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Metal-Free Arylation of Ethyl Acetoacetate with Hypervalent Diaryliodonium Salts: an Immediate Access to Diverse 3-Aryl-4(1*H*)-Quinolones

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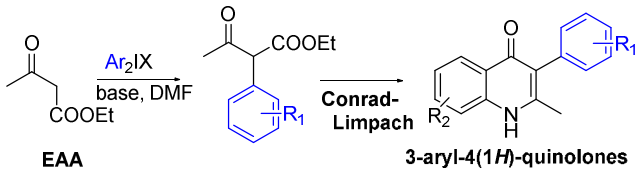


ABSTRACT. A clean arylation protocol of ethyl acetoacetate was developed using hypervalent diaryliodonium salts under mild and metal-free conditions. The scope of the reaction, using symmetric and unsymmetric iodonium salts with varying sterics and electronics was examined. Further, this method has been applied for the synthesis of antimalarial compound ELQ-300, which is currently in preclinical development.

INTRODUCTION

Ethyl acetoacetate (EAA) is a versatile and well-established reagent in organic synthesis. EAA's combined electrophilic and nucleophilic nature makes it a convenient reagent for the preparation of a variety of products of different structural complexity. In medicinal chemistry, 2-aryl substituted EAAs provide access to diverse classes of biologically active scaffolds such as important heterocyclics. Various 2-aryl EAA derived compounds were well documented in the literature as antifungal, antibacterial, antitubercular and antitumoral agents.[1] These also served as TNF-α inhibitors, α2C-adrenoreceptor antagonists, DMT1 blockers and HCV NS5B polymerase

inhibitors.[2] In addition, a series of 3-aryl-4(1*H*)-quinolone compounds, synthesized from corresponding aniline and 2-phenyl EAA, were reported to have excellent low nanomolar activity against malaria.[3] Notably, extensive development of this 3-aryl-4(1*H*)-quinolone chemotype against *P. falciparum* and *P. vivax* malaria at all parasite life cycle stages resulted in **ELQ-300** (Scheme 1), which recently entered preclinical studies.[4] Based on the advantage and importance of 2-aryl EAAs as starting materials, suitable and straightforward access to these compounds is required.

Historically, 2-aryl EAAs are prepared using various metal-mediated and metal-free reaction conditions (Figure 1).[5] In a classical approach, 2-aryl-2-acylacetonitriles are converted to 2-aryl EAAs in two steps under harsh acidic conditions via an imidate intermediate in low to moderate yields.[5a] Alternatively, ethyl 2-arylacetate is also acylated under basic conditions with acetyl chloride or acetic anhydride to obtain the target compounds.[5b] These transformations, however, are low yielding and produce the deacylated by-product (starting material), which in most cases is inseparable from the EAA product. Finally, under Pd-mediated[2c,5c] or Cu-mediated[5d,5e,6] conditions with the appropriate metal ligands, EAA is treated with aryl halides and base to obtain the target compounds at elevated temperatures. In turn, metal-catalyzed reactions suffer from accompanying ligand arylations and product deacylation that is heavily dependent on the nature and quantity of the base used. Moreover, minimal or no usage of expensive metal catalysts is highly advisable in drug discovery because of malfunctions caused by metal contamination at the cellular level.[7] All of these facts prompted us to develop a protocol in which the 2-aryl EAAs can be obtained easily under mild metal-free reaction conditions.

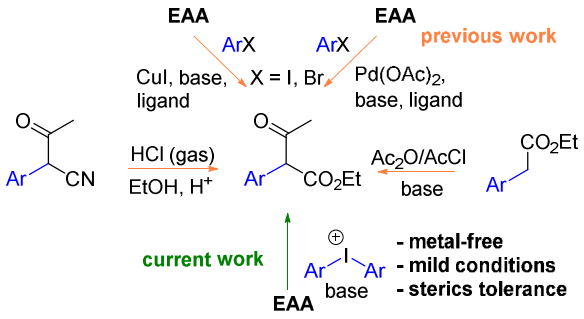


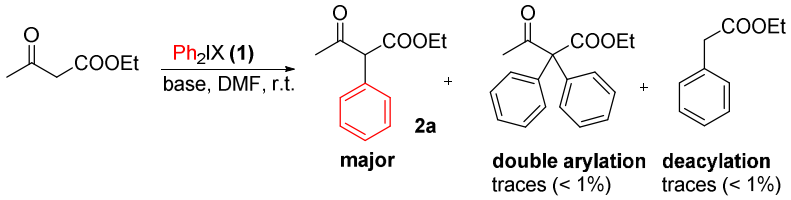
Figure 1. Synthesis of 2-aryl EAA.

Hypervalent iodine compounds and diaryliodonium salts in particular have recently captured the attention of synthetic chemists as mild and selective reagents.[8] One of the biggest advantages of the diaryliodonium salts is the possibility to use metal-free reaction conditions to overcome cost and toxicity of the organometallic chemistry in medicinally interesting compounds.[9] In recent literature, arylation of hetereoatom nucleophiles like O, N, P etc under various conditions was reported with excellent yields using highly electrophilic hypervalent iodonium salts.[10] Significant amount of research has also been documented on α-arylation of carbonyl compounds such as malonates, ketones, ketoesters, esters using diaryliodonium salts.[11] However, most of the attempts were limited to cyclic substrates or α-substituted carbonyl compounds which led to tetra substituted products. To the best of our knowledge, the arylation of EAA with diaryliodonium salts has not been explored by any research group except of a single entry attempt in 1984.[12] Interestingly, a failure effort of arylation of EAA with diphenyliodonium salt was reported in 1999.[10e] By the virtue of having one-pot synthetic access to various diaryliodonium salts[13] and with some of them being commercially available nowadays, it was envisioned to establish a general, simple, and mild arylation protocol of EAA.

RESULTS AND DISCUSSION

Diphenyliodonium tetrafluoroborate **1a** was chosen as a test substrate in the optimization of arylation reaction conditions resulting in 2-phenyl EAA in DMF with *t*BuOK (Table 1). Generally, one equivalent of base with respect to nucleophile was used in all entries in order to avoid double arylation.

Table 1. Optimization of the arylation reaction[a]



Entry	Base (1 eq)	Time (h)	X	Yield (**2a**) (%)[b]
1	*t*-BuOK	18	BF_4 (**1a**)	53
2	Cs_2CO_3	20	BF_4 (**1a**)	55
3	KOH	24	BF_4 (**1a**)	35
4	K_2CO_3	28	BF_4 (**1a**)	25
5	NaH	20	BF_4 (**1a**)	40
6	*t*-BuOK	24	OTf (**1b**)	45
7	*t*-BuOK	24	Br (**1c**)	10
8	*t*-BuOK	24	PF_6 (**1d**)	60

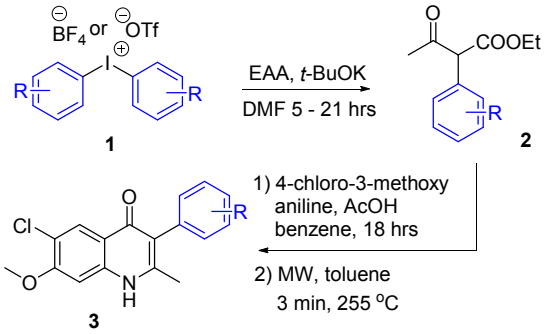
[a]Reaction conditions: salt **1** was added to the enolate solution of EAA and ran for tabulated time.
[b]Isolated yields in keto and enol form.

To prevent any possible solubility issues with iodonium salts, DMF was the solvent of preference, though most of the salts with BF_4 and OTf anions are soluble in nonpolar solvents. When 1:1 ratio of iodonium salt and EAA was used, the reaction was low yielding because of the formation of double arylated products evident by LC-MS. However, improved yields were obtained when 1:2.5 ratio of iodonium salt and EAA was used. On top, the formation of side products was suppressed according to ^{1}H-NMR analysis of the crude product. It was found that after reaction completion, the addition of HCl solution in one portion is mandatory to avoid the formation of the deacylated product via a retro-Claisen reaction. Noteworthy, one equivalent of

aryl iodide is obtained during course of the reaction and could be reused in case of hardly accessible substrates for diaryliodonium salt formation. Among the different bases screened, Cs_2CO_3 and *t*BuOK resulted in the best and most reproducible yields (Table 1) in the scale up to 5 grams. Of the two bases, *t*BuOK was preferred due to its low cost. Subsequently, having these conditions set, the influence of various diphenyliodonium anions on the course of the arylation reaction was examined. Arylations with a diphenyliodonium triflate provided similar yields to the tetrafluoroborate, however, the hexafluorophosphate resulted in 60% yield. The reaction with an iodonium salt with a bromide anion resulted in poor yields possibly due to a combination of competing nucleophilicity of the bromide anion and the low solubility of the bromide salt in DMF as reported before.[10d] Although the yield with the PF_6 salt is slightly better than the arylations with BF_4 and OTf anions, it was preferred to proceed with the latter two due to their accessibility and shorter reaction time. Despite initial moderate yields with the unsubstituted diphenyliodonium salt, we wanted to explore the reaction further by probing diverse electron-rich, electron-deficient and sterically hindered electrophiles with the reasonable assumption of getting improved results particularly when using iodonium salts substituted at the aryl rings with electron withdrawing groups.

Firstly, various symmetrical iodonium salts with tetrafluoroborate or triflate anions were prepared and subsequently treated with EAA under optimized conditions.[13-14] The resultant 2-aryl EAAs were then converted to the corresponding 3-aryl-4(1*H*)-quinolones under modified Conrad-Limpach conditions using 4-chloro-3-methoxyaniline (see the Supporting Information for more details). All the results are summarized in Table 2.

Table 2. Arylation of EAA with symmetrical salts



Entry	R	Anion **1**	Yield **2**[a] (%)	Yield **3**[a] (%)
1	H (**1a**)	BF_4	53 (**2a**)	60 (**3a**)
2	2-CH_3 (**1e**)	BF_4	73 (**2b**)	42 (**3b**)
3	2,4,6-tri CH_3 (**1f**)	OTf	10 (**2c**)	N.R.(**3c**)
4	4-CF_3 (**1g**)	BF_4	93 (**2d**)	62 (**3d**)
5	2-F (**1h**)	BF_4	75 (**2e**)	54 (**3e**)
6	4-Cl (**1i**)	BF_4	70 (**2f**)	68 (**3f**)
7	4-*t*Bu (**1j**)	OTf	65 (**2g**)	67 (**3g**)
8	2,4-di CH_3 (**1k**)	BF_4	60 (**2h**)	38 (**3h**)
9	4-$COOCH_3$ (**1l**)	BF_4	90 (**2i**)	67 (**3i**)
10	4-OCH_3 (**1m**)	OTf	N.R.[b]	n/a

[a]Isolated yields. [b]no reaction

Generally, arylations of numerous *ortho*-substituted substrates are problematic in metal-mediated conditions and result in poor yields due to steric bulkiness.[5d] Remarkably, the *ortho* substitution was tolerated well in our case with salts **1h** and **1e** getting converted to greater than 70% of product signifying an advantage of the selected methodology. In addition, the arylation with 2,4-dimethyl substituted salt **1k** delivered 60% yield, whereas dimesityliodonium example **1c** resulted in only 10% yield. Noteworthy, compound **2c** was obtained in the enol form exclusively, impeding the formation of the enamine during the Conrad-Limpach cyclization. Unsurprisingly, increasing the substitution of the aromatic ring resulted in slightly lower yields in the cyclization step due to steric factors (Table 2).

The arylation of EAA using electron-rich electrophiles like 4-*tert*-butyl took relatively longer times and revealed marginally lower yields. Moreover, any attempts with 4-methoxy substituted salt **1m** did not deliver the required product even after prolonged reaction times. The unreactivity

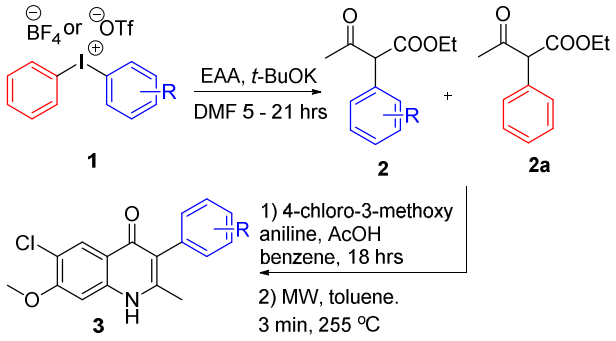
of salt **1m** is probably due to reduced electrophilicity of the iodine center. 4-Chloro substituted salt **1i** produced the corresponding product in respectable yields under these reaction conditions. Noticeably, salts **1g** and **1l**, which contain electron-withdrawing groups, behaved excellently, reacting to the corresponding arylated products in less time with yields over 90%. Likely, these results can be linked to an enhanced electrophilicity of the iodine center.

Traditionally, the Conrad-Limpach reaction, which was initially reported in 1887[15], is low-yielding and involves harsh conditions requiring high-boiling solvents like diphenyl ether or polyphosphoric acid.[3,16]

In this report, we were able to improve the overall yields, in average by 10%, by using microwave assisted conditions in toluene and reducing the cyclization time to 3 minutes (Table 2). Under classical thermal conditions in Ph_2O, the formation of quinolone is usually accompanied with multiple side products, which interfere with the isolation. Switching the reaction solvent to toluene in a microwave allowed the isolation of analytically pure samples by precipitation with no further need of crystallization.

Next, the chemoselectivity trends were examined with unsymmetrical salts.[17] A few salts with varying sterics and electronics were prepared for this purpose followed by treatment under optimized arylation conditions. The results are summarized in the Table 3.

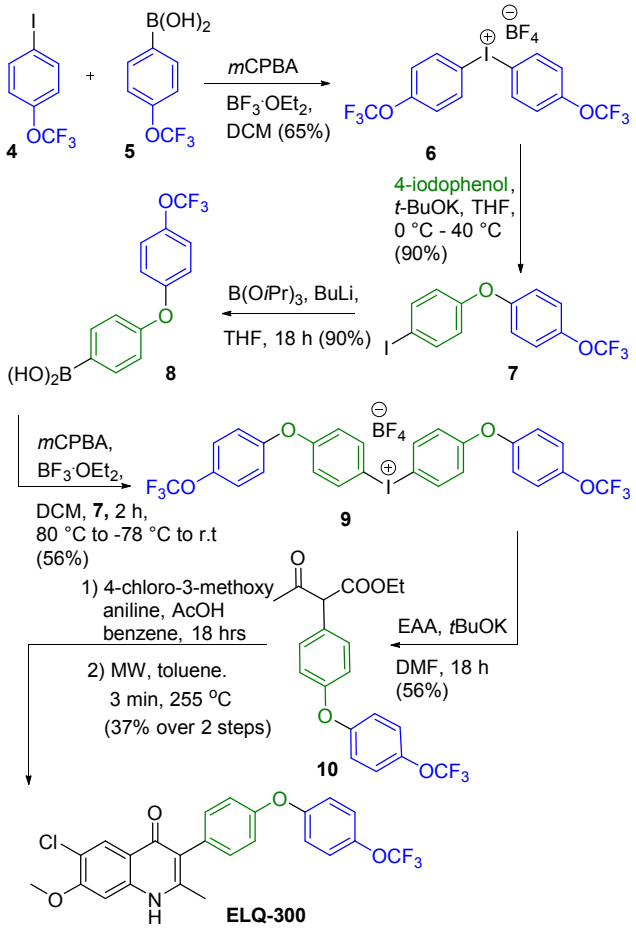
Table 3. Arylation of EAA with unsymmetrical salts



Entry	R	Anion **1**	Yield **2/2a** (%)	Yield **3** (%)
1	mesityl (**1n**)	OTf	**2c/2a** 36/0	N.R. (**3c**)
2	4-NO_2 (**1o**)	BF_4	**2j/2a** 83/0	39 (**3j**)
3	4-CF_3 (**1p**)	OTf	**2d/2a** 89/0	62 (**3k**)
4	4-Cl-3-pyridyl (**1q**)	OTf	**2k/2a** 50/12	Trace (**3l**)

Excellent chemoselectivity was observed in the case of phenylmesityl substituted salt **1n**, resulting in EAA **2c** exclusively in 36% yield. The mesityl group was readily transferred compared to the phenyl group. The latest result was contrary to the one reported in case of sterically hindered aryl group delivery using diethylmalonate as nucleophile.[17] In contrast to the symmetrical salt **1f**, the improved yield for this arylation may be due to the steric differences of both rings attached to the iodine center.

During the arylation of salts **1o** and **1p**, the electron-deficient rings were selectively transferred to produce the products **2j** and **2d** in excellent yields. Arylation with salt **1q** resulted in a 4:1 ratio of the pyridyl ring and phenyl ring products in 62% overall yield. However the Conrad-Limpach cyclization of **2k** did not perform well and produced only trace amounts of corresponding 4(1*H*)-quinolone after several attempts of purification. Arylation pursuits using the 4-anisyl(phenyl) iodonium salt were not successful. The electron-poor rings are preferentially transferred over the electron-rich rings and bulky rings readily transferred over rings lacking in sterics (so-called *ortho* effect[18]).



Scheme 1. Synthesis of ELQ-300 via salt route.

After having the arylation conditions set, this strategy was applied for the synthesis of antimalarial compound **ELQ-300** (Scheme 1).[4,19] The iodonium salt **6** was prepared according to the reported procedure and subsequently treated with 4-iodophenol to obtain the diaryl ether **7** in excellent yield.[9a] Next, boronic acid **8** was prepared from aryl iodide **7** and cleanly converted to the appropriate iodonium salt **9**. The salt **9** was then treated with EAA under standard arylation conditions providing the corresponding substituted EAA **10** in 52% yield in its pure form of the keto-enol tautomers. This result is better than our previous arylation attempts via the Cu-catalyzed reaction, in which only 30% yield was obtained with the contamination of the

inseparable deacylated product (unpublished data). Additionally, one equivalent of the iododiaryl ether **7** was isolated during the reaction, which could be reused to make the salt **9** proving atom-economy of the reaction. Finally, EAA **10** was treated with 4-chloro-3-methoxy aniline under Conrad-Limpach conditions to furnish **ELQ-300**.

In conclusion, a metal-free arylation of EAA using diaryliodonium salts was broadly studied for the first time. Commercial availability or straightforward accessibility of iodonium salts makes this method convenient and operationally simple. The arylation with symmetrical salts with electron-rich rings delivers good yields with the exception of the reaction with 4-methoxy substituted diaryliodonium salt. Lower yields were also obtained for highly hindered substrates as mesityl analog. Nonetheless, excellent results are obtained with symmetrical salts containing electron-deficient rings. Importantly, the acceptable yields for arylations using *ortho*-substituted iodonium salts stands in stark contrast to metal-mediated synthetic approaches with similar substrates, which usually do not perform well. Finally, impressive chemoselectivities were also obtained in the case of unsymmetrical salts. Overall this method demonstrated enhanced selectivity and versatility giving straightforward access to medicinally and pharmaceutically interesting EAA derived molecules.

Experimental Section

General Experimental Methods. All reagents and solvents were purchased from commercial sources and used without further purification unless otherwise noted. All reactions were run under an argon atmosphere unless otherwise indicated. Prior to use of solvents in reactions, they were purified by passing the degassed solvents through a column of activated alumina and transferred by an oven-dried syringe or cannula. The identity of all title compounds

was verified by via ^{1}H NMR, ^{13}C NMR, and HRMS. The chemical purity of the titled compounds was determined by LC/MS using the following conditions: a LC/MSD with a Phenomenex Kinetex (50 mm x 4.6 mm, 2.6 μm, C18, 100A) reversed phase column; method: 10% (v/v) of acetonitrile (+0.1% FA) in 90% (v/v) of H_2O (+0.1% FA), ramped to 100% acetonitrile (+0.1% FA) over 5.5 min, and holding at 100% acetonitrile for 1 min with a flow rate of 1.3 mL/min, UV detector, 254 nm. The purity of each compound was ≥95% in this analysis. NMR spectra were recorded at ambient temperature on a 400, 500 or 600 MHz NMR spectrometer in the solvent indicated. All ^{1}H NMR experiments are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals for chloroform (7.26 ppm) and dimethylsulfoxide (2.50 ppm). All ^{13}C NMR spectra were reported in ppm relative to the signals for chloroform (77 ppm) and dimethylsulfoxide (39.5 ppm) with ^{1}H decoupled observation. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant (Hz), whereas ^{13}C-NMR analyses were obtained at 101 or 126 MHz and reported in terms of chemical shift and multiplicity. NMR data was processed by using MestReNova Software ver. 8.1. High resolution mass spectra (HRMS) were performed on an LC/MS Q-TOF system. Microwave experiments were performed on a microwave reactor using sealed reaction vessels and the reaction temperature was monitored with IR sensor. Preparative HPLC was used to separate several compounds by reverse phase (column Eclipse XDB-C18, 5 μM, 9.4x250 mm). Compounds were eluted using a gradient elution of 70/30 to 50/50 A/B over 30 minutes at a flow rate of 5.0 mL/min, where solvent A was 0.1% TFA in water and solvent B was 0.1% TFA in acetonitrile. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates (0.25 mm). and components were visualized by ultraviolet light (254 nm).

Silica gel 60. with 230-400 (particle size 40-63 μm) mesh was used for all flash column chromatography.

General procedure for the synthesis of diaryliodonium salts: All the diaryliodonium salts were obtained as described by Bielawski et al.[13]

General procedure for arylation of ethyl acetoacetate (EAA): A flame dried flask was charged with 10 mmol (1eq) of sublimed potassium *tert*-butoxide in anhydrous DMF (50 mL) at room temperature under argon. Then 10 mmol (1 eq) of freshly distilled EAA was added to the reaction mixture and stirred for 30 minutes at 0 ^{o}C followed by dropwise addition of diaryliodonium salt (4 mmol, 0.4 eq to EAA) in 10 ml of DMF. Reaction was left stirring at room temperature for the time mentioned in the table. After confirming complete consumption of iodonium salt (by LCMS), to the reaction mixture was added 1M HCl in one portion to bring the pH around 5.0. The crude was extracted with diethyl ether until the aqueous layer is devoid of product. Organic layer was dried over sodium sulfate and solvent was removed in vacuo. The product was purified by flash column chromatography (0.5-2% of hexane in ethyl acetate).

General procedure for Conrad-Limpach cyclization: To a round bottom flask was added 4-chloro-3-methoxyaniline (1 mmol), aryl substituted ethyl acetoacetate (1.2 mmol), 10 mol% of AcOH, 5 mL of benzene. The contents were brought to reflux in a Dean-Stark trap with the azeotropic removal of water. After 24-36h the reaction was cooled to room temperature and concentrated in vacuo. A quick chromatography was done to separate any unreacted aniline from the enamine. The resulting enamine was dissolved in 2-3 ml toluene and reacted in microwave at 260 ^{o}C for three minutes. The crashed out solid was filtered off and washed with excess amount of diethyl ether and dried. No further purification was needed.

Diphenyliodonium tetrafluoroborate (1a). Compound **1a** was prepared following general procedure for the synthesis of diaryliodonium salts in 85% yield (7.9 g) as off white solid. m.p.: 132-134 ^{o}C; Analytic data matches with the previously reported.[13a] ^{1}H NMR (500 MHz, DMSO) δ 8.28 – 8.23 (m, 4H), 7.69 – 7.64 (m, 2H), 7.55 – 7.51 (m, 4H). ^{13}C NMR (126 MHz, DMSO) δ 135.2, 132.1, 131.8, 116.6. ^{19}F NMR (376 MHz, DMSO) δ -147.72, -147.77. HRMS (ESI-TOF) m/z: $[M - BF_4^-]^+$ calcd for $C_{12}H_{10}I$ 280.9822; found 280.9816.

Di-*o*-tolyliodonium tetrafluoroborate (1e). Compound **1e** was prepared following general procedure for the synthesis of diaryliodonium salts in 73% yield (5.0 g) as white solid. m.p.: 163-164 ^{o}C; Analytic data matches with the previously reported.[13a] ^{1}H NMR (500 MHz, DMSO) δ 8.32 (d, J = 7.9 Hz, 2H), 7.61 – 7.53 (m, 4H), 7.33 – 7.27 (m, 2H), 2.61 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 140.6, 137.2, 132.8, 131.6, 129.3, 120.6, 24.0. ^{19}F NMR (376 MHz, DMSO) δ -147.76, -147.82. HRMS (ESI-TOF) m/z: $[M - BF_4^-]^+$ calcd for $C_{14}H_{14}I$ 309.0135; found 309.01379.

Dimesityliodonium trifluoromethanesulfonate (1f). Compound **1f** was prepared following general procedure for the synthesis of diaryliodonium salts in 58% yield (2.4 g) as white solid. m.p.: 191-192 ^{o}C; Analytic data matches with the previously reported.[13b] ^{1}H NMR (400 MHz, DMSO) δ 7.19 (s, 4H), 2.46 (s, 12H), 2.29 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 142.7, 141.9, 130.3, 120.7 (q, J = 322.3 Hz), 118.9, 25.3, 20.4. ^{19}F NMR (376 MHz, DMSO) δ -77.29. HRMS (ESI-TOF) m/z: $[M - OTf^-]^+$ calcd for $C_{18}H_{22}I$ 365.0761; found 365.0766.

Bis(4-(trifluoromethyl)phenyl)iodonium tetrafluoroborate (1g). Compound **1g** was prepared following general procedure for the synthesis of diaryliodonium salts in 63% yield (4.1 g) as white solid. m.p.: 191-192 ^{o}C; Analytic data matches with the previously reported.[13a] ^{1}H NMR (500 MHz, DMSO) δ 8.51 (d, J = 8.3 Hz, 4H), 7.94 (d, J = 8.5 Hz, 4H). ^{13}C NMR (126

MHz, DMSO) δ 136.3, 132.1 (q, *J* = 32.6 Hz), 128.5 (q, *J* = 3.6 Hz), 123.4 (q, *J* = 273.1 Hz), 121.0.[19]F NMR (376 MHz, DMSO) δ -61.25, -147.70, -147.75. HRMS (ESI-TOF) m/z: [M - BF_4^-]$^+$ calcd for $C_{14}H_8F_6I$ 416.9569; found 416.9577.

Bis(2-fluorophenyl)iodonium tetrafluoroborate (1h). Compound **1h** was prepared following general procedure for the synthesis of diaryliodonium salts in 60% yield (1.8 g) as white solid. m.p.: 175-176 ^oC; Analytic data matches with the previously reported.[13a] ^1H NMR (500 MHz, DMSO) δ 8.46 – 8.37 (m, 2H), 7.73 (dd, *J* = 12.2, 7.6 Hz, 2H), 7.59 (t, *J* = 7.9 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 160.1, 158.1, 137.1, 136.6 – 135.3 (m), 127.8, 117.0 (d, *J* = 22.0 Hz), 104.1 (d, *J* = 23.7 Hz). ^{19}F NMR (376 MHz, DMSO) δ -97.42 (dt, *J* = 11.8, 6.1 Hz), -147.74, -147.80. HRMS (ESI-TOF) m/z: [M - BF_4^-]$^+$ calcd for $C_{12}H_8F_2I$ 316.9633; found 316.9634.

Bis(4-chlorophenyl)iodonium tetrafluoroborate (1i). Compound **1i** was prepared following general procedure for the synthesis of diaryliodonium salts in 78% yield (5.0 g) as white solid. m.p.: 167-170 ^oC; Analytic data matches with the previously reported.[20] ^1H NMR (500 MHz, DMSO) δ 8.26 (d, *J* = 8.8 Hz, 4H), 7.62 (d, *J* = 8.8 Hz, 4H). ^{13}C NMR (126 MHz, DMSO) δ 137.5, 137.0, 131.8, 114.7. ^{19}F NMR (376 MHz, DMSO) δ -147.65, -147.71. HRMS (ESI-TOF) m/z: [M - BF_4^-]$^+$ calcd for $C_{12}H_8Cl_2I$ 348.9042; found 348.9031.

Bis(4-(*tert*-butyl)phenyl)iodonium trifluoromethanesulfonate (1j). Compound **1j** was prepared following general procedure for the synthesis of diaryliodonium salts in 30% yield (2.1 g) as white solid. m.p.: 153-154 ^oC; Analytic data matches with the previously reported.[13b] ^1H NMR (500 MHz, DMSO) δ 8.13 (d, *J* = 8.7 Hz, 4H), 7.53 (d, *J* = 8.7 Hz, 4H), 1.25 (s, 18H). ^{13}C NMR (126 MHz, DMSO) δ 155.2, 135.0, 128.9, 120.8 (q, *J* = 322.2 Hz), 113.6, 35.0, 30.9. ^{19}F

NMR (376 MHz, DMSO) δ -77.29. HRMS (ESI-TOF) m/z: $[M - OTf^-]^+$ calcd for $C_{20}H_{26}I$ 393.1074; found 393.1086.

Bis(2,4-dimethylphenyl)iodonium trifluoromethanesulfonate (1k). Compound **1k** was prepared following general procedure for the synthesis of diaryliodonium salts in 50% yield (4.1 g) as white solid. m.p.: 169-170 ^oC; Analytic data matches with the previously reported.[17] ^1H NMR (500 MHz, DMSO) δ 8.15 (d, *J* = 8.2 Hz, 2H), 7.35 (s, 2H), 7.10 (dd, *J* = 8.2, 2.0 Hz, 2H), 2.55 (s, 6H), 2.30 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 143.1, 140.3, 137.0, 132.1, 129.9, 120.7 (q, *J* = 322.3 Hz), 117.0, 24.7, 20.7. ^{19}F NMR (376 MHz, DMSO) δ -77.27. HRMS (ESI-TOF) m/z: $[M - OTf^-]^+$ calcd for $C_{16}H_{18}I$ 337.0448; found 337.0449.

Bis(4-(methoxycarbonyl)phenyl)iodonium tetrafluoroborate (1l). Compound **1l** was prepared following general procedure for the synthesis of diaryliodonium salts in 70% yield (3.8 g) as brownish solid. m.p.: 201-203 ^oC; Analytic data matches with the previously reported.[21] ^1H NMR (500 MHz, DMSO) δ 8.40 (d, *J* = 8.6 Hz, 4H), 8.03 (d, *J* = 8.6 Hz, 4H), 3.86 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 165.1, 135.7, 132.7, 132.0, 121.6, 52.7. ^{19}F NMR (376 MHz, DMSO) δ -147.74, -147.79. HRMS (ESI-TOF) m/z: $[M - BF_4^-]^+$ calcd for $C_{16}H_{14}IO_4$ 396.9931; found 396.9932.

Mesityl(phenyl)iodonium trifluoromethanesulfonate (1n). Compound **1n** was prepared following general procedure for the synthesis of diaryliodonium salts. Analytic data matches with the previously reported.[22] ^1H NMR (400 MHz, DMSO) δ 7.98 (dd, *J* = 7.6, 0.7 Hz, 2H), 7.63 (dd, *J* = 11.3, 4.1 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.22 (s, 2H), 2.60 (s, 6H), 2.29 (s, 3H). 13C NMR (101 MHz, DMSO) δ 143.1, 141.6, 134.5, 131.9, 131.8, 129.8, 122.5, 114.5, 26.3, 20.5.

(4-Nitrophenyl)(phenyl)iodonium tetrafluoroborate (1o). Compound **1o** was prepared following general procedure for the synthesis of diaryliodonium salts to give pure diaryliodonium tetrafluoroborate salt in 51% yield (1.8 g) as a grey solid. Analytic data matches with the previously reported.[13b] ^{1}H NMR (400 MHz, DMSO) δ 8.50 – 8.43 (m, 2H), 8.34 – 8.26 (m, 4H), 7.68 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 149.4, 136.4, 135.4, 132.3, 131.9, 126.2, 123.3, 117.4. HRMS (ESI-TOF) m/z: [M - BF4-]+ calcd for $C_{12}H_9INO_2$ 325.9672; found 325.9675.

Phenyl(4-(trifluoromethyl)phenyl)iodonium trifluoromethanesulfonate (1p). Compound **1p** was prepared following general procedure for the synthesis of diaryliodonium salts. Analytic data matches with the previously reported.[13b]

(6-Chloropyridin-3-yl)(phenyl)iodonium trifluoromethanesulfonate (1q). Compound **1q** was prepared following general procedure 1.1. Analytic data matches with the previously reported.[13b] ^{1}H NMR (400 MHz, DMSO) δ 9.17 (d, *J* = 2.3 Hz, 1H), 8.70 (dd, *J* = 8.5, 2.4 Hz, 1H), 8.28 (d, *J* = 8.1 Hz, 2H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.70 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 2H).

Ethyl 3-oxo-2-phenylbutanoate (2a). Compound **2a** was prepared following general procedure for arylation of ethyl acetoacetate in 53% yield (0.53 g) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.13 (s, 0.3H), 7.41 – 7.27 (m, 4H), 7.18 – 7.13 (m, 1H), 4.69 (s, 0.7H), 4.27 – 4.15 (m, 2H), 2.19 (s, 2H), 1.86 (s, 1H), 1.28 (t, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7, 174.0, 172.7, 168.6, 135.4, 132.8, 131.4, 129.4, 129.0, 128.4, 128.1, 127.0, 104.5, 65.9, 61.8, 60.8, 28.9, 20.0, 14.3, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{14}O_3$ 207.1016; found 207.1018.

Ethyl 3-oxo-2-(*o*-tolyl)butanoate (2b). Compound **2b** was prepared following general procedure for arylation of ethyl acetoacetate in 73% yield (4.5 g) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.07 (s, 0.7H), 7.32 – 7.14 (m, 3H), 7.06 (d, *J* = 7.3 Hz, 1H), 4.91 (s, 0.3H), 4.30 – 4.06 (m, 2H), 2.35 (s, 1H), 2.18 (s, 1H), 2.17 (s, 2H), 1.75 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 1H), 1.17 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.1, 173.6, 172.5, 168.9, 138.1, 136.8, 134.7, 131.6, 131.6, 131.0, 129.9, 128.9, 128.3, 127.7, 127.6, 126.7, 125.8, 125.8, 125.8, 125.8, 103.1, 62.4, 61.7, 60.6, 20.0, 19.8, 19.6, 14.4, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{16}O_3$ 221.1172; found 221.1167.

Ethyl (Z)-3-hydroxy-2-mesitylbut-2-enoate (2c). Compound **2c** was prepared following general procedure for arylation of ethyl acetoacetate in 10% (0.32 g) and 36% (0.41 g) yields with the symmetric and unsymmetric salts respectively as colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.07 (s, 1H), 6.89 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.29 (s, 3H), 2.09 (s, 6H), 1.67 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 172.6, 137.9, 137.0, 131.1, 128.3, 100.9, 60.4, 21.2, 20.2, 19.0, 14.49. HRMS (ESI-TOF) m/z: [M + H]+ calcd for $C_{15}H_{20}O_3$ 249.1485; found 249.1495.

Ethyl 3-oxo-2-(4-(trifluoromethyl)phenyl)butanoate (2d). Compound **2d** was prepared following general procedure for arylation of ethyl acetoacetate in 93% yield (1.0 g) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.17 (s, 0.5H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 4.76 (s, 0.5H), 4.29 – 4.14 (m, 2H), 2.23 (s, 1.5H), 1.86 (d, *J* = 0.7 Hz, 1.5H), 1.28 (t, *J* = 7.1 Hz, 1.5H), 1.19 (t, *J* = 7.1 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.4, 174.5, 172.2, 168.0, 139.3, 136.5, 131.8, 130.7 (q, *J* = 32.6 Hz), 130.0, 129.2 (q, *J* = 32.4 Hz), 125.9 (q, *J* = 3.8 Hz), 125.1 (q, *J* = 3.7 Hz), 124.9 (d, *J* = 272.0 Hz), 124.8 (q, *J* = 272.0 Hz), 103.6, 65.4, 62.2, 61.0, 29.2, 20.1, 14.3, 14.2. ^{19}F NMR (376

MHz, $CDCl_3$) δ -63.05, -63.32. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{13}F_3O_3$ 275.089; found 275.0897.

Ethyl 2-(2-fluorophenyl)-3-oxobutanoate (2e). Compound **2e** was prepared following general procedure for arylation of ethyl acetoacetate in 75% yield (0.7g) as colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 13.21 (s, 0.5H), 7.41 (td, *J* = 7.6, 1.7 Hz, 0.5H), 7.37 – 7.26 (m, 1H), 7.21 – 7.03 (m, 2.5H), 5.04 (s, 0.5H), 4.31 – 4.10 (m, 2H), 2.24 (s, 1H), 1.86 (s, 2H), 1.28 (t, *J* = 7.1 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.8, 174.9, 172.2, 168.1, 160.8 (d, *J* = 245.6 Hz), 160.6 (d, *J* = 247.0 Hz), 133.4 (d, *J* = 2.9 Hz), 130.9 (d, *J* = 3.2 Hz), 130.2 (d, *J* = 8.3 Hz), 129.4 (d, *J* = 8.2 Hz), 124.6 (d, *J* = 3.8 Hz), 123.8 (d, *J* = 3.8 Hz), 122.9 (d, *J* = 16.5 Hz), 120.3 (d, *J* = 14.6 Hz), 115.7 (d, *J* = 22.4 Hz), 115.5 (d, *J* = 22.5 Hz), 97.9, 62.0, 60.9, 57.8, 29.2, 19.8, 14.3, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.94 (dd, *J* = 17.2, 6.4 Hz), -117.92 (dd, *J* = 18.1, 6.3 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}FO_3$ 225.0922; found 225.093.

Ethyl 2-(4-chlorophenyl)-3-oxobutanoate (2f). Compound **2f** was prepared following general procedure for arylation of ethyl acetoacetate in 70% yield (0.2 g) as colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ 13.10 (s, 0.35H), 7.36 – 7.25 (m, 3H), 7.07 (dd, *J* = 8.5, 0.6 Hz, 1H), 4.65 (s, 0.65H), 4.18 (m, 2H), 2.18 (s, 2H), 1.83 (s, 1H), 1.25 (t, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.0, 174.2, 172.4, 168.2, 134.5, 133.8, 133.0, 132.7, 131.2, 130.8, 129.2, 128.4, 103.4, 65.0, 62.0, 60.9, 29.0, 20.0, 14.3, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}ClO_3$ 241.0626; found 241.063.

Ethyl 2-(4-(*tert*-butyl)phenyl)-3-oxobutanoate (2g). Compound **2g** was prepared following general procedure for arylation of ethyl acetoacetate in 65% yield (0.5 g) as colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 13.15 (s, 0.25H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.33 (d, *J* = 8.3 Hz,

1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.66 (s, 0.75H), 4.28 – 4.15 (m, 2H), 2.18 (s, 2H), 1.86 (s, 1H), 1.34 (s, 3H), 1.31 (s, 6H), 1.28 (t, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 174.0, 172.9, 168.9, 151.3, 149.7, 132.1, 130.9, 129.6, 129.0, 126.0, 125.0, 104.3, 65.5, 61.7, 60.7, 34.7, 34.6, 31.5, 31.4, 28.9, 20.1, 14.4, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{22}O_3$ 263.1642; found 263.1632.

Ethyl 2-(2,4-dimethylphenyl)-3-oxobutanoate (2h). Compound **2h** was prepared following general procedure for arylation of ethyl acetoacetate in 60% yield (0.6 g) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.07 (s,0.9H), 7.19 – 6.88 (m, 3H), 4.86 (s, 0.1H), 4.17 (m, 2H), 2.33 (s, 2.7H), 2.32 (s, 0.3H), 2.30 (s, 0.3H), 2.16 (s, 0.3H), 2.12 (s, 2.7H), 1.75 (s, 2.7H), 1.27 (t, *J* = 7.1 Hz, 0.3H), 1.17 (t, *J* = 7.1 Hz, 2.7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 173.7, 172.7, 169.1, 138.1, 137.9, 137.2, 136.6, 131.8, 131.7, 131.4, 130.8, 129.1, 128.8, 127.4, 126.6, 102.9, 62.1, 61.7, 60.6, 21.3, 21.2, 19.9, 19.8, 19.7, 14.5, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{18}O_3$ 235.1329; found 235.1336.

Methyl 4-(1-ethoxy-1,3-dioxobutan-2-yl)benzoate (2i). Compound **2i** was prepared following general procedure for arylation of ethyl acetoacetate in 70% yield (4.5 g) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.16 (s, 0.5H), 8.05 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 4.75 (s, 0.5H), 4.29 – 4.12 (m, 2H), 3.92 (s, 3H), 2.20 (s, 1.5H), 1.86 (s, 1.5H), 1.27 (t, *J* = 7.2 Hz, 1.5H), 1.17 (t, *J* = 7.1 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.7, 174.3, 172.2, 168.0, 167.1, 166.8, 140.4, 137.6, 131.5, 130.2, 130.2, 129.6, 129.4, 128.8, 103.9, 65.7, 62.1, 61.0, 52.4, 52.3, 29.1, 20.1, 14.23 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{16}O_5$ 265.1071; found 265.1073.

Ethyl 2-(4-nitrophenyl)-3-oxobutanoate (2j). Compound **2j** was prepared following general procedure for arylation of ethyl acetoacetate in 82% yield (0.23 g) as yellow oil; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 13.23 (s, 0.5H), 8.24 (d, *J* = 8.9 Hz, 1H), 8.20 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.34 (d, *J* = 8.9 Hz, 1H), 4.83 (s, 0.5H), 4.31 – 4.15 (m, 2H), 2.27 (s, 1.5H), 1.89 (s, 1.5H), 1.29 (t, *J* = 7.1 Hz, 1.5H), 1.19 (t, *J* = 7.1 Hz, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 174.78, 171.7, 167.5, 148.0, 147.0, 142.6, 139.6, 132.4, 130.7, 124.0, 123.4, 103.1, 65.2, 62.4, 61.2, 29.4, 20.2, 14.3, 14.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{12}H_{13}NO_5$ 252.0867; found 252.0871.

Ethyl 2-(6-chloropyridin-3-yl)-3-oxobutanoate (2k). Compound **2k** was prepared following general procedure for arylation of ethyl acetoacetate in 50% yield (0.12 g) as colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.21 (s, 0.6H), 8.30 (d, *J* = 2.4 Hz, 0.4H), 8.19 (d, *J* = 2.4 Hz, 0.6H), 7.77 (dd, *J* = 8.3, 2.5 Hz, 0.4H), 7.47 (dd, *J* = 8.2, 2.5 Hz, 0.6H), 7.36 (d, *J* = 8.4 Hz, 0.4H), 7.32 (d, *J* = 8.2 Hz, 0.6H), 4.73 (s, 0.4 H), 4.21 (m, 2H), 2.28 (s, 1.2H), 1.89 (s, 1.8H), 1.28 (t, *J* = 7.2 Hz, 1.2H), 1.18 (t, *J* = 7.1 Hz, 1.8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4, 175.1, 171.7, 167.3, 151.5, 150.0, 149.8, 141.4, 139.8, 130.1, 127.5, 124.3, 123.7, 99.8, 62.3, 61.9, 61.1, 29.3, 19.9, 14.1, 14.0. HRMS (ESI-TOF) m/z: [M + H]+ calcd for $C_{11}H_{12}ClNO_3$ 242.0579; found 242.0570.

6-Chloro-7-methoxy-2-methyl-3-phenylquinolin-4(1*H*)-one (3a). Compound **3a** was prepared following general procedure for Conrad-Limpach cyclization in 60% yield (0.28 g) as white solid. m.p.: >300^{o}C (decomp); Analytic data matches with the previously reported.[3] ^{1}H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 7.99 (s, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.2 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.06 (s, 1H), 3.96 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.5, 156.7, 146.4, 139.6, 135.9, 130.9, 127.8, 126.5, 126.2, 120.8, 118.8, 117.9, 99.4, 56.4, 18.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{14}ClNO_2$ 300.0786; found 300.0794.

6-Chloro-7-methoxy-2-methyl-3-(*o*-tolyl)quinolin-4(1*H*)-one (3b). Compound **3b** was prepared following general procedure for Conrad-Limpach cyclization in 42% yield (0.33 g) as white solid. m.p.: >300^{o}C (decomp); Analytic data matches with the previously reported.[23] ^{1}H NMR (500 MHz, DMSO) δ 11.69 (s, 1H), 7.99 (s, 1H), 7.22 (m, 3H), 7.09 (s, 1H), 7.03 (d, *J* = 7.3 Hz, 1H), 3.96 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.2, 156.6, 146.6, 139.7, 137.4, 136.0, 130.8, 129.5, 127.1, 126.1, 125.5, 120.5, 118.6, 117.9, 99.5, 56.4, 19.4, 18.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{16}ClNO_2$ 314.0942; found 314.0943.

6-Chloro-7-methoxy-2-methyl-3-(4-(trifluoromethyl)phenyl)quinolin-4(1*H*)-one (3d). Compound **3d** was prepared following general procedure for Conrad-Limpach cyclization in 62% yield (2.1 g) as white solid. m.p.: >300^{o}C (decomp); Analytic data matches with the previously reported.[23] ^{1}H NMR (500 MHz, DMSO) δ 11.75 (s, 1H), 8.00 (s, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.07 (s, 1H), 3.96 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.2, 156.9, 146.9, 140.4, 139.6, 131.9, 127.1 (q, *J* = 31.6 Hz), 126.1, 124.6 (q, *J* = 3.6 Hz), 124.5 (q, *J* = 271.9 Hz), 119.4, 118.7, 118.3, 99.5, 56.4, 18.9. ^{19}F NMR (376 MHz, DMSO) δ -60.36. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{13}ClF_3NO_2$ 368.066; found 368.0662.

6-Chloro-3-(2-fluorophenyl)-7-methoxy-2-methylquinolin-4(1*H*)-one (3e). Compound **3e** was prepared following general procedure for Conrad-Limpach cyclization in 54% yield (0.35 g) as white solid. m.p.: 309-310 ^{o}C; ^{1}H NMR (500 MHz, DMSO) δ 11.77 (s, 1H), 7.99 (s, 1H), 7.39 (dddd, *J* = 8.1, 7.2, 5.4, 2.0 Hz, 1H), 7.30 – 7.19 (m, 3H), 7.08 (s, 1H), 3.97 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.5, 160.6 (d, *J* = 243.5 Hz), 157.3, 147.8, 140.2, 133.8 (d, *J* = 3.7 Hz), 129.7 (d, *J* = 8.2 Hz), 126.5, 124.4 (d, *J* = 3.3 Hz), 123.8 (d, *J* = 16.8 Hz), 118.8

(d, J = 28.0 Hz), 115.8, 115.6, 115.2, 100.0, 56.9, 18.9. ^{19}F NMR (376 MHz, DMSO) δ -113.09 (dd, J = 16.1, 6.4 Hz). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}ClFNO_2$ 318.0692; found 318.0698.

6-Chloro-3-(4-chlorophenyl)-7-methoxy-2-methylquinolin-4(1*H*)-one (3f). Compound **3f** was prepared following general procedure for Conrad-Limpach cyclization in 68% yield (0.48 g) as white solid. m.p.: >300°C (decomp); ^{1}H NMR (400 MHz, DMSO) δ 11.68 (s, 1H), 7.99 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.2 Hz, 2H), 7.05 (s, 1H), 3.95 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.3, 156.7, 146.7, 139.6, 134.7, 132.8, 131.2, 127.8, 126.1, 119.4, 118.7, 118.1, 99.5, 56.4, 18.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}Cl_2NO_2$ 334.0396; found 334.0405.

3-(4-(*tert*-butyl)phenyl)-6-chloro-7-methoxy-2-methylquinolin-4(1*H*)-one (3g). Compound **3g** was prepared following general procedure for Conrad-Limpach cyclization in 67% yield (0.39 g) as white solid. m.p.: >300°C (decomp); ^{1}H NMR (500 MHz, DMSO) δ 11.64 (s, 1H), 7.99 (s, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 2H), 7.06 (s, 1H), 3.96 (s, 3H), 2.20 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (126 MHz, DMSO) δ 173.6, 156.7, 148.7, 146.5, 139.6, 132.8, 130.6, 126.2, 124.5, 120.6, 118.7, 117.9, 99.4, 56.4, 34.3, 31.2, 19.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{22}ClNO_2$ 356.1412; found 356.1422.

6-Chloro-3-(2,4-dimethylphenyl)-7-methoxy-2-methylquinolin-4(1H)-one (3h). Compound **3h** was prepared following general procedure for Conrad-Limpach cyclization in 38% yield (0.2 g) as white solid. m.p.: >300°C (decomp); ^{1}H NMR (500 MHz, DMSO) δ 11.66 (s, 1H), 7.99 (s, 1H), 7.07 (s, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.90 (d, J = 7.6 Hz, 1H), 3.95 (s, 3H), 2.30 (s, 3H), 2.04 (s, 3H), 1.97 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.2, 156.6, 146.7,

139.7, 137.1, 136.0, 132.9, 130.7, 130.3, 126.1, 120.3, 118.6, 117.9, 99.5, 56.4, 20.8, 19.3, 18.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}ClNO_2$ 328.1099; found 328.1104.

Methyl 4-(6-chloro-7-methoxy-2-methyl-4-oxo-1,4-dihydroquinolin-3-yl)benzoate (3i). Compound **3i** was prepared following general procedure for Conrad-Limpach cyclization in 67% yield (0.35 g) as white solid. m.p.: >300°C (decomp); ^{1}H NMR (500 MHz, DMSO) δ 11.76 (s, 1H), 8.00 (s, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.07 (s, 1H), 3.96 (s, 3H), 3.87 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.2, 166.3, 156.8, 146.8, 141.2, 139.6, 131.4, 128.6, 127.8, 126.2, 119.7, 118.7, 118.2, 99.5, 56.4, 52.1, 18.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}ClNO_4$ 358.0841; found 358.0847.

6-Chloro-7-methoxy-2-methyl-3-(4-nitrophenyl)quinolin-4(1*H*)-one (3j). Compound **3j** was prepared following general procedure for Conrad-Limpach cyclization in 39% yield (0.1 g) as pale yellow solid. ^{1}H NMR (500 MHz, DMSO) δ 11.80 (s, 1H), 8.23 (d, *J* = 8.7 Hz, 2H), 7.99 (s, 1H), 7.56 (d, *J* = 8.6 Hz, 2H), 7.05 (s, 1H), 3.95 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.0, 156.9, 147.1, 146.0, 143.5, 139.6, 132.4, 126.1, 122.8, 118.7, 118.7, 118.4, 99.6, 56.4, 18.9. HRMS (ESI-TOF) m/z: [M + H]+ calcd for C17H13ClN2O4 345.0637; found 345.0646.

6-Chloro-3-(6-chloropyridin-3-yl)-7-methoxy-2-methylquinolin-4(1*H*)-one (3k). Compound **3k** was prepared following general procedure for Conrad-Limpach cyclization in trace amounts. ^{1}H NMR (500 MHz, DMSO) δ 11.87 (s, 1H), 8.30 (dd, *J* = 2.4, 0.4 Hz, 1H), 8.01 (s, 1H), 7.78 (dd, *J* = 8.2, 2.5 Hz, 1H), 7.55 (dd, *J* = 8.2, 0.4 Hz, 1H), 7.10 (s, 1H), 3.97 (s, 3H), 2.26 (s, 3H). HRMS (ESI-TOF) m/z: [M + H]+ calcd for $C_{16}H_{12}Cl_2N_2O_2$ 335.0349; found 335.0336.

Bis(4-(trifluoromethoxy)phenyl)iodonium tetrafluoroborate (6). Compound **6** was prepared following general procedure for the synthesis of diaryliodonium salts in 65% yield (10.2 g) as white solid. m.p.: 105-108 ^{o}C; ^{1}H NMR (600 MHz, DMSO) δ 8.42 (d, *J* = 9.1 Hz, 4H), 7.55 (d, *J* = 8.5 Hz, 4H). ^{13}C NMR (151 MHz, DMSO) δ 150.8, 137.8, 124.1, 119.9 (q, *J* = 258.3 Hz), 114.41.. ^{19}F NMR (376 MHz, DMSO) δ -120.85, -211.91. HRMS (ESI-TOF) m/z: [M - BF_4^-]$^+$ calcd for $C_{14}H_8F_6IO_2$ 448.9468; found 448.9462.

1-Iodo-4-(4-(trifluoromethoxy)phenoxy)benzene (7). To a suspension of potassium *tert*-butoxide (1.1 equiv, 6.4 g, 57 mmol) in THF (180 mL) was added 4-iodophenol (1.0 equiv, 52.3 mmol) at 0 °C and the reaction was left to stir at this temperature for 15 min. Diaryliodonium salt (1.1 equiv, 57.2 mmol) solution in dry THF was cannulated and the reaction was stirred in the preheated to 40 °C oil bath for 2 hours (until TLC indicated complete consumption of phenol). The reaction was then quenched with H_2O at 0 °C, the organic phase was separated and the aqueous phase was extracted with diethyl ether (3×200 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The crude material was purified by flash chromatography (hexanes 100%) to give pure 1-iodo-4-(4-(trifluoromethoxy)phenoxy)benzene in 90% yield (2.7 g) as a colorless liquid.[9a] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 9.2 Hz, 2H), 6.78 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0, 155.3, 145.0 (q, *J* = 1.9 Hz), 139.0, 122.9 (d, *J* = 0.6 Hz), 121.2, 120.6 (q, *J* = 256.8 Hz), 120.0, 86.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.77.

(4-(4-(Trifluoromethoxy)phenoxy)phenyl)boronic acid (8). Compound **8** was prepared as described in literature[24] in 90% yield (1.2 g) as white solid. m.p.: 101-103 ^{o}C; ^{1}H NMR (500 MHz, DMSO) δ 8.02 (s, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 7.12

(d, J = 9.1 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H). ^{13}C NMR (126 MHz, DMSO) δ 158.0, 155.3, 144.8 (q, J = 1.9 Hz), 136.3, 123.0, 120.1, 120.1 (q, J = 255.7 Hz), 117.6. ^{19}F NMR (376 MHz, DMSO) δ -56.69.

Bis(4-(4-(trifluoromethoxy)phenoxy)phenyl)iodonium tetrafluoroborate (9). Compound **9** was prepared following modified procedure (for the electron-rich diaryliodonium substrates) of diaryliodonium salts in 56% yield (0.52 g) as white solid. m.p.: 184-186 ^{o}C; ^{1}H NMR (500 MHz, DMSO) δ 8.23 (d, J = 9.1 Hz, 4H), 7.46 (d, J = 8.4 Hz, 4H), 7.23 (d, J = 9.1 Hz, 4H), 7.14 (d, J = 9.1 Hz, 4H). ^{13}C NMR (126 MHz, DMSO) δ 160.2, 154.1, 145.3 (q, J = 1.8 Hz), 138.0, 123.7, 122.0, 121.2, 120.5 (q, J = 256.2 Hz), 109.4. ^{19}F NMR (376 MHz, DMSO) δ -56.66, -147.78, -147.84. HRMS (ESI-TOF) m/z: $[M - BF_4^-]^+$ calcd for $C_{26}H_{16}F_6IO_4$ 632.9992; found 633.001.

Ethyl 3-oxo-2-(4-(4-(trifluoromethoxy)phenoxy)phenyl)butanoate (10). Compound **10** was prepared following general procedure for arylation of EAA and purified by preparative HPLC in 52% yield (0.13 g) as colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.12 (s, 0.4H), 7.33 (d, J = 8.7 Hz, 1H), 7.22 – 7.17 (m, 2H), 7.13 (d, J = 8.7 Hz, 1H), 7.01 (m, 4H), 4.68 (s, 0.6H), 4.29 – 4.15 (m, 2H), 2.22 (s, 2H), 1.88 (s, 1H), 1.29 (t, J = 7.2 Hz, 2H), 1.20 (t, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 201.4, 174.2, 172.7, 168.6, 157.1, 155.9, 155.7, 155.4, 144.9, 144.7, 132.8, 131.1, 130.8, 128.0, 122.8, 122.7, 120.6 (q, J = 255.9 Hz), 120.2, 120.0, 119.1, 118.5, 103.7, 65.0, 61.9, 60.8, 29.0, 20.1, 14.3, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -58.78. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{17}F_3O_5$ 383.1101; found 383.1101.

6-Chloro-7-methoxy-2-methyl-3-(4-(4-(trifluoromethoxy)phenoxy)phenyl)quinolin-4(1*H*)-one (ELQ-300). Compound **ELQ-300** was prepared following general procedure for Conrad-Limpach cyclization in 30% yield (0.4 g), after recrystallization from ethanol and couple

of drops of DMSO as off white solid. Analytic data matches with the previously reported.[4] ^{1}H NMR (400 MHz, DMSO) δ 11.67 (s, 1H), 8.00 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 9.1 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 7.06 (s, 1H), 3.96 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 173.5, 156.7, 155.8, 154.8, 146.6, 143.6, 139.6, 132.7, 131.5, 126.2, 123.0, 120.1 (q, *J* = 255.7 Hz), 119.9, 119.8, 118.7, 118.3, 118.0, 99.4, 56.4, 18.9. ^{19}F NMR (376 MHz, DMSO) δ -57.21. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{17}ClF_3NO_4$ 476.0871; found 476.0889.

Supporting Information

^{1}H, ^{13}C and ^{19}F NMR copies of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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