5	K_3PO_4	3.5	NR
6	NaOAc	3.5	NR
7	DBU	3.5	2 (62)
8	DIPEA	3.5	6 (89)
9	DABCO	3.5	4 (92)
10	dtbpy	3.5	NR
11	*t*BuOLi	1	7 (87)
12	*t*BuOLi	2	4 (92)
13	*t*BuOLi	5	68 (15)

[1] Reaction conditions: **1** (1 equiv), **2a** (1 equiv), CuI (30 mol%), Base (n equiv) was stirred in dioxane (0.37 M) under microwave irradiation at 130 °C for 6 h. [2] NMR yields are calculated using 1,3,5-trimethoxybenzene as internal standard. [3] % of recovered starting material **1**. [4] Degradation of the reaction mixture was observed.

Upon examining a series of solvent and base, the use of 3.5 equiv of *t*BuOLi in dioxane at 130 °C was optimal, giving a ratio of 3a:1 of ca. 3:1 prior to purification. We also examined the counteranion effect and the diphenyliodonium salt with an anion of OTf was proven to be the best choice. No improvement was observed when we reduced or increased the amounts of diphenyliodonium triflate (See Table S4, Supplementary Material). Whatever the reaction conditions, the complete consumption of the starting material was not observed.

With the optimized conditions in hand, the scope of the reaction was undertaken by using N^8-benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1 with a range of symmetrical diaryliodonium triflates 2a-k, bearing electron-donating or -withdrawing groups (Scheme 2). A series of diverse diaryliodonium salts were synthesized from the corresponding aryl iodide using versatile procedures reported by Olofsson and others [30,33,50–52]. We were pleased to observe the formation of the desired C2-arylated products 3a-k in moderate yields, except with the diaryliodonium triflate 2g bearing a sensitive aldehyde functional group. In the last case, the reaction failed to produce the corresponding arylated product. Given the importance of the trifluoromethyl group in medicinal chemistry, we synthesized compounds 3c and 3k where the aromatic group bearing para or meta CF_3 group transfers. It is worth noting that halogen-substituted aryl rings are tolerated in this Cu(I)-catalyzed transformation since the reactions using diaryliodonium triflates bearing reactive chlorine or bromine proceeded without any by-products. The reaction of dinaphthyliodonium triflate 2 h with 1 proceeded smoothly to give the desired compounds 3 h in 55% yield.



Scheme 2. Scope of diverse diaryliodonium triflates in the copper-catalyzed C–H arylation of N^8-benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1.

While most of examples were conducted with symmetrical diaryliodonium salts, unsymmetrical salts were also explored to transfer a heteroaryl group. The reaction of phenyl(2-thienyl)iodonium triflate 2l (Figure 1) with 1 proceeded smoothly to yield 22% of 2-thienyl-thiazoloquinazolinone product 3l. However, a mixture of the analogous phenylated compound was obtained using 2l as the arylation reagent (Table 3, entry 1). Notably, the unsymmetrical mesityl/heteroaryl-substituted iodonium reagents (Mes–I–HetAr)OTf 2m and 2n provided both arylated products in moderate isolated yields. In the reaction of 2m with N^8-benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1 a mixture of the two arylated products 3m and 3o was obtained, with the sterically more demanding mesityl group (Mes) being transferred preferentially. When 2n is used as an arylating reagent, the bulkier aryl group's transfer is favored, and no heteroarylated product was formed under optimized reaction conditions (Table 3, entry 3).

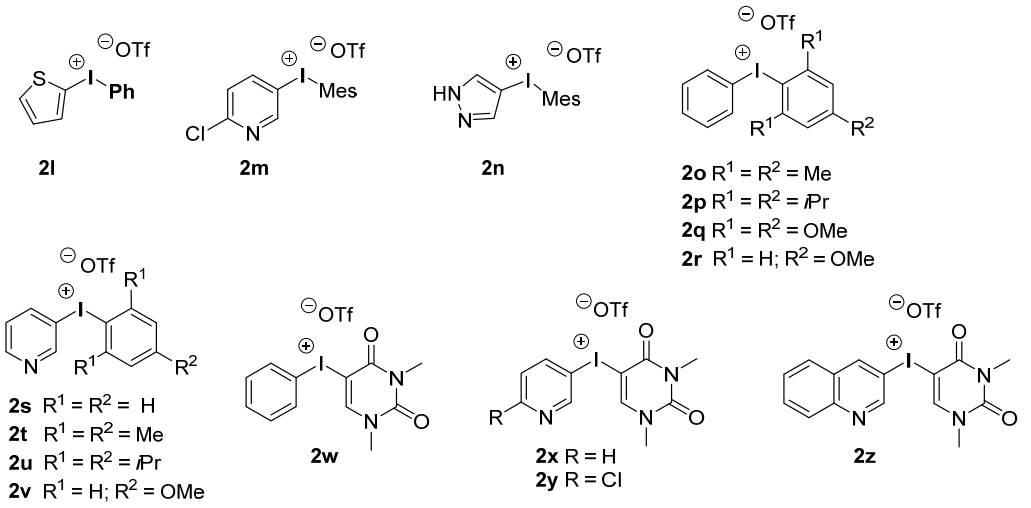
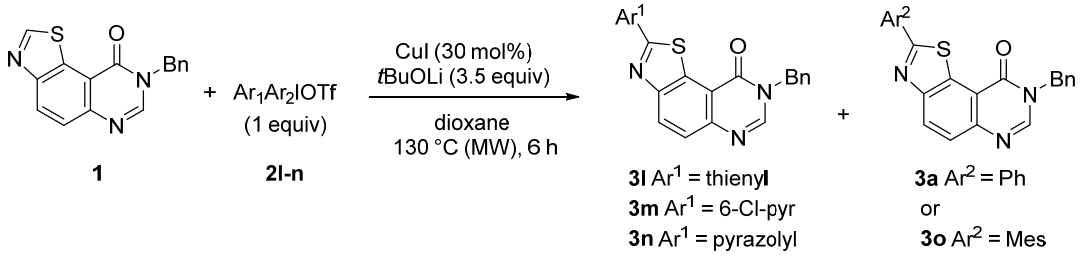


Figure 1. Unsymmetrical diaryliodonium triflates 2l–z that were used in this study.

Table 3. Heteroarylation versus phenylation of 1 with unsymmetrical diaryliodonium salts 2l–n [1].



Entries	Ar^1Ar^2IOTf	Products	NMR Yield (%) [2]
1	2l	3l/3a	22/23
2	2m	3m/3o	6/53
3	2n	3o	69

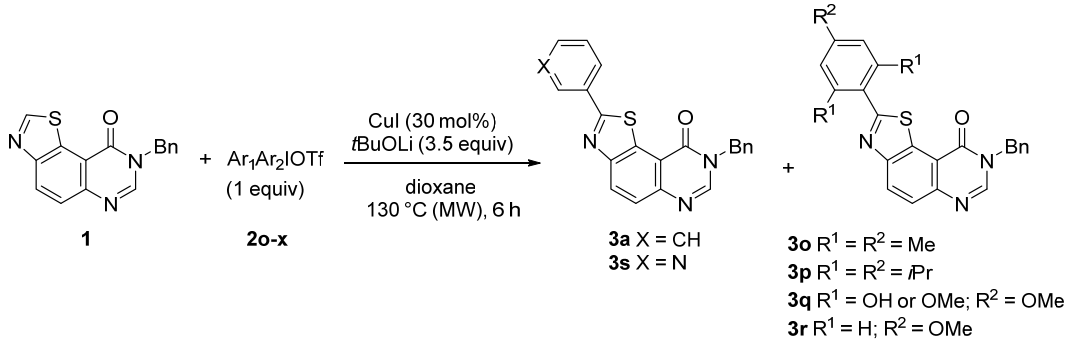
[1] Reaction conditions: 1 (1 equiv), 2l–m (1 equiv), CuI (30 mol%), *t*BuOLi (3.5 equiv) was stirred in dioxane (0.37 M) under microwave irradiation (MW) at 130 °C for 6 h. [2] NMR yields are calculated using 1,3,5-trimethoxybenzene as internal standard.

It is known that steric factors often control the selectivity in metal-catalyzed arylations and hindered groups such as 2,4,6-trimethylphenyl (Mes) and 2,4,6-triisopropylphenyl (TRIP) are usually recognized as efficient dummy groups. In the absence of steric effects, the most electron-donating aryl group's transfer is often favored with moderate selectivity [23]. In this context, the chemoselectivity of unsymmetrical diaryliodonium salts was further investigated using phenyl-(2,4,6-trimethylphenyl)iodonium triflate 2o, phenyl-(2,4,6-triisopropylphenyl)iodonium triflate 2p, phenyl-(2,4,6-trimethoxyphenyl)iodonium triflate 2q and phenyl-(*p*-methoxyphenyl)iodonium triflate 2r as model substrates (Figure 1).

In addition to the desired phenylated product 3a, a large amount of the mesitylated product 3o was also isolated, formed by donation of the sterically hindered mesityl group (Table 4, entry 1). In an attempt to prevent this non-selective arylation, the optimized conditions were used with another sterically-hindered 2,4,6-triisopropylphenyl group on the iodonium salt 2p. This however, did not have the desired effect, as it appeared to lower the reactivity of the system and reduce product selectivity, with the ratio of 3a to triisopropylphenyl side product 3p being 2:3. Diaryliodonium salts bearing an electro-donating group as "dummy group" such as phenyl-(2,4,6-trimethoxyphenyl)iodonium triflate 2q or phenyl-(*p*-methoxyphenyl)iodonium triflate 2r give unselective reactions (Table 4, entries 3 and 4). These results suggest that steric factors are a major contribution to the transfer of aryl group in this reaction. It could also be noted that the reaction with phenyl-(TMP)iodonium triflate 2q led to the deprotection of one methoxy group. Finally, a

uracil-derived "dummy" ligand in 2w gave lower reactivity but high selectivity towards the phenylated product (Table 4, entry 5).

Table 4. C–H (hetero)-arylation using dissymmetrical diaryliodonium triflates [1].



1 **2o-x**

3a X = CH
3s X = N

3o $R^1 = R^2$ = Me
3p $R^1 = R^2$ = *i*Pr
3q R^1 = OH or OMe; R^2 = OMe
3r R^1 = H; R^2 = OMe

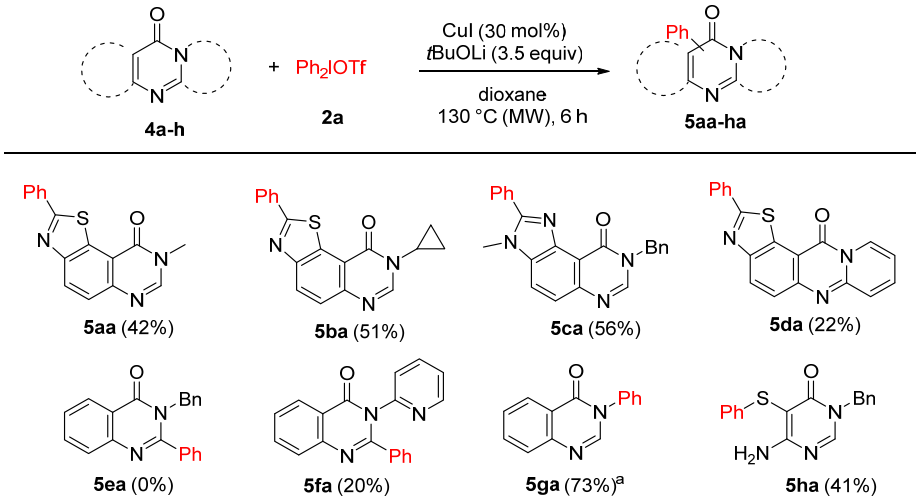
Entries	Ar^1Ar^2IOTf	Products	Isolated Yields (%)
1	2o	3a/3o	24/36
2	2p	3a/3p	21/31
3	2q	3a/3q	18/35
4	2r	3a/3q	16/23
5	2w	3a	16
6	2s	3a/3s	13/10
7	2t	3o/3s	56/8
8	2u	3p/3s	50/6
9	2v	3q/3s	12/10
10	2x	3s	22

[1] Reaction conditions: 1 (1 equiv), 2o-x (1 equiv), CuI (30 mol%), *t*BuOLi (3.5 equiv) was stirred in dioxane (0.37 M) under microwave irradiation at 130 °C for 6 h.

The arylation reactions of 1 with salts 2s−v follow the trend described above (Table 4, entries 6–9): salts 2t–u give a 1:8 preference for the transfer of the sterically more demanding mesityl group (Mes) or TRIP, not in line with the electronic effects but with the ortho effect. The best selectivity was again obtained using the diaryliodonium 2x bearing an uracil-derived "dummy" ligand and the 3-pyridinyl derivative was obtained as the sole product in 22% yield. Exclusive pyridyl and quinolinyl transfer were then attempted using di(hetero)-aryliodonium triflates 2y and 2z. However, the corresponding 2-heteroarylated products were formed in low yield (<10%) along with a large amount of starting material 1.

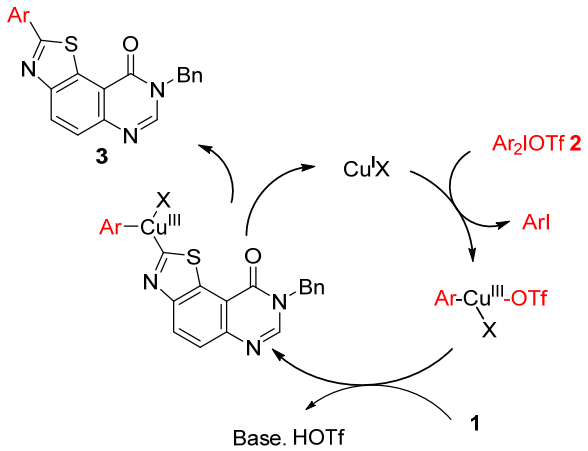
To further examine the versatility of this methodology, the arylation was attempted with fused-pyrimidinones using diphenyliodonium salt 2a as the arylation reagent. (Scheme 3). The chemical modification of fused-pyrimidinones is an attractive area for medicinal chemists due to the potential activity exhibited as kinase inhibitors, antiviral and antitumor agents. Similar to N^8-benzylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1, N^8-methylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 4a and N^8-cyclopropylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one 4b were successfully arylated under standard conditions affording the desired compounds 5aa and 5ba. Furthermore, 12*H*-Pyrido[2,1-*b*]thiazolo[5,4-*f*]quinazolin-12-one 5d was also effective, providing the desired product 5da in 22% yield along with starting material. We were pleased to find that N^8-benzylimidazolo[5,4-*f*]quinazolin-9(8*H*)-one 4c led to the corresponding phenylated compound 5c in 56% yield. No arylation reaction was observed using N^3-benzylquinazolin-4-one 4e as starting material whereas N^3-pyridinylquinazolin-4-one 4f gave access to the corresponding phenylated compound 5fa highlighting the need for a directing group for this copper-catalyzed C–H arylation. In addition, unprotected N^2-H quinazolin-4-one 4g led to N-phenylquinazolin-4-one 5ga in 73% yield using three equivalents of the diphenyliodonium triflate 2a. Besides quinazolinones and fused quinazolinones, thiazolopyrimidinone 4h underwent arylation to afford the corresponding 6-amino-5-phenylsulfanylpyrimidinone 5ha instead of the expected phenylated product. Aryl iodides are known to undergo a C–S

cross-coupling reaction with benzothiazole via ring opening under copper catalysis to afford the corresponding 2-aminophenyl sulfide derivatives. This reaction was previously mentioned with diaryliodonium salts but only in polar solvents such as DMF or DMSO [45].



Scheme 3. Scope of fused-pyrimidinone derivatives for the copper-catalyzed C–H phenylation. [a] 3 equiv of 2a was used.

Finally, we proposed a mechanism based on a Cu^{I}/Cu^{III} catalytic cycle for the C–H arylation of various *N*-containing heterocycles with diaryliodonium triflates [53,54]. Oxidative addition of the diaryliodonium salt 2a to Cu^{I} may generate the highly electrophilic Cu^{III} intermediate. Subsequent C–H activation affords the Cu^{III} species which led to the arylated product with the concomitant release of Cu^{I} species after reductive elimination from the high-valent copper center (Scheme 4).



Scheme 4. Plausible mechanism of the copper-catalyzed C–H arylation of heteroarenes with diaryliodonium triflate as arylating reagent.

3. Materials and Methods

3.1. General Information

All reagents were purchased from commercial suppliers and were used without further purification except for DMF, which was stored under argon and activated molecular sieves. All reactions were monitored by thin-layer chromatography with silica gel 60 F254 precoated aluminum plates (0.25 mm). Visualization was performed with a UV light at wavelengths of 254 nm. Purifications were conducted with a flash column chromatography system (Puriflash) equipped with a dual UV/Vis spectrophotometer (200–600 nm), a

fraction collector (176 tubes), a dual piston pump (1 to 200 mL/min, Pmax = 15 bar), which allowed quaternary gradients and an additional inlet for air purge (Interchim, Montluçon, France). Melting points of solid compounds were measured with an SMP3 Melting Point instrument (STUART, Bibby Scientific Ltd, Roissy, France) with a precision of 1.5 °C. IR spectra were recorded with a Spectrum 100 Series FTIR spectrometer (PerkinElmer, Villebon S/Yvette, France). Liquids and solids were investigated with a single-reflection attenuated total reflectance (ATR) accessory; the absorption bands are given in cm^{-1}. NMR spectra (^{1}H and ^{13}C) were acquired at 295 K using an AVANCE 300 MHz spectrometer (Bruker, Wissembourg, France) at 300 and 75.4 MHz, using TMS as an internal standard. Coupling constants J are in Hz, and chemical shifts are given in ppm. Mass spectrometry was performed by the Mass Spectrometry Laboratory of the University of Rouen. The mass spectra (ESI, EI, and field desorption (FD)) were recorded with an LCP 1er XR spectrometer (WATERS, Guyancourt, France). Microwaves-assisted reactions were carried out in sealed tubes with a Biotage Initiator microwave synthesis instrument and temperatures were measured by IR-sensor (Biotage, Uppsala, Sweden). Time indicated in the various protocols is the time measured when the mixtures were at the programmed temperature.

3.2. Chemistry

Compounds 1, 3a, 3b, 3d and 3f were described in [11]; compounds 3s and 5ba were described in [12]; The new products 3c, 3e, 3h, 3i, 3j, 3k, 5aa, 5ca, 5da and 5ha are described below. ^{1}H-NMR and ^{13}C-NMR spectra of these new compounds are available in Supplementary Materials (Section S1–S25). General information and procedures for synthesis of some reactants are also described in this section.

General Procedure for the Synthesis of 2-Aryl-N^{8}-substitued-thiazolo[5,4-*f*]quinazolin-9(8*H*)-Ones (3a–s) and Fused Pyrimidines (5aa–5ha).

In a 2–6 mL sealed tube, a suspension of CuI (19.5 mg, 0.10 mmol, 30 mol%), *t*BuOLi (95.3 mg, 1.19 mmol, 3.5 equiv), diaryliodonium triflate 2 (0.34 mmol, 1 equiv) and the corresponding N^{8}-substituted thiazolo[5,4-*f*]quinazolin-9(8*H*)-one 1 or 4a–h (0.34 mmol, 1 equiv.) in dioxane (0.91 mL, 0.37 M) was heated under microwave irradiation at 130 °C for 6 h. After cooling, the solvent was removed in vacuo and the resulting mixture was diluted with ethyl acetate, washed with an aqueous solution of NH_3 (5%) and with brine twice. The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (CH_2Cl_2/EtOAc; 100/0 to 30/70, v/v as eluent) afforded the desired product 3a–s or 5aa–5ha.

8-Benzyl-2-(4-(trifluoromethyl)phenyl)thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3c): 75.1 mg (50%) as a yellow solid, m.p. 243–244 °C. IR (neat) ν_{max}: 1662, 1601, 1584, 1454, 1323, 1162, 1152, 1131, 1104, 1068, 840, 828, 764, 727, 698, 602, 500 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, J = 8.7 Hz, 1H, H_4), 8.30 (d, J = 8.1 Hz, 2H, H_{Ar}), 8.26 (s, 1H, H_7), 7.89 (d, J = 8.7 Hz, 1H, H_5), 7.79 (d, J = 8.2 Hz, 2H, H_{Ar}), 7.45–7.34 (m, 5H, H_{Ar}), 5.33 (s, 2H, CH_2).^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (C), 160.0 (C), 153.5 (C), 147.1 (C), 146.2 (CH), 136.8 (C), 135.4 (CH), 132.9 (C), 132.5 (C), 132.1 (C), 129.5 (CH), 129.3 (2 CH), 128.8 (CH), 128.4 (2 CH), 127.9 (CH), 126.7 (CH), 126.3 (CH), 126.3 (CH), 125.8 (C), 122.1 (C), 50.2 (CH_2). HRMS (EI^+) m/z, calculated for $C_{23}H_{15}N_3OSF_3$ $(M + H)^+$: 438.0888; found: 438.0897.

8-Benzyl-2-(4-bromophenyl)thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3e): 40.5 mg (27%) as a yellow solid, m.p. > 261 °C. IR (neat) ν_{max}: 2981, 1661, 1586, 1453, 1338, 1153, 1067, 951, 825, 733, 697, 531 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.8 Hz, 1H, H_4), 8.25 (s, 1H, H_7), 8.05 (d, J = 8.6 Hz, 1H, H_{Ar}), 7.84 (d, J = 8.8 Hz, 1H, H_5), 7.64 (d, J = 8.6 Hz, H, H_{Ar}), 7.41–7.26 (m, 5H), 5.32 (s, 2H). HRMS (EI^+) m/z, calculated for $C_{22}H_{15}BrN_3OS$ $(M + H)^+$: 448.0119; found: 448.0116.

8-Benzyl-2-(naphthalen-1-yl)thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3h): 78.0 mg (55%) as a pale-yellow solid, m.p. 212–213 °C. IR (neat) ν_{max}: 3044, 1652, 1600, 1583, 1448, 1339, 1152, 1095, 1077, 832, 798, 767, 758, 727, 697, 641, 605, 500 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, J = 9.4 Hz, 1H, H_{Ar}), 8.55 (d, J = 8.8 Hz, 1H, H_4), 8.27 (s, 1H, H_7), 8.07–8.01 (m, 2H,

H_{Ar}), 7.97–7.93 (m, 1H, H_{Ar}), 7.91 (d, J = 8.8 Hz, 1H, H_5), 7.68–7.55 (m, 3H, H_{Ar}), 7.46–7.30 (m, 5H, H_{Ar}), 5.35 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (C), 160.1 (C), 153.5 (C), 146.7 (C), 146.0 (CH), 135.5 (C), 134.2 (C), 132.2 (C), 131.4 (CH), 130.7 (C), 129.9 (CH), 129.5 (CH), 129.3 (2 CH), 128.6 (CH), 128.6 (CH), 128.3 (2 CH), 127.8 (CH), 126.7 (CH), 126.2 (CH), 126.0 (CH), 125.3 (CH), 116.7 (C), 50.0 (CH_2). HRMS (EI^+) m/z, calculated for $C_{26}H_{18}N_3OS$ $(M + H)^+$: 420.1171; found: 420.1175.

8-Benzyl-2-(o-tolyl)thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3i): 75.0 mg (58%) as a yellow solid, m.p. 162–163 °C. IR (neat) ν_{max}: 2980, 2939, 1651, 1585, 1446, 1340, 1155, 948, 836, 757, 731, 697, 600, 515, 475 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 8.7 Hz, 1H, H_4), 8.23 (s, 1H, H_7), 7.89 (d, J = 7.5 Hz, 1H, H_{Ar}), 7.84 (d, J = 8.7 Hz, 1H, H_5), 7.43–7.28 (m, 8H, H_{Ar}), 5.30 (s, 2H, CH_2), 2.71 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 160.0 (C), 153.1 (C), 146.6 (C), 145.9 (CH), 137.4 (C), 135.5 (C), 132.9 (C), 132.3 (C), 131.8 (CH), 130.8 (CH), 130.3 (CH), 129.3 (2 CH), 129.2 (CH), 128.6 (2 CH), 128.2 (CH), 126.4 (CH), 126.0 (CH), 116.6 (C), 50.0 (CH_2), 21.8 (CH_3). HRMS (EI^+) m/z, calculated for $C_{23}H_{18}N_3OS$ $(M + H)^+$: 384.1171; found: 384.1174.

8-Benzyl-2-(2-methoxyphenyl)thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3j): 66.9 mg (49%) as a yellow solid, m.p. 212–213 °C. IR (neat) ν_{max}: 1669, 1581, 1494, 1446, 1342, 1254, 1159, 1115, 1017, 957, 8221, 749, 725, 696, 605, 521 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (dd, J = 7.9, 1.7 Hz, 1H, H_{ar}), 8.45 (d, J = 8.7 Hz, 1H, H_4), 8.22 (s, 1H, H_7), 7.85 (d, J = 8.7 Hz, 1H, H_5), 7.53–7.46 (m, 1H, H_{Ar}), 7.44–7.32 (m, 5H, H_{Ar}), 7.19–7.09 (m, 2H, H_{Ar}), 5.35 (s, 2H, CH_2), 4.13 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (C), 160.2 (C), 157.6 (C), 151.7 (C), 146.3 (C), 145.8 (CH), 135.6 (C), 133.4 (C), 132.2 (CH), 129.6 (CH), 129.3 (2 CH), 129.0 (CH), 128.6 (CH), 128.1 (2 CH), 125.6 (CH), 122.3 (C), 121.2 (CH), 116.7 (C), 111.7 (CH), 55.9 (C), 49.9 (CH_2). HRMS (EI^+) m/z, calculated for $C_{23}H_{18}N_3O_2S$ $(M + H)^+$: 400.1120; found: 400.1108.

8-Benzyl-2-(2-(trifluoromethyl)phenyl)thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3k): 62.6 mg (42%) as a yellow solid, m.p. 138–140 °C. IR (neat) ν_{max}: 3064, 3035, 1663, 1602, 1586, 1442, 1367, 1341, 1306, 1258, 1152, 1139, 1120, 1063, 1035, 950, 835, 773, 729, 701, 667, 639, 598, 561, 533 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.49 (d, J = 8.8 Hz, 1H, H_4), 8.26 (s, 1H, H_7), 7.79–7.64 (m, 2H, H_5, H_{Ar}), 7.78–7.66 (m, 3H, H_{Ar}), 7.44–7.32 (m, 5H, H_{Ar}), 5.34 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8 (C), 160.0 (C), 152.7 (C), 147.0 (C), 146.2 (CH), 135.4 (C), 133.0 (C), 132.7 (C), 132.5 (CH), 131.9 (CH), 130.3 (CH), 129.8 (CH), 129.3 (2 CH), 129.3 (C), 128.7 (CH), 128.3 (2 CH), 127.1 (CH), 127.1 (CH), 126.5 (CH), 121.9 (C), 116.6 (C), 50.0 (CH_2). HRMS (EI^+) m/z, calculated for $C_{23}H_{15}N_3OSF_3$ $(M + H)^+$: 438.0888; found: 438.0884.

8-Benzyl-2-mesityl-thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3o): 78.2 mg (56%) as a yellow solid, m.p. 114–115 °C. IR (neat) ν_{max}: 2916, 1659, 1585, 1450, 1339, 1150, 919, 834, 720, 696, 560, 509, 460, 414 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (d, J = 8.7 Hz, 1H, H_4), 8.31 (s, 1H, H_7), 7.89 (d, J = 8.7 Hz, 1H, H_5), 7.43–7.31 (m, 5H, H_{Ar}), 6.97 (s, 2H, H_{Ar}), 5.33 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 2.17 (s, 6H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9 (C), 160.0 (C), 152.9 (C), 146.3 (C), 146.0 (CH), 139.6 (C), 137.3 (2 C), 135.4 (C), 133.2 (C), 130.4 (C), 129.4 (CH), 129.2 (2 CH), 128.6 (CH), 128.6 (2 CH), 128.2 (2 CH), 125.7 (CH), 116.7(C), 50.0 (CH_2), 21.3 (CH_3), 20.3 (2 CH_3). HRMS (EI^+) m/z, calculated for $C_{25}H_{22}N_3OS$ $(M + H)^+$: 411.1484; found: 411.1475.

8-Benzyl-2-(2,4,6-triisopropylphenyl)thiazolo[5,4-*f*]quinazolin-9(8*H*)-one (3p): 84.4 mg (50%) as a yellow solid, m.p. 188–189 °C. IR (neat) ν_{max}: 2961, 2927, 2681, 1664, 1603, 1448, 1337, 1153, 1066, 993, 954, 875, 838, 812, 759, 723, 700, 640, 599, 561, 532, 498, 414 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, J = 8.7 Hz, 1H, H_4), 8.28 (s, 1H, H_7), 7.88 (d, J = 8.7 Hz, 1H, H_5), 7.44–7.30 (m, 5H, H_{Ar}), 7.12 (s, 2H), 5.33 (s, 2H, CH_2), 2.97 (p, J = 6.8 Hz, 1H), 2.66 (p, J = 6.8 Hz, 2H), 1.31 (d, J = 6.9 Hz, 6H, CH_3), 1.18 (d, J = 6.8 Hz, 12H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (C), 160.0 (C), 152.7 (C), 151.0 (C), 148.1 (C), 146.5 (C), 146.0 (CH), 135.4 (C), 133.3 (C), 126.5 (CH), 129.2 (2 CH), 128.6 (CH), 128.4 (CH), 128.2 (2 CH), 125.8 (CH), 121.1 (CH), 116.6 (C), 49.9 (CH_2), 34.6 (CH), 31.0 (2 CH), 24.4 (4 CH_3), 24.1 (2 CH_3). HRMS (EI^+) m/z, calculated for $C_{31}H_{34}N_3OS$ $(M + H)^+$: 496.2423; found: 496.2408.

8-Methyl-2-phenylthiazolo[5,4-*f*]quinazolin-9(8*H*)-one (5aa): 57.1 mg (42%) as a yellow solid, m.p. 195–199 °C. IR (neat) ν_{max}: 3051, 1661, 1587, 1443, 1346, 1164, 815, 840, 829, 763, 729, 688, 564, 532 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J = 8.8 Hz, 1H, H_4), 8.20–8.16 (m, 3H, H_{Ar}, H_7), 7.85 (d, J = 8.8 Hz, 1H, H_5), 7.56–7.48(m, 3H, H_{Ar}), 3.73 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 160.4 (C), 153.5 (C), 146.9 (C), 146.3 (CH), 133.6 (C), 131.6 (C), 131.2 (CH), 129.3 (2 CH), 129.0 (CH), 127.7 (2 CH), 126.2 (CH), 116.4 (C), 34.3 (CH_3). HRMS (EI^+) m/z, calculated for $C_{16}H_{12}N_3OS$ $(M + H)^+$: 294.0701; found: 294.0701.

8-Benzyl-3-methyl-2-phenyl-3,8-dihydro-9H-imidazo[4,5-*f*]quinazolin-9-one (5ca): 70.2 mg (56%) as a yellow solid, m.p. 251–252 °C IR (neat) ν_{max}: 2962, 1656, 1604, 1468, 1360, 1260, 1019, 797,750, 703, 509 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (s, 1H, H_7), 7.90–7.82 (m, 2H, H, H_{Ar}), 7.79 (d, J = 8.7 Hz, 1H, H_4), 7.66 (d, J = 8.7 Hz, 1H, H_5), 7.55–7.43 (m, 5H, H_{Ar}), 7.35–7.27 (m, 3H, H_{Ar}), 5.29 (s, 2H, CH_2), 3.97 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 155.9 (C), 146.2 (C), 145.3 (CH), 140.3 (C), 136.3 (C), 135.3 (C), 130.0 (2 CH), 129.9 (C), 129.0 (3 CH), 128.6 (3 CH), 128.2 (2 CH), 122.6 (CH), 116.3 (CH), 113.7 (C), 46.5 (CH_2), 32.1 (CH_3**).** HRMS (EI^+) m/z, calculated for $C_{23}H_{19}N_4O$ $(M + H)^+$: 367.1559; found: 367.1563.

2-Phenyl-12H-pyrido[2,1-b]thiazolo[5,4-*f*]quinazolin-12-one (5da): 22.8 mg (22%) as a yellow solid, m.p. 246–247 °C IR (neat) ν_{max}: 1686, 1639, 1557, 1521, 1474, 1441, 1359, 835, 764, 701, 687, 500 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 9.02 (d, J = 7.3 Hz, 1H), 8.50 (d, J = 8.9 Hz, 1H), 8.23–8.16 (m, 2H), 7.90 (t, J = 6.8 Hz, 1H), 7.69–7.48 (m, 5H), 7.06–6.98 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 157.5 (C), 151.8 (C), 147.6 (C), 147.2 (C), 134.4 (CH), 133.8 (C), 132.2 (C), 131.0 (CH), 130.3 (CH), 129.3 (2 CH), 127.5 (2 CH), 126.8 (CH), 126.7 (CH), 126.0 (CH), 113.7 (CH), 110.6 (C). HRMS (EI^+) m/z, calculated for $C_{19}H_{12}N_3OS$ $(M + H)^+$: 330.0701; found: 330.0696.

6-Amino-3-benzyl-5-(phenylthio)pyrimidin-4(3H)-one (5ha): 53.6 mg (41%) as a pale yellow solid, m.p. 151–152 °C IR (neat) ν_{max}: 3420, 3145, 1614, 1516, 1454, 1141, 780, 734, 684, 604, 591, 473, 405 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H, H_2), 7.37–7.29 (m, 6H, H_{Ar}), 7.25–7.15 (m, 4H, H_{Ar}), 7.14–7.06 (m, 1H, H_{Ar}), 5.48 (s, 2H, NH_2), 5.07 (s, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6 (C), 161.2 (C), 151.3 (CH), 135.8 (C), 135.5 (C), 129.1 (3 CH), 128.4 (3 CH), 126.4 (3 CH), 125.8 (CH), 89.2 (C), 50.0 (CH_2). HRMS (EI^+) m/z, calculated for $C_{17}H_{16}N_3O$ $(M + H)^+$: 310.1014; found: 310.1011.

4. Conclusions

An efficient protocol for regioselective synthesis of 2-arylthiazoloquinazolinones has been developed via copper-catalyzed cross-coupling reaction of polycyclic heteroarenes with diaryliodonium salts in moderate to good yields under microwave irradiation. The reaction was successfully extended to the phenylation of various fused-pyrimidinones such as quinazolinone and imidazolo[5,4-*f*]quinazolin-9(8*H*)-one derivatives. This late-stage arylation is a valuable and useful strategy for expedient synthesis of biologically substantial biaryl compounds helpful in drug discovery.

Supplementary Materials: The following are available online at https://www.mdpi.com/2073-4344/11/1/28/s1, ^1H-NMR and ^{13}C-NMR spectra of new compounds.

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