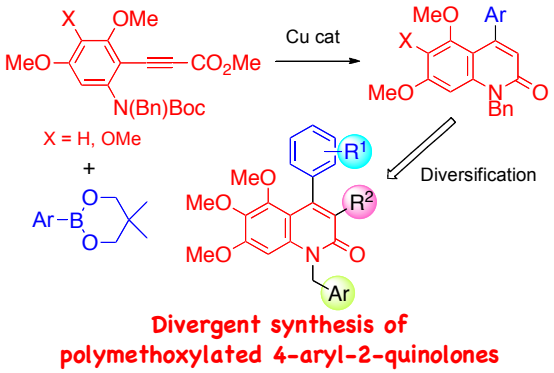
Divergent Synthesis of Polymethoxylated 4-Aryl-2-quinolones

Tsukasa Murayama, Masatoshi Shibuya, and Yoshihiko Yamamoto*

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

*yamamoto-yoshi@ps.nagoya-u.ac.jp



ABSTRACT: Polymethoxylated 4-aryl-2-quinolones were synthesized from the corresponding (*o*-aminophenyl)propiolates *via* Cu-catalyzed hydroarylation and subsequent deprotection/lactam cyclization. Selective iodination of the C3 position of the product followed by coupling reactions of the resulting 3-iodinated 4-aryl-2-quinolone afforded 3-substituted-4-aryl-2-quinolones. Moreover, the *N*-benzyl protecting group was successfully replaced with other polyoxygenated benzyl groups.

INTRODUCTION

4-Phenyl-2-quinolone is an important nitrogen-containing heterocyclic scaffold found in natural products and drug molecules (Figure 1).[1,2] Therefore, a wide variety of methods have been developed for the efficient construction of 4-aryl-2-quinolone core structures.[3] In this respect, the diversification of 4-aryl-2-quinolones would provide a promising strategy for efficiently generating potent drug candidates.[4] Nevertheless, such an intriguing tactic has received less attention, and to the best of our knowledge, no divergent synthesis of polymethoxylated analogs has been reported.[5]

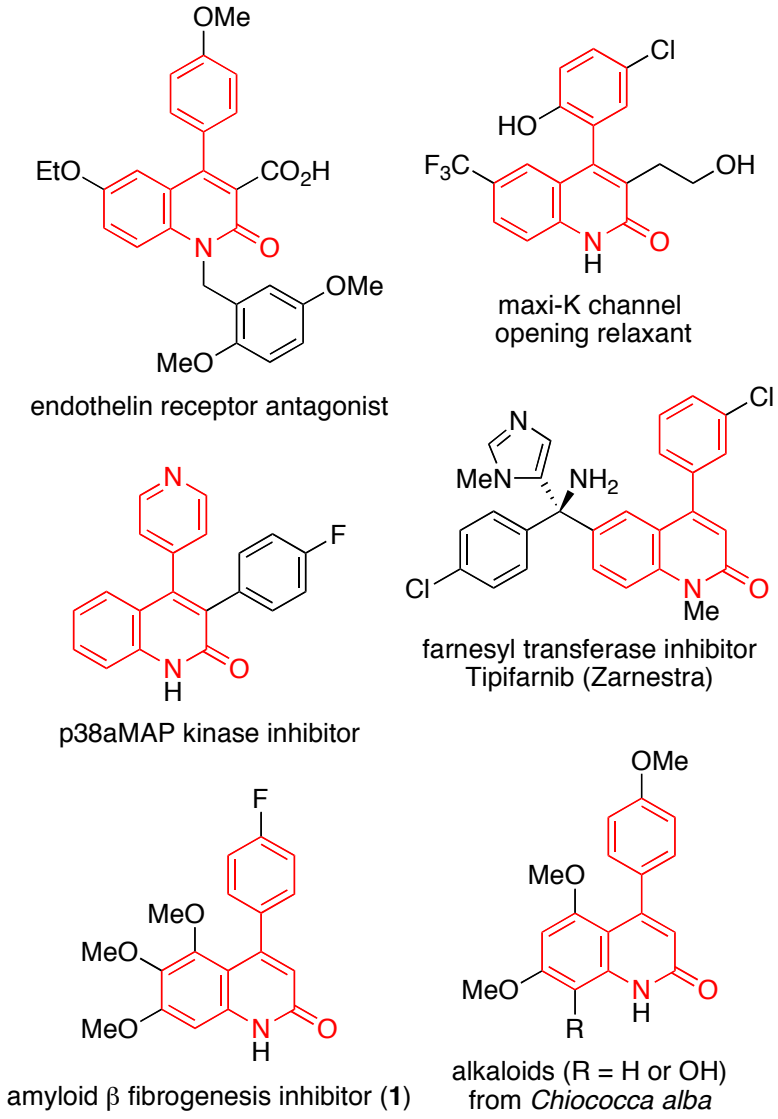


Figure 1. Examples of bioactive 4-aryl-2-quinolones.

Therefore, we focused on the efficient construction and diverted transformations of a polymethoxylated quinolone core (Figure 2). This is because Tsubuki and co-workers reported that 4-(4-fluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (**1**) is a potential inhibitor of amyloid β fibrogenesis (Figure 1).[6] Moreover, 2-quinolone alkaloids with a

dimethoxylated 2-quinolone core were also isolated from *Chiococca alba*; however, no biological activity was reported (Figure 1).[1a] The diversification of such a polymethoxylated 4-aryl-2-quinolone may lead to the discovery of novel bioactive compounds. To this end, we selected the C4 aryl groups, C3 substituents, and *N*-benzyl groups as the diversifying points, because the reported bioactive compounds show considerable diversities in these substituents as shown in Figure 1.

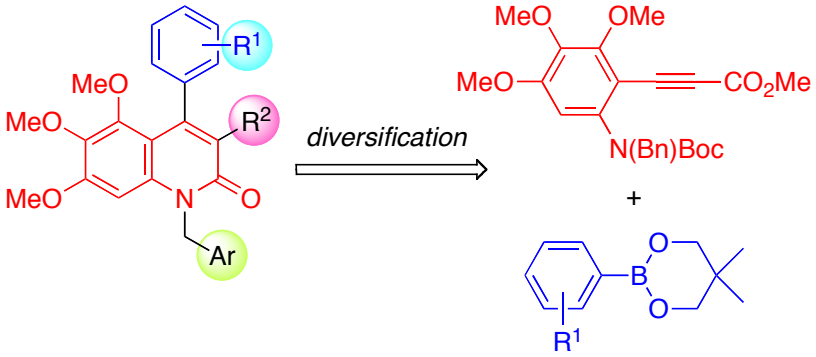


Figure 2. Divergent synthesis of polymethoxy 4-aryl-2-quinolone.

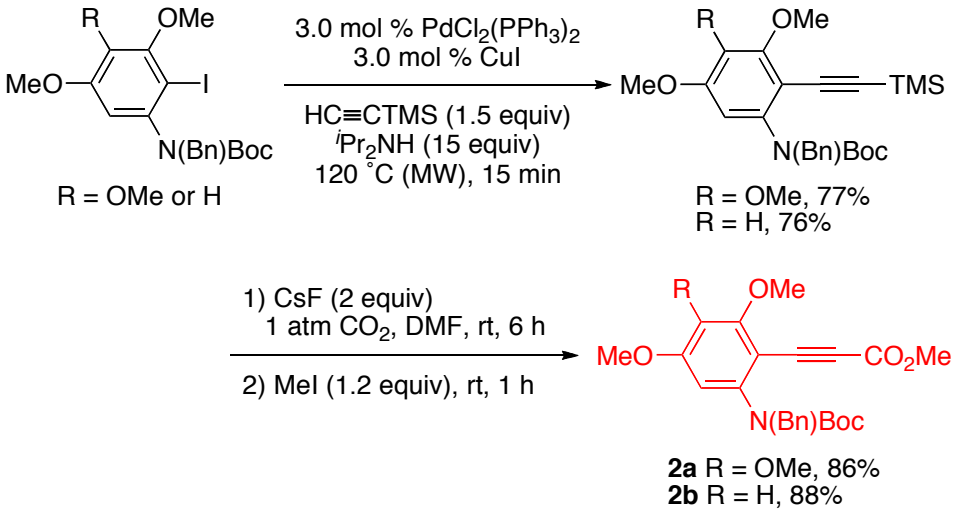
To exemplify this strategy, it is essential to efficiently install aryl groups at the C4 position of a polymethoxylated quinolone core. Previously, we reported the modular synthesis of 4-aryl-2-quinolones *via* the Cu-catalyzed hydroarylation of (*o*-aminophenyl)propiolates with arylboronates and subsequent deprotection/lactam formation.[7] This method enabled the synthesis of diverse 4-aryl-2-quinolones including a hepatitis B virus inhibitor.[2f] However, a serious drawback was observed when this method was applied to the 4-methoxyaniline-derived propiolate substrate: 6-methoxy-4-aryl-2-quinolones were obtained in low-to-moderate yields when using

p-substituted phenylboronates. Since this inefficiency can be ascribed to the diminished electrophilicity of the propiolate due to the electron-donating effect of the methoxy substituent, the synthesis of polymethoxylated analogs using this method seems to be a formidable challenge. Herein, we report the successful synthesis of polymethoxylated 4-aryl-2-quinolones and the diversity-oriented transformations of the product (Figure 2).

RESULTS AND DISCUSSION

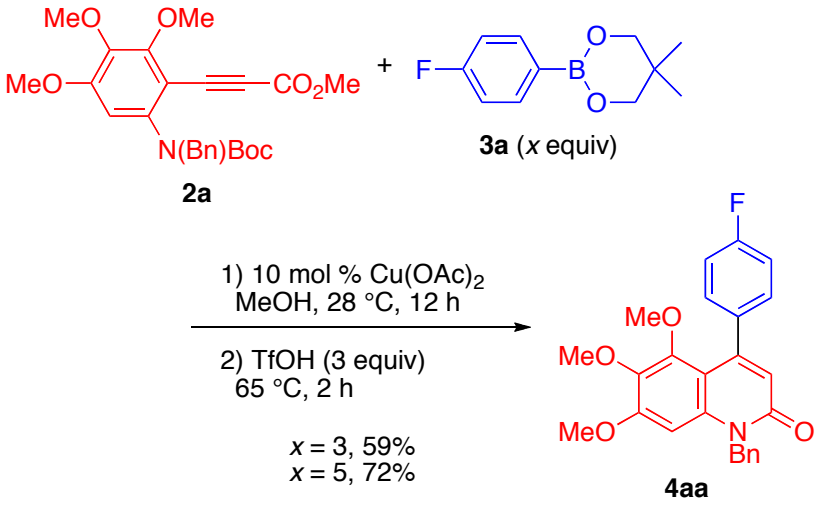
Syntheses of amyloid β fibrogenesis inhibitor 1 and natural product 6. First, the one-pot Cu-catalyzed hydroarylation/lactam formation was investigated using polymethoxylated (*o*-aminophenyl)propiolates **2a** and **2b** as the substrates. Propiolates **2a** and **2b** were prepared following the previously reported method (Scheme 1). Although harsh reaction conditions were required, the Sonogashira coupling of the corresponding polymethoxylated iodobenzenes with trimethylacetylene afforded the required silylalkyne precursors. The subsequent Kondo's carboxylation of the silylalkynes efficiently proceeded in DMF at room temperature to afford the desired propiolates **2a** and **2b** in high yields.[8]

Scheme 1. Preparation of polymethoxylated (*o*-aminophenyl)propiolates **2a** and **2b**.



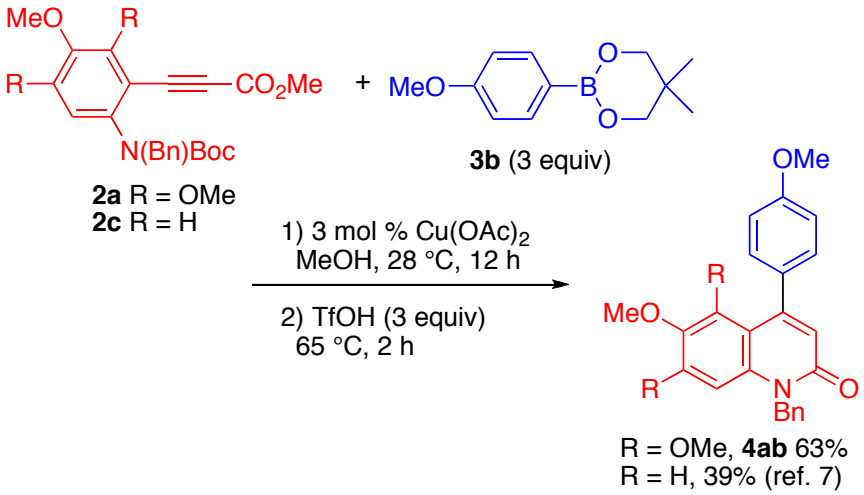
According to our previously established procedure,[7] the hydroarylation of **2a** with 3 equiv of *p*-fluorophenylboronate **3a** was carried out in the presence of $Cu(OAc)_2$ in MeOH at 28 °C for 12 h (Scheme 2). To ensure high conversion, the Cu catalyst loading was increased to 10 mol %. Then, the Boc group was removed by adding TfOH (3 equiv) to the same pot and stirring the reaction mixture at 65 °C for 2 h. The desired benzyl-protected 2-quinolone **4aa** was obtained in 59% yield. Gratifyingly, the yield further increased to 72% when the loading of **2a** was increased to 5 equiv.

Scheme 2. Synthesis of 4-aryl-2-quinolone **4aa** from **2a** and **3a**.



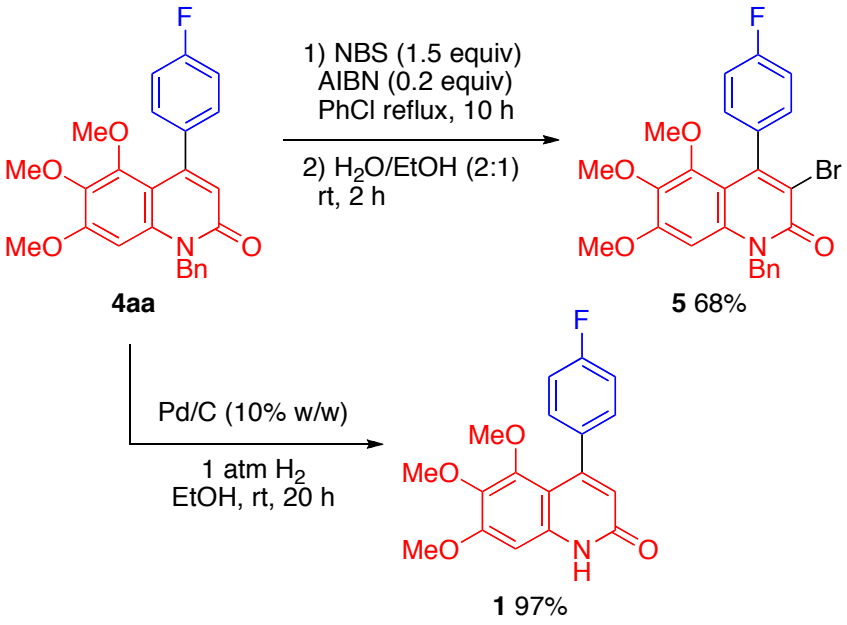
Accordingly, **2a** was exemplified to be a good substrate for the 4-aryl-2-quinolone synthesis as opposed to our initial anticipation that the multiple substitution with electron-donating methoxy groups renders it much less reactive than previously reported (2-amino-5-methoxyphenyl)propiolate **2c**.[7] To compare the reactivity of **2a** and **2c**, the reaction of **2a** with *p*-anisylboronate **3b** was performed under the exactly same conditions previously reported (Scheme 3).[7] As a result, **4ab** was obtained in 63% yield, which is significantly higher than that for the reaction of **2c** with **3b** (39%).

Scheme 3. Hydroarylation/cyclization of propiolates **2a** and **2c** (ref. 7) with *p*-anisylboronate **3b**.



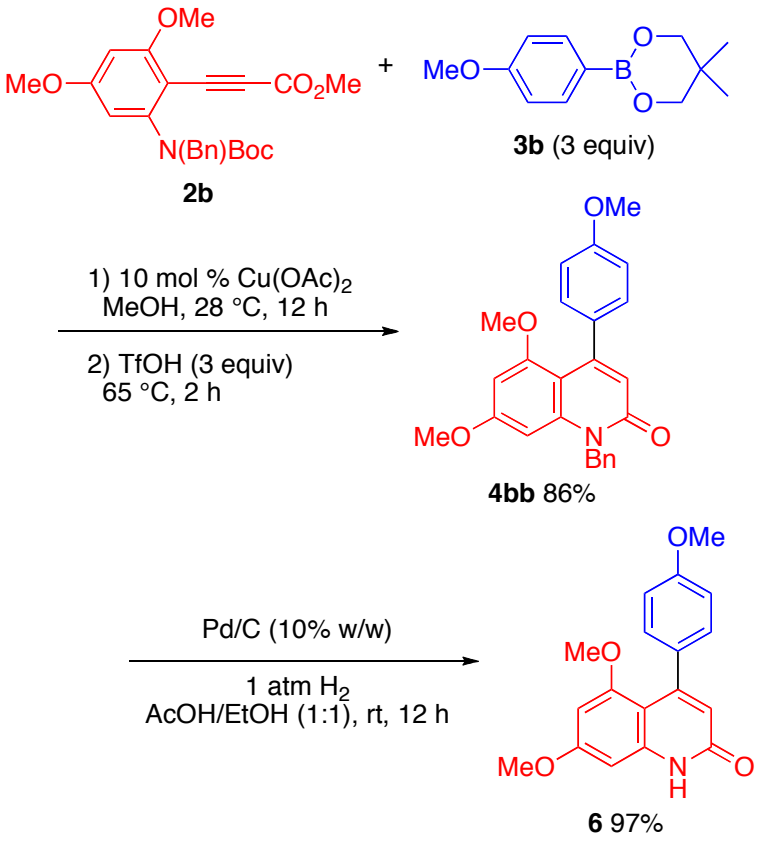
Then, **4aa** was debenzylated to obtain **1** under radical conditions as per a previous report (Scheme 4),[9] because we previously found that hydrogeneolysis using Pd/C was totally incompetent for *N*-benzyl-4-(*p*-chlorophenyl)-2(1*H*)-quinolone.[7] Thus, **4aa** was treated with *N*-bromosuccinimide (NBS, 1.5 equiv) in the presence of azobisisobutyronitrile (AIBN, 0.2 equiv) in chlorobenzene under reflux for 10 h, and the reaction mixture was then stirred at room temperature for another 2 h after adding H_2O/EtOH. However, C3-bromination product **5** was unexpectedly obtained in 68% yield. The formation of **5** can be attributed to the electrophilic dehydrobromination at the C3 position (*vide infra*). Next, the standard hydrogenolysis conditions (Pd/C, 1 atm H_2, EtOH, rt) were applied to **4aa**. The debenzylation proceeded for 20 h, affording the desired product **1** in 97% yield.

Scheme 4. Debenzylation of 4-aryl-2-quinolone **4aa**.



Having accomplished the synthesis of **1**, the synthesis of naturally occurring alkaloid **6** was attempted to evaluate if this method has general applicability. Alkaloid **6** has a characteristic substitution pattern: naturally occurring 2-quinolones generally contain oxygen functional groups at the C4 position, whereas **6** has a *p*-anisyl group at this position.[1a,10] The Cu-catalyzed hydroarylation of dimethoxylated substrate **2b** with *p*-anisylboronate **3b** (3.0 equiv) followed by the acidic removal of the Boc group afforded **4bb** in 86% yield (Scheme 5). Notably, 3.0 equiv of **3b** was enough to obtain a high yield of **4bb**, in contrast to the reaction of **2a** with **3a**. Because the debenzylation of **4bb** under hydrogenolysis conditions failed in EtOH, the debenzylation was conducted in a mixed solvent of AcOH/EtOH (1:1 v/v) for 12 h, affording the desired product **6** in 97% yield.

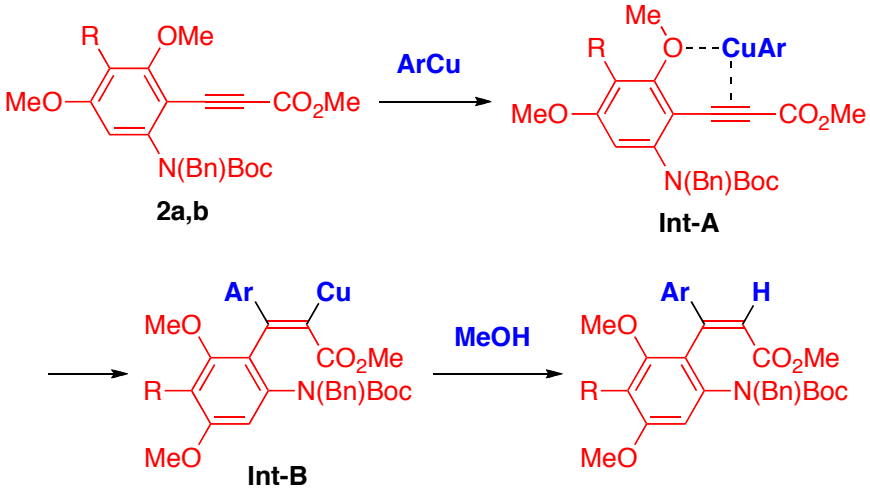
Scheme 5. Synthesis of alkaloid **6** from **2b** and **3b**.



As shown above, polymethoxylated phenylpropiolates **2a** and **2b** exhibited higher reactivity compared to monomethoxy analog **2c**, although the increased number of electron-donating methoxy substituents decreases the electrophilicity of **2a** and **2b**. In fact, the density functional theory calculations (see Supporting Information for details) showed that the LUMO level of **2a** (–0.07052 eV) and **2b** (–0.07021 eV) is higher than that of **2c** (–0.07814 eV). Therefore, the reason for the higher reactivity of **2a** and **2b** should be considered. Previously, we found that a propargylic methoxy group increases the reactivity of the propiolate substrate, resulting in the formation of multiple insertion products.[11] In this case, the chelate formation of vinylcopper intermediates with the

additional propiolate substrate was proposed as a cause. In a similar manner, the methoxy substituents at the 6 position of the aniline terminal of **2a** and **2b** possibly direct arylcopper species in close proximity to the alkyne, facilitating the carbocupuration (**Int-A** → **Int-B** in Scheme 6). Because the decrease in the electrophilicity owing to additional methoxy substituents was significantly compensated by this directing effect.

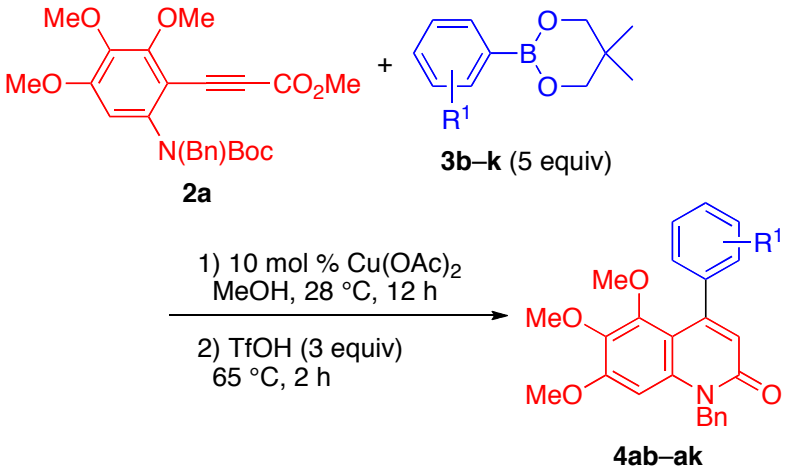
Scheme 6. Plausible methoxy-group-directed carbocupration of **2a** and **2b**.

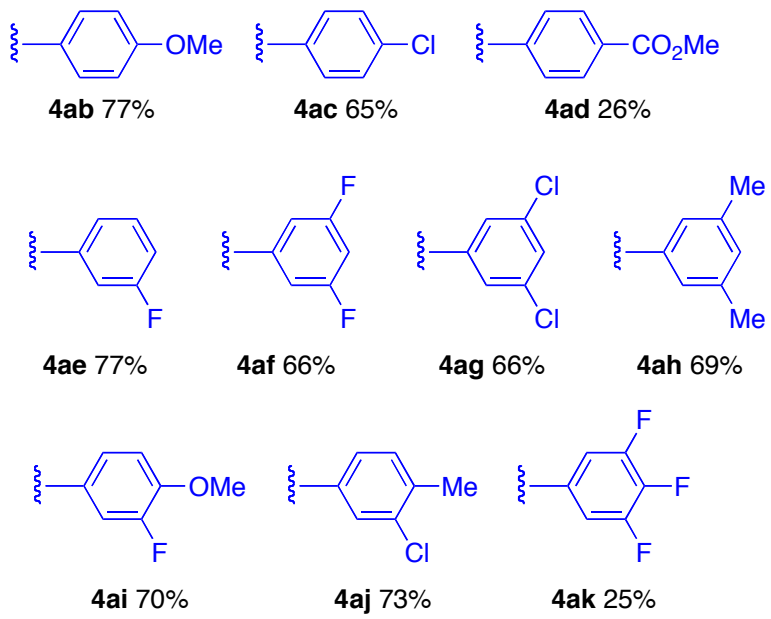


Divergent synthesis of the analogs of 1. The method was extended to the synthesis of polymethoxylated 4-aryl-2-quinolones, closely relevant to **1**. To this end, the one-pot Cu-catalyzed hydroarylation/lactam formation was investigated using **2a** with various arylboronates (Scheme 7). Consequently, the desired products **4ab**–**4ak**, possessing electron-donating and electron-withdrawing groups were obtained in 25–77% yields. Substitutions at the *para* and *metha* positions were allowed, although *o*-fluorophenylboronate did not afford the corresponding product. 3,4- or

3,5-Disubstituted phenylboronates could be used without significant lowering product yields. However, the reaction using *p*-(methoxycarbonyl)phenylboronate **3d** and 3,4,5-trifluorophenylboronate **3i** resulted in a low yield of **4ad** and **4ai**. It is reasoned that these electron-defficient arylboronates decrease efficiency of the reaction with less electrophilic propiolate **2a**.

Scheme 7. Synthesis of 4-aryl-2-quinolones **4ab**–**4ak**.

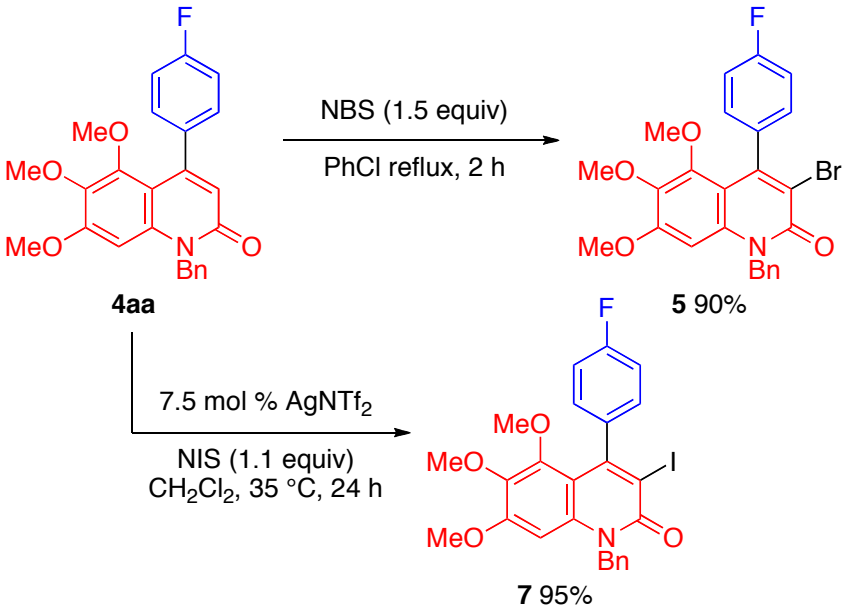




As described above, the debenzylation of **4aa** was attempted under the radical conditions, but the unexpected C3-bromination product **5** was obtained instead of **1** (Scheme 4). Because Csp^2–X bonds can be used for further derivatization *via* transition-metal-catalyzed cross-coupling reactions, the dehydrohalogenation of **4aa** was investigated in detail (Scheme 8). It was previously reported that dehydrobromination and

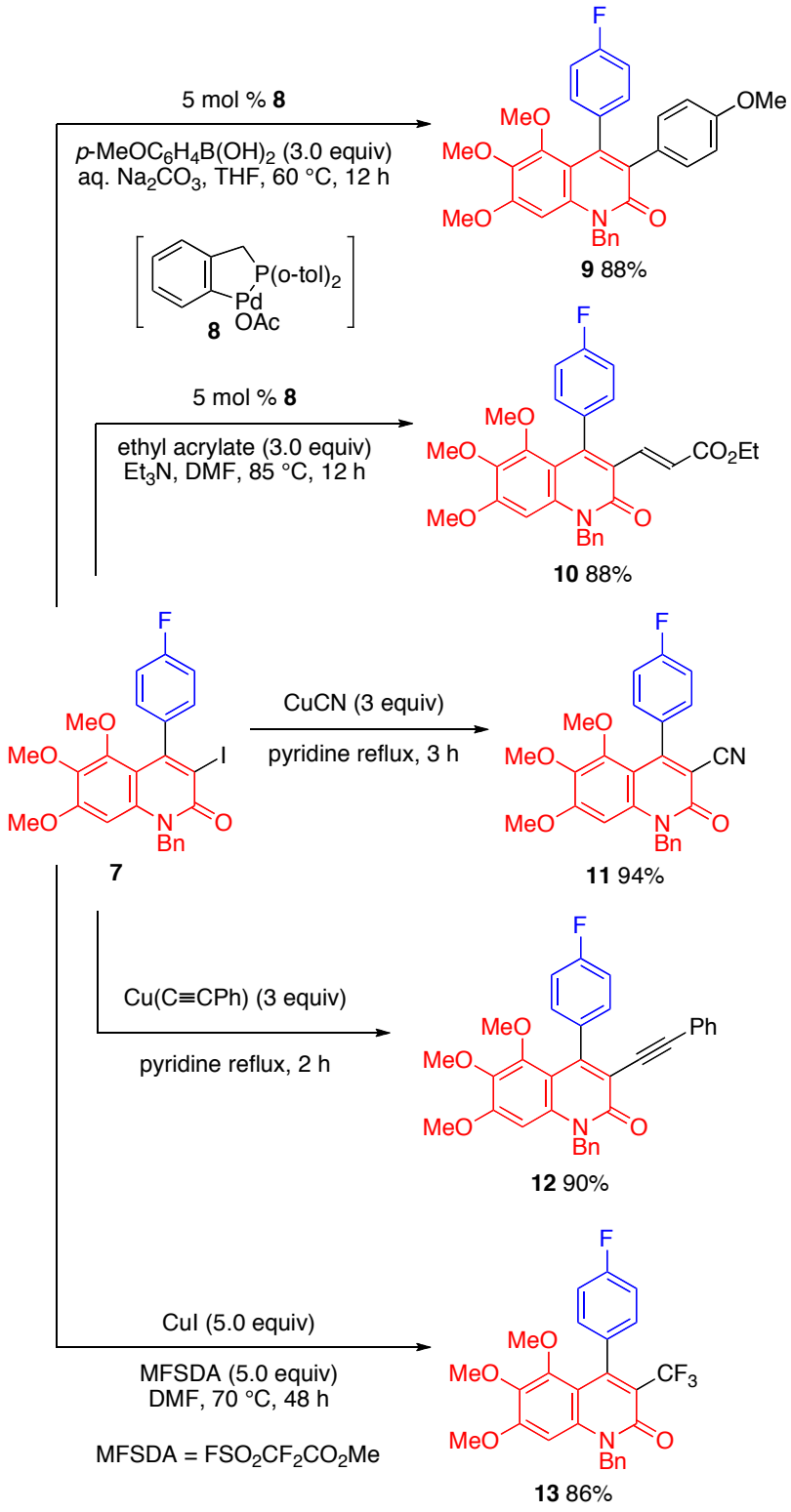
dehydrochlorination occurred at the C3 position of 2-quinolones under radical conditions.[12] On the other hand, it was also reported that the dehydrobromination of 4-phenyl-1-methyl-2-quinolone occurred at both the C3 and C6 positions in the absence of radical initiator AIBN.[13] In our hand, when **4aa** was treated with NBS (1.5 equiv) in the absence of AIBN, **5** was obtained as a single product with an improved yield of 90%. Because iodides are generally more reactive than the corresponding bromides in transition-metal-catalyzed cross-coupling reactions, the dehydroiodination of **4aa** was attempted using *N*-iodosuccinimide (NIS) under similar conditions. However, the corresponding iodination product was not obtained. This is because of the lower electrophilicity of NIS than NBS. Sutherland and co-workers recently reported the iodination of arenes with NIS in the presence of a catalytic amount of $AgNTf_2$. Thus, this catalytic method was applied to our 2-quinolone system. In the presence of 7.5 mol % $AgNTf_2$,[14] **4aa** was treated with 1.1 equiv of NIS in dichloromethane at 35 °C for 24 h, exclusively providing C3-iodination product **7** in 95% yield.

Scheme 8. Dehydrobromination and dehydroiodination of **4aa**.



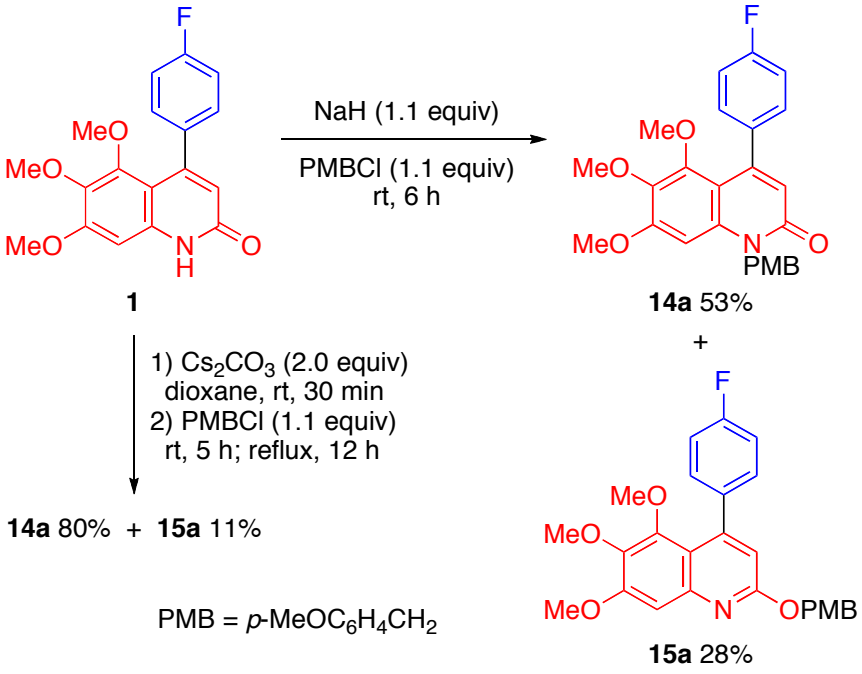
Further derivatizations of iodinated 2-quinolone **7** were conducted as summarized in Scheme 9. The Suzuki–Miyaura coupling[15] with *p*-anisylboronic acid and Mizoroki–Heck reaction[16] with ethyl acrylate were performed using the Herrmann's palladacycle catalyst (**8**),[17] affording 3-arylation product **9** and 3-olefination product **10** in 88% yields, respectively. On the other hand, **7** was treated with CuCN (3 equiv) or Cu(C≡CPh) (3 equiv) in pyridine at reflux for 3 h, affording 3-cyano-2-quinolone **11** and 3-alkynyl-2-quinolone **12** in high yields.[18] Moreover, Cu-mediated trifluoromethylation[19] was conducted using methyl difluoro(fluorosulfonyl)acetate (MFSDA), affording 3-trifluoromethyl-2-quinolone **13** in 86% yield. These high-yield syntheses of the C3-fuctionalized polymethoxylated derivatives of **1** well demonstrated the versatility of our diversification strategy.

Scheme 9. Coupling reactions of 3-iodo-2-quinolone **7**.

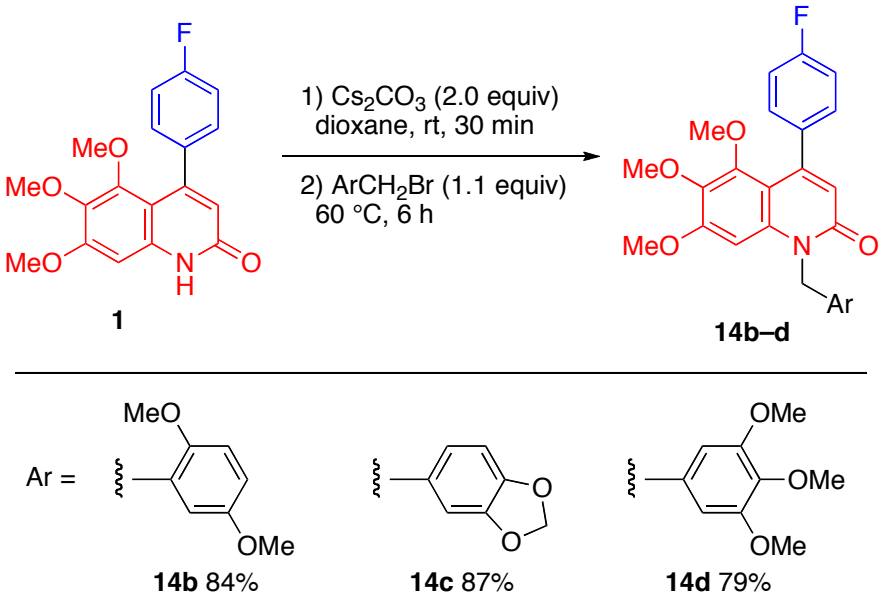


Finally, the selective *N*-benzylation of **1** was investigated to synthesize the corresponding derivative possessing a polyoxygenated *N*-benzyl group (Scheme 10). It is known that the benzylation of 2-quinolones produces the corresponding *N*-benzylation products along with *O*-benzylation products with different selectivity depending on the reaction conditions.[20] In fact, when **1** was treated with 1.1 equivs of NaH and *p*-methoxybenzyl chloride (PMBCl) in DMF at room temperature for 6 h, the desired 2-quinolone **14a** and quinoline byproduct **15a** were obtained in 53% and 28% yields, respectively. Thus, a method that selectively affords *N*-benzylation products was used.[21] The reaction of **1** with PMBCl (1.1 equiv) was performed in the presence of Cs_2CO_3 (2.0 equiv) in dioxane at room temperature. However, the reaction was sluggish; therefore, the reaction mixture was refluxed for 12 h. Thus, **14a** was selectively obtained in 80% yield along with reduced amounts of **15a** (11%). Similarly, the reaction of **1** with 2-(bromomethyl)-1,4-dimethoxybenzene (1.1 equiv) was performed at a lower temperature of 60 °C for 6 h, affording *N*-benzylation product **14b** in 84% yield (Scheme 11). The reactions using 5-(bromomethyl)benzo[*d*][1,3]dioxole and 5-(bromomethyl)-1,2,3-trimethoxybenzene also afforded *N*-benzylation products **14c** and **14d** in 87% and 79% yields, respectively. In these cases, the formation of the corresponding *O*-benzylation by-products was effectively suppressed (<10%).

Scheme 10. Selective benzylation of **1** with PMBCl



Scheme 11. Synthesis of **14b–d** via benzylation of **1**.



CONCLUSIONS

The divergent synthesis of polymethoxylated 4-aryl-2-quinolones was successfully achieved. First, amyloid β fibrogenesis inhibitor **1** and natural alkaloid **6** with polymethoxylated 2-quinolone cores were efficiently synthesized by one-pot Cu-catalyzed hydroarylation/lactam formation and subsequent debenzylation. The one-pot hydroarylation/lactam formation was carried out using various arylboronates, affording the derivatives of *N*-benzylated **1** and **6**, possessing different aryl groups at the C4 position.

Then, the diversification of **1** afforded diverse derivatives. The Ag-catalyzed dehydroiodination of *N*-benzylated **1** produced the C3-iodination product, and subsequent palladium-catalyzed cross-coupling reactions such as Suzuki–Miyaura coupling and Mizoroki–Heck reaction, and Cu-mediated cyanation, alkynylation, and trifluoromethylation reactions afforded the corresponding C3-functionalized derivatives of **1**. The selective *N*-benzylation of **1** also afforded several analogs of **1**, possessing polyoxygenated *N*-benzyl groups in high yields.

EXPERIMENTAL SECTION

General. Column chromatography was performed on silica gel (Cica silica gel 60N) with solvents specified below. ^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained for samples in $CDCl_3$ solutions at 25 °C. ^{1}H NMR chemical shifts are reported in terms of chemical shift (δ, ppm) relative to the singlet at 7.26 ppm for chloroform. ^{19}F NMR spectra are reported in terms of chemical shift (δ, ppm) relative to the singlet at δ –63.7 ppm for α,α,α-trifluorotoluene as an external standard. Splitting patterns are designated as follows:

s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; sept, septet; m, multiplet. Coupling constants are reported in Hz. ^{13}C NMR spectra were fully decoupled and are reported in terms of chemical shift (δ, ppm) relative to the triplet at δ 77.0 ppm for $CDCl_3$. High resolution mass spectra (HRMS) were obtained on a ESI-TOF mass spectrometer. Dry solvents were purchased and used as received. Microwave-heating experiments were carried out with a single-mode microwave reactor (CEM Discover Lab-Mate). Closed reaction vessels were used, and the temperature was monitored by an online IR detector.

Preparation of (*o*-Aminophenyl)propiolates 2

Representative procedure for protection of anilines – Synthesis of *tert*-butyl 3,4,5-trimethoxyphenylcarbamate:[22] In a flask, a solution of 3,4,5-trimethoxyaniline (1.73 g, 9.5 mmol) in di-*t*-butyl dicarbonate (3.5 mL, 3.31g, 15.2 mmol) was heated at 90 °C for 3 h. After cooled to room temperature, the reaction mixture was concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 4:1~2:1) to afford *tert*-butyl 3,4,5-trimethoxyphenylcarbamate (2.44 g, 91%) as an white solid (mp 149.4-153.2 °C, lit[22] mp 151–153 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 6.65 (s, 2 H), 6.40 (br s, 1 H), 3.85 (s, 6 H), 3.80 (s, 3 H) 1.51 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 153.4, 152.7, 134.5, 133.7, 96.1, 80.5, 61.0, 56.1, 28.3.

***tert*-Butyl 3,5-dimethoxyphenylcarbamate:**[23] The title compound was similarly prepared from 3,5-dimethoxy-2-aniline; 2.48 g, 98%; white solid (mp 81.2–82.3 °C, lit[23]

mp 75–76 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 6.59 (d, J = 2.0 Hz, 2 H), 6.43 (br s, 1 H), 6.16 (t, J = 2.0 Hz, 1 H), 3.77 (s, 6 H), 1.51 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.1, 152.5, 140.2, 96.6, 95.5, 80.5, 55.3, 28.3.

Synthesis of *tert*-butyl 2-iodo-3,4,5-trimethoxyphenylcarbamate: The title compound was prepared according to the report.[24] To a solution of *tert*-butyl 3,4,5-trimethoxyphenylcarbamate (1.04 g, 3.68 mmol) in chloroform (110 mL) was added iodine (1.03 g, 11.0 mmol) and grinded silver trifluoroacetate (2.44 g, 0.19 mmol) at room temperature. The reaction mixture was stirred at room temperature for 8 h. Insoluble materials were filtered off and rinsed with chloroform (10 mL), and the filtrate was concentrated in vacuo. The obtained crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford *tert*-butyl 2-iodo-3,4,5-trimethoxyphenylcarbamate (1.12 g, 80%) as a white solid (mp 135.6–136.4 ˚C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.66 (s, 1 H), 6.89 (s, 1 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.81 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 154.1, 152.8, 152.7, 137.7, 135.2, 99.8, 80.9, 76.2, 61.0, 60.8, 56.1, 28.3; IR (neat) 3392 (N–H), 1730 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{20}INO_5$•Na 432.0284, found 432.0282 $[M+Na]^+$.

Synthesis of *tert*-butyl 2-iodo-3,5-dimethoxyphenylcarbamate: To a solution of *tert*-butyl 3,5-dimethoxyphenylcarbamate (126.4 mg, 0.50 mmol) in dichloromethane (1.0 mL) was added *N*-iodosuccinimide (123.4 g, 0.55 mmol) at room temperature. The reaction mixture was stirred at room temperature for 3 h. Then, the mixture was washed with H_2O (2 × 10 mL), brine (10 mL), and dried over Na_2SO_4. After concentration in vacuo, the

obtained crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 100:1) to afford *tert*-butyl 2-iodo-3,5-dimethoxyphenylcarbamate (81.6 mg, 43%) as a white solid (mp 129.0–129.7 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.52 (d, J = 2.4 Hz, 1 H), 7.10 (br s, 1 H), 6.18 (d, J = 2.4 Hz, 1 H), 3.842 (s, 3 H), 3.835 (s, 3 H), 1.53 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.6, 158.5, 152.5, 140.4, 96.5, 94.2, 80.9, 69.5, 56.3, 55.6, 28.3; IR (neat) 2974 (N–H), 1700 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{18}INO_4$•Na 402.0178, found 402.0177 $[M+Na]^+$.

Representative procedure for benzylation of *o*-iodoaniline – Synthesis of *tert*-butyl benzyl(2-iodo-3,4,5-trimethoxyphenyl)carbamate: To a solution of the *tert*-butyl 2-iodo-3,4,5-trimethoxyphenylcarbamate (1.09 g, 2.66 mmol) in DMF (13.3 mL) was added sodium hydride (60% oil, 0.21 g, 5.33 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. To the resultant mixture was added benzyl bromide (0.38 mL, 3.20 mmol). The reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. NH_4Cl (10 mL), and the mixture was extracted with AcOEt (3 × 30 mL). The combined organic layer was washed with water (2 × 20 mL), brine (10 mL), and dried over $MgSO_4$. After concentration in vacuo, the crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford *tert*-butyl benzyl(2-iodo-3,4,5-trimethoxyphenyl)carbamate (1.28 g, 96%) as a white solid (mp 85.4–86.0 °C): a mixture of two rotamers; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.55–7.00 (major+minor) (br m, 5 H), 6.21 (minor)/6.03 (major) (br s, 1 H), 5.33 (major)/5.22 (minor) (br d, J = 15 Hz, 1 H), 4.01 (minor)/3.97 (minor) (br d, J = 15 Hz, 1 H), 3.88 (minor)/3.85(major) (br s, 3 H), 3.88 (major)/3.83(minor) (br s, 3 H), 3.54 (minor)/3.50

(major) (br s, 3 H), 1.57 (minor)/1.39 (major) (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 154.1 (major)/153.8 (minor), 153.9 (minor)/153.42 (major), 153.35 (minor)/153.0 (major), 141.3 (minor)/141.1 (major), 139.8 (minor)/139.5 (major), 138.0 (minor)/137.9 (major), 129.1 (major)/128.5 (minor), 128.2 (major)/127.3 (minor), 110.3 (minor)/110.1 (major), 87.9 (major+minor), 80.9 (minor)/80.2 (major), 60.9 (minor)/60.8 (major), 55.7 (major+minor), 53.8 (minor)/52.4 (major), 28.4 (minor)/28.2 (major); IR (neat) 1702 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{26}INO_5$•Na 522.0753, found 522.0744 $[M+Na]^+$.

***tert*-Butyl benzyl(2-iodo-3,5-dimethoxyphenyl)carbamate:** The title compound was prepared from *tert*-butyl 2-iodo-3,5-dimethoxyphenylcarbamate using the above procedure; 1.70 g, 94%; white solid (mp 98.8–99.4 °C): a mixture of two rotamers; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.30–7.18 (major+minor) (br m, 5 H), 6.31 (minor+major) (br s, 1 H), 6.09 (minor)/5.90 (major) (br s, 1 H), 5.31 (minor)/4.00 (major) (d, J = 15 Hz, 1 H), 5.19 (minor)/4.04 (major) (d, J = 15 Hz, 1 H), 3.85 (major+minor) (br s, 3 H), 3.56 (minor)/3.54 (major) (br s, 3 H), 1.55 (minor)/1.38 (major) (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.0 (minor)/160.5 (major), 159.8 (minor)/159.4 (major), 154.2 (major)/153.9 (minor), 146.0 (minor)/145.7 (major), 138.2 (minor)/138.0 (major), 129.2 (major)/128.5 (minor), 128.2 (major)/127.3 (minor), 107.4 (major+minor), 98.4 (minor)/97.8 (major), 81.6 (minor)/81.4 (major), 80.9 (minor)/80.3 (major), 56.5 (major+minor), 55.4 (major+minor), 53.9 (minor)/52.5 (major), 28.5 (minor)/28.3 (major); IR (neat) 1700 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{24}INO_4$•Na 492.0648, found 492.0641 $[M+Na]^+$.

Representative procedure for Sonogashira coupling of *o*-iodoaniline – Synthesis of *tert*-butyl benzyl(3,4,5-trimethoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate: In a shield tube, to a solution of *tert*-butyl benzyl(2-iodo-3,4,5-trimethoxyphenyl)carbamate (499.1 mg, 1.0 mmol) and diisopropylamine (1.52 g, 15.0 mmol) in DMF (0.5 mL) was added $PdCl_2(PPh_3)_2$ (21.1 mg, 0.03 mmol), CuI (5.6 mg, 0.03 mmol) and trimethylsilylacetylene (207.0 μL, 1.50 mmol) at room temperature. The shield tube was irradiated with a microwave reactor (300 W output, 250 PSI) at 120 °C for 15 min. After adding sat. NH_4Cl (10 mL), the reaction mixture was extracted with AcOEt (3 × 20 mL). The combined organic layer was washed with water (20 mL), brine (10 mL), and dried over $MgSO_4$. After concentration in vacuo, the crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 10:1) to afford *tert*-butyl benzyl(3,4,5-trimethoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate (0.36 g, 77%) as a yellow oil; a mixture of two rotamers; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.32–7.18 (major+minor) (br m, 5 H), 6.21 (minor)/6.02 (major) (br s, 1 H), 5.23 (minor)/5.20 (major) (br s, 1 H), 4.26 (major)/4.23 (minor) (br s, 1 H), 3.98 (minor)/3.95 (major) (br s, 3 H), 3.80 (major+minor) (br s, 3 H), 3.63 (minor)/3.58 (major) (br s, 3 H), 1.51 (minor)/1.37 (major) (br s, 9 H), 0.25 (major+minor) (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 155.4 (minor)/155.0 (major), 154.7 (major)/154.5 (minor), 153.5 (minor)/153.1 (major), 141.0 (minor)/140.8 (major), 140.6 (major/minor), 138.5 (minor)/138.3 (major), 128.9 (major/minor), 128.1 (major/minor), 127.1 (major/minor), 110.0 (minor+major), 109.3 (minor)/108.9 (major), 101.8 (major/minor), 97.7(major/minor), 80.6 (minor)/79.8 (major), 61.1 (major+minor), 55.8 (major+minor), 53.9 (minor)/52.6 (major), 28.4 (minor)/28.2

(major), –0.1 (major+minor); IR (neat) 2154 (C≡C), 1704 (C=O), 1250 (Si–CH_3), 843 (Si–CH_3) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{35}NO_5Si$•Na 492.2182, found 492.2196 $[M+Na]^+$.

***tert*-Butyl benzyl(3,5-dimethoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate:** The title compound was prepared from *tert*-butyl benzyl(2-iodo-3,5-dimethoxyphenyl)carbamate using the above procedure; 0.51 g, 76%; yellow oil; a mixture of two rotamers; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.32–7.17 (major+minor) (br m, 5 H), 6.29 (major+minor) (br s, 1 H), 6.12 (minor)/5.89 (major) (br s, 1 H), 5.29 (minor)/5.25 (major) (br s, 1 H), 4.24 (major)/4.20 (minor) (br s, 1 H), 3.84 (major+minor) (s, 3 H), 3.63 (minor)/3.59 (major) (br s, 3 H), 1.50 (minor)/1.37 (major) (br s, 9 H), 0.26 (major+minor) (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.1 (minor)/161.5 (major), 160.4 (minor)/160.0 (major), 154.6 (major)/154.2 (minor), 146.8 (major+minor), 138.5 (minor)/138.2 (major), 128.7 (minor)/128.1 (major), 127.0 (major/minor), 106.6 (major+minor), 104.6 (minor)/104.4 (major), 101.7 (major+minor), 98.0 (major+minor), 97.5 (minor)/97.0 (major), 80.4 (minor)/79.7 (major), 55.9 (major+minor), 55.2 (major+minor), 53.7 (minor)/52.4 (major), 28.3 (minor)/28.2 (major), 0.0 (major+minor); IR (neat) 2153 (C≡C), 1703 (C=O), 1250 (Si–CH_3), 842 (Si–CH_3) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{33}NO_4Si$•Na 462.2077, found 462.2089 $[M+Na]^+$.

Representative procedure for carboxylation of silylalkyne – Synthesis of methyl 3-(6-(benzyl(*tert*-butoxycarbonyl)amino)-2,3,4-trimethoxyphenyl)propiolate (2a): In a flask, cesium fluoride (1.51 g, 9.9 mmol) was heated under vacuum at 120 °C for 1 h. The flask was filled with CO_2 and then with dry DMF (2.5 mL). To the resultant suspension

was added dropwise a solution of *tert*-butyl benzyl(3,4,5-trimethoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate (1.88 g, 5.0 mmol) in dry DMF (10 mL) at room temperature. The reaction mixture was stirred at room temperature for 6 h. After addition of methyl iodide (0.37 mL, 5.9 mmol), the stirring was continued at room temperature for another 1 h. The reaction was quenched with sat. NH_4Cl (20 mL) and the whole mixture was extracted with AcOEt (3 × 50 mL). The combined organic layer was washed with water (2 × 30 mL), brine (10 mL), and dried over $MgSO_4$. After concentration in vacuo, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 15:1) to yield propiolate **2a** (1.56 g, 86%) as a white solid (mp 82.6–84.8 °C): a mixture of two rotamers; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.32–7.18 (major+minor) (br m, 5 H), 6.27 (minor)/6.12 (major) (br s, 1 H), 5.40–4.20 (major+minor) (br m, 2 H), 3.99 (minor)/3.96 (major) (br s, 3 H), 3.82 (minor)/3.81 (major) (br s, 6 H), 3.65 (br s, 3 H), 1.53 (minor)/1.39 (major) (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 156.2 (major+minor), 155.7 (major+minor), 155.2 (major+minor), 154.3 (major+minor), 142.5 (major+minor) 141.7 (major+minor), 140.7 (major+minor), 138.1 (major+minor), 137.8 (major+minor), 128.9 (minor)/128.3 (major), 127.4 (major+minor), 108.8 (minor)/ 108.4 (major), 106.9 (major+minor), 87.0 (major/minor), 81.3 (minor)/80.6 (major), 61.7 (major+minor), 61.1 (major+minor), 55.9 (major+minor), 54.4 (major+minor), 53.2 (minor)/52.5 (major), 28.2 (major+minor); IR (neat) 2217 (C≡C), 1709 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{29}NO_7$•Na 478.1842, found 478.1828 $[M+Na]^+$.

Methyl

3-(2-(benzyl(*tert*-butoxycarbonyl)amino)-4,6-dimethoxyphenyl)propiolate (2b): The title compound was prepared from *tert*-butyl benzyl(3,5-dimethoxy-2-((trimethylsilyl)ethynyl)phenyl)carbamate using the above procedure; 226.1 mg, 88%; white solid (mp 99.6–100.8 °C); a mixture of two rotamers; ^{1}H NMR ($CDCl_3$, 400 MHz, 25 °C) δ 7.30–7.17 (br, 5 H), 6.31 (minor+major) (br s, 1 H), 6.18 (minor)/6.04 (major) (br s, 1 H), 5.22–4.38 (major+minor) (br m, 2 H), 3.84 (major+minor) (s, 3 H), 3.80 (major+minor) (s, 3 H), 3.67 (major+minor) (s, 3 H), 1.50 (minor)/1.40 (major) (br s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 163.3 (major+minor), 162.3 (major+minor), 154.6 (major+minor), 154.2 (major+minor), 148.6 (minor)/147.9 (major), 138.1 (minor)/137.7 (major), 128.8 (minor)/128.2 (major), 127.3 (major+minor), 106.3 (major+minor), 101.5 (major+minor), 97.3 (minor)/ 96.8 (major), 87.4 (major/minor), 81.3 (major+minor), 81.2 (minor)/80.6 (major), 56.1 (major+minor), 55.5 (major+minor), 54.3 (minor)/53.2 (major), 52.5 (major+minor), 28.2 (major+minor); IR (neat) 2214 (C≡C), 1706 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{27}NO_6$•Na 448.1736, found 448.1723 $[M+Na]^+$.

The ^{1}H NMR spectra for **2a** and **2b** were also obtained for samples in toluene-d_8 at 60 °C: **2a**: ^{1}H NMR (400 MHz, toluene-d_8, 60 °C) δ 7.23 (d, J = 7.2 Hz, 2 H), 7.07–6.95 (m, 3 H), 6.12 (s, 1 H), 4.78 (br s, 2 H), 3.78 (s, 3 H), 3.56 (s, 3 H), 3.38 (s, 3 H), 3.08 (s, 3 H), 1.46 (s, 9 H); **2b**: ^{1}H NMR (400 MHz, toluene-d_8, 60 °C) δ 7.27 (d, J = 7.2 Hz, 2 H), 7.08–6.92 (m, 3 H), 6.10 (br s, 1 H), 5.98 (s, 1 H), 4.85 (br s, 2 H), 3.38 (s, 3 H), 3.16 (s, 3 H), 3.10 (s, 3 H), 1.45 (s, 9 H).

Synthesis of 4-Aryl-2-quinolones

Representative procedure for one-pot hydroarylation/cyclization – Synthesis of 1-benzyl-5,7-dimethoxy-4-(4-methoxyphenyl)quinolin-2(1*H*)-one (4bb): To a solution of propiolate **2b** (127.8 mg, 0.30 mmol) in dry methanol (0.6 mL) was added *p*-methoxyphenylboronate **3b** (198.8 mg, 0.90 mmol) and $Cu(OAc)_2$ (5.44 mg, 0.03 mmol) at room temperature under an argon atmosphere. The mixture was degassed at –78 °C and stirred at 28 °C for 12 h. After addition of trifluoromethanesulfonic acid (79.0 μL, 0.90 mmol), the stirring was continued at 65 ˚C for another 2 h. The reaction was quenched with 10% NaOH (10 mL) and the whole mixture was extracted with AcOEt (3 × 20 mL). The combined organic layer was washed with brine (10 mL) and dried over $MgSO_4$. After concentration in vacuo, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford 2-quinolone **4bb** (103.9 mg, 86%) as a white solid (mp 142.3–144.2 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.35–7.23 (m, 5 H), 7.21 (m, 2 H), 6.90 (m, 2 H), 6.42 (s, 1 H), 6.41 (d, J = 2.4 Hz, 1 H), 6.17 (d, J = 2.4 Hz, 1 H), 5.57 (br s, 2 H), 3.87 (s, 3 H), 3.70 (s, 3 H), 3.42 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.3, 162.1, 159.0, 158.7, 150.3, 142.7, 136.7, 134.5, 128.8, 128.5, 127.2, 126.6, 119.2, 112.5, 105.6, 93.8, 92.3, 55.3, 55.2, 46.7; IR (neat) 1648 (C=O), 1606 (C=C) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{23}NO_4$•Na 424.1525, found 424.1513 $[M+Na]^+$.

4-Aryl-2-quinolones **4aa**–**4ak** were also synthesized according to the above procedure, except for using 5 equiv of arylboronates.

1-Benzyl-4-(4-fluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4aa): 90.1 mg, 72%; white solid (mp 147.5–150.9 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ

7.38–7.26 (m, 7 H), 7.08 (tt, J = 8.6, 2.4 Hz, 2 H), 6.59 (s, 1 H), 6.46 (s, 1 H), 5.58 (br s, 2 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0 (d, J = 244.1 Hz), 161.7, 155.8, 151.3, 149.1, 138.0, 137.3, 137.0 (d, J = 3.8 Hz), 136.5, 129.1 (d, J = 7.6 Hz), 129.0, 127.4, 126.7, 120.7, 114.1 (d, J = 21.9 Hz), 109.2, 94.6, 60.9, 60.7, 55.7, 46.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –115.18; IR (neat) 1653 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{22}FNO_4$•Na 442.1431, found 442.1421 $[M+Na]^+$.

1-Benzyl-5,6,7-trimethoxy-4-(4-methoxyphenyl)quinolin-2(1*H*)-one (4ab): 99.7 mg, 77%; white solid (mp 117.0–119.5 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.37–7.24 (m, 7 H), 6.93 (d, J = 8.8 Hz, 2 H), 6.59 (s, 1 H), 6.47 (s, 1 H), 5.58 (br s, 2 H), 3.87 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.9, 158.8, 155.6, 151.6, 150.0, 138.1, 137.4, 136.7, 133.5, 128.9, 128.8, 127.4, 126.7, 120.6, 112.6, 109.5, 94.6, 61.0, 60.9, 55.7, 55.3, 46.7; IR (neat) 1652 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{25}NO_5$•Na 454.1630, found 454.1631 $[M+Na]^+$.

1-Benzyl-4-(4-chlorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4ac): 85.0 mg, 65%; white solid (mp 103.5–106.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.40–7.24 (m, 9 H), 6.59 (s, 1 H), 6.44 (s, 1 H), 5.58 (br s, 2 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.7, 155.9, 151.3, 149.0, 139.7, 138.0, 137.4, 136.5, 133.0, 128.9, 128.8, 127.4, 126.7, 120.6, 109.0, 94.6, 60.9, 60.7, 55.8, 46.7; IR (neat) 1653 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{22}ClNO_4$•Na 458.1135, found 458.1133 $[M+Na]^+$.

1-Benzyl-4-[4-(methoxycarbonyl)phenyl]-5,6,7-trimethoxyquinolin-2(1*H*)-one (4ad): 35.5 mg, 26%; white solid (mp 152.5–154.6 °C); ^{1}H NMR (400 MHz, $CDCl_3$,

25 °C) δ 8.08 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 7.37–7.25 (m, 5 H), 6.59 (s, 1 H), 6.45 (s, 1 H), 5.59 (br s, 2 H), 3.96 (s, 3 H), 3.738 (s, 3 H), 3.735 (s, 3 H), 3.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 166.9, 161.7, 156.0, 151.2, 149.1, 146.1, 137.9, 137.4, 136.5, 128.9, 128.8, 128.7, 127.5, 127.4, 126.8, 120.2, 108.9, 94.6, 60.9, 60.6, 55.8, 52.1, 46.8; IR (neat) 1722 (C=O), 1653 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{25}NO_6$•Na 482.1580, found 482.1586 $[M+Na]^+$.

1-Benzyl-4-(3-fluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4ae): 96.6 mg, 77%; white solid (mp 114.0–116.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.39–7.27 (m, 6 H), 7.12–7.01 (m, 3 H), 6.59 (s, 1 H), 6.46 (s, 1 H), 5.58 (br s, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.8 (d, *J* = 244.1 Hz), 161.7, 155.9, 151.3, 148.7, 143.4 (d, *J* = 7.6 Hz), 138.0, 137.4, 136.5, 128.9, 128.8, 127.4, 126.7, 123.1 (d, *J* = 1.9 Hz), 120.4, 114.6 (d, *J* = 21.9 Hz), 113.9 (d, *J* = 21.0 Hz), 109.0, 94.5, 60.9, 60.7, 55.8, 46.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –114.22; IR (neat) 1652 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{22}FNO_4$•Na 442.1431, found 442.1435 $[M+Na]^+$.

1-Benzyl-4-(3,5-difluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4af): 87.0 mg, 66%; white solid (mp 60.0-63.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.38–7.26 (m, 5 H), 6.89–6.79 (m, 3 H), 6.58 (s, 1 H), 6.44 (s, 1 H), 5.57 (br s, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0 (dd, *J* = 247.0, 13.4 Hz), 161.5, 156.1, 151.0, 147.7, 144.5 (t, *J* = 10.1 Hz), 138.0, 137.4, 136.4, 128.9, 127.5, 126.7, 120.3, 110.6 (dd, *J* = 18.6, 7.2 Hz), 108.6, 102.4 (t, *J* = 24.8 Hz), 94.6, 60.9, 60.8, 55.8, 46.8; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –110.72; IR (neat) 1653 (C=O)

cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{21}F_2NO_4$•Na 460.1336, found 460.1331 $[M+Na]^+$.

1-Benzyl-4-(3,5-dichlorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4ag): 93.8 mg, 66%; white solid (mp 175.6–177.9 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.37 (t, *J* = 2.0 Hz, 1 H), 7.36–7.25 (m, 5 H), 7.22 (d, *J* = 2.0 Hz, 2 H), 6.57 (s, 1 H), 6.43 (s, 1 H), 5.57 (br s, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.36 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.5, 156.2, 151.0, 147.2, 144.1, 137.9, 137.4, 136.4, 133.9, 128.9, 127.5, 127.1, 126.7, 125.8, 120.4, 108.6, 94.6, 60.9, 60.7, 55.8, 46.8; IR (neat) 1654 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{21}Cl_2NO_4$•Na 492.0745, found 492.0760 $[M+Na]^+$.

1-Benzyl-4-(3,5-dimethylphenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4ah): 88.4 mg, 69%; white solid (mp 140.9–141.8 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.37–7.23 (m, 5 H), 6.99 (br s, 1 H), 6.93 (br s, 2 H), 6.57 (s, 1 H), 6.46 (s, 1 H), 5.58 (br s, 2 H), 3.74 (s, 3 H), 3.73 (s, 3 H), 3.28 (s, 3 H), 2.36 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.9, 155.6, 151.6, 150.6, 141.2, 138.0, 137.4, 136.7, 136.6, 128.9, 128.6, 127.4, 126.8, 125.1, 120.3, 109.5, 94.4, 60.85, 60.77, 55.7, 46.7, 21.3; IR (neat) 1652 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{27}NO_4$•Na 452.1838, found 452.1841 $[M+Na]^+$.

1-Benzyl-4-(3-fluoro-4-methoxyphenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4ai): 94.9 mg, 70%; yellow paste; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.37–7.23 (m, 5 H), 7.11–7.04 (m, 2 H), 6.98 (t, *J* = 8.4 Hz, 1 H), 6.58 (s, 1 H), 6.46 (s, 1 H), 5.58 (br s, 2 H), 3.95 (s, 3 H), 3.76 (s, 3 H), 3.73 (s, 3 H), 3.29 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.8, 155.8, 151.4, 151.2 (d, *J* = 244.1 Hz), 148.7, 146.8 (d, *J* = 11.4 Hz), 138.1, 137.4, 136.6, 134.1 (d, *J* = 7.6 Hz), 128.9, 127.4, 126.7, 123.3 (d, *J* = 3.8 Hz), 120.8, 115.9 (d, *J* = 19.1 Hz), 112.2, 109.1, 94.6, 61.0, 60.9, 56.3, 55.8, 46.7; ^{19}F NMR (376 MHz,

$CDCl_3$, 25 °C) δ –136.59; IR (neat) 1652 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{24}FNO_5$•Na 472.1536, found 472.1540 $[M+Na]^+$.

1-Benzyl-4-(3-chloro-4-methylphenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (4aj): 98.6 mg, 73%; yellow paste; ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.39–7.23 (m, 7 H), 7.12 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.58 (s, 1 H), 6.44 (s, 1 H), 5.58 (br s, 2 H), 3.75 (s, 3 H), 3.73 (s, 3 H), 3.30 (s, 3 H), 2.44 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.8, 155.9, 151.4, 148.7, 140.3, 138.0, 137.4, 136.6, 134.7, 133.2, 129.8, 128.9, 127.9, 127.4, 126.8, 125.7, 120.6, 109.1, 94.6, 60.9, 60.8, 55.8, 46.7, 19.8; IR (neat) 1652 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{24}ClNO_4$•Na 472.1292, found 472.1305 $[M+Na]^+$.

1-Benzyl-5,6,7-trimethoxy-4-(3,4,5-trifluorophenyl)quinolin-2(1*H*)-one (4ak): 34.2 mg, 25%; white solid (mp 114.8–118.5 °C); ^1H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.38–7.26 (m, 5 H), 6.96 (dd, *J* = 7.6, 6.4 Hz, 2 H), 6.58 (s, 1 H), 6.43 (s, 1 H), 5.57 (br s, 2 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.4, 156.2, 151.0, 150.3 (ddd, *J* = 248.9, 10.5, 3.8 Hz), 146.9, 138.9 (dt, *J* = 249.8, 15.3 Hz) 138.0, 137.4, 137.2 (dt, *J* = 8.1, 4.7 Hz), 136.3, 128.9, 127.5, 126.7, 120.6, 111.8 (dd, *J* = 16.2, 6.6 Hz), 108.4, 94.7, 60.9, 60.8, 55.8, 46.8; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –135.30 (d, *J* = 22.9 Hz), –162.28 (t, *J* = 22.9 Hz); IR (neat) 1653 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{20}F_3NO_4$•Na 478.1242, found 478.1235 $[M+Na]^+$.

Procedure for debenzylation of 4aa – Synthesis of 4-(4-fluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (1): A suspension of **4aa** (46.4 mg, 0.11 mmol) and $Pd(OH)_2/C$ (4.66 mg, 10 g/w%) in ethanol (0.55 mL) was stirred at room temperature under H_2 for 20 h. The reaction completion was checked by TLC

analysis. The reaction mixture was filtered through a pad of Celite® and washed with dichloromethane (20 mL). The filtrate was concentrated in vacuo to afford 2-quinolone **1** (35.4 mg, 97%) as a white solid (mp 276.3–278.0 °C, lit[6] mp 282–283 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 12.4 (brs, 1 H), 7.31 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.09 (t, *J* = 8.8 Hz, 2 H), 6.71 (s, 1 H), 6.35 (s, 1 H), 3.98 (s, 3 H), 3.80 (s, 3 H), 3.28 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 163.8, 162.1 (d, *J* = 245.1 Hz), 156.7, 151.5, 150.8, 138.7, 137.0, 136.9 (d, *J* = 15.2 Hz), 129.3 (d, *J* = 30.4 Hz), 120.1, 114.2 (d, *J* = 84.0 Hz), 108.4, 94.5, 61.1, 60.7, 56.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –114.87; IR (neat) 2929 (NH), 1657 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{16}FNO_4$•Na 352.0961, found 352.0951 $[M+Na]^+$.

Procedure for debenzylation of 4bb – Synthesis of 5,7-dimethoxy-4-(4-methoxyphenyl)quinolin-2(1*H*)-one (6): A suspension of **4bb** (40.1 mg, 0.10 mmol) and $Pd(OH)_2$/C (4.06 mg, 10 g/w%) in ethanol (0.50 mL) and acetic acid (0.50 mL) was stirred at room temperature under H_2 for 12 h. The reaction completion was checked by TLC analysis. The reaction mixture was filtered through a pad of Celite® and washed with dichloromethane (20 mL). The filtrate was concentrated in vacuo, the crude material was purified by flash column chromatography on silica gel (chloroform /methanol = 10:1) to afford 2-quinolone **6** (30.1 mg, 97%) as a white solid (mp 289.1–290.2 °C). The following spectral data are in good accordance with those previously reported:[6] ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C) δ 11.63 (br s, 1 H), 7.18–7.13 (m, 2 H), 6.93–6.88 (m, 2 H), 6.52 (d, *J* = 2.4 Hz, 1 H), 6.26 (d, *J* = 2.4 Hz, 1 H), 5.89 (s, 1 H), 3.79 (s, 3 H) 3.78 (s, 3 H), 3.39 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) δ 161.9,

161.2, 158.4, 158.1, 150.8, 142.3, 133.7, 128.6, 119.1, 112.4, 103.4, 93.8, 91.2, 55.34, 55.32 55.0; IR (KBr) 1659 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{18}H_{17}NO_4$•Na 334.1055, found 334.1053 $[M+Na]^+$.

Procedure for dehydrobromination of 4aa – Synthesis of 1-benzyl-3-bromo-4-(4-fluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (5): To a solution of **4aa** (84.0 mg, 0.20 mmol) in dry chlorobenzene (1.0 mL) was added NBS (42.1 mg, 0.24 mmol) at room temperature under an argon atmosphere. The mixture was stirred at reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The obtained crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to afford 3-bromo-2-quinolone **5** (89.3 mg, 90%) as a white solid (mp 186.4–188.9 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.39–7.26 (m, 5 H), 7.21-7.13 (m, 4 H), 6.61 (s, 1 H), 5.66 (br s, 2 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.9 (d, *J* = 245.0 Hz), 158.5, 155.9, 150.9, 148.3, 138.4, 137.8 (d, *J* = 3.8 Hz), 136.2, 136.0, 129.0, 128.7 (d, *J* = 7.6 Hz), 127.7, 126.9, 118.6, 114.9 (d, *J* = 21.9 Hz), 110.0, 94.3, 60.8, 60.7, 55.8, 48.8; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –114.84; IR (neat) 1644 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{21}BrFNO_4$•Na 520.0536, found 520.0521 $[M+Na]^+$.

Procedure for dehydroiodination of 4aa – Synthesis of 1-benzyl-4-(4-fluorophenyl)-3-iodo-5,6,7-trimethoxyquinolin-2(1*H*)-one (7): The iodination of **4aa** was performed according to the reported procedure.[14] To a solution of **4aa** (84.3 mg, 0.20 mmol) in dichloromethane (2.0 mL) was added NIS (49.6 mg, 0.22 mmol) and $AgNTf_2$ (5.9 mg, 0.08 mmol) at room temperature under air. The mixture was

stirred at 35 °C for 12 h. The reaction completion was checked by TLC analysis. After cooled to room temperature, the reaction was quenched with sat. $NaHCO_3$ (5 mL) and the whole mixture was extracted with dichloromethane (3 × 10 mL). The combined organic layer was washed with sat. Na_2SO_3 (5 mL) and brine (10 mL), and dried over Na_2SO_4. After concentration *in vacuo*, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 2:1) to afford 3-iodo-2-quinolone **7** (104.2 mg, 95%) as a white solid (mp 211.4–215.2 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.39–7.27 (m, 5 H), 7.17 (tt, *J* = 8.4, 2.4 Hz, 2 H), 7.16–7.10 (m, 2 H), 6.61 (s, 1 H), 6.46 (s, 1 H), 5.67 (br s, 2 H), 3.74 (s, 3 H), 3.71 (s, 3 H), 3.22 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.9 (d, *J* = 245.0 Hz), 159.3, 156.2, 153.5, 150.6, 142.0 (d, *J* = 3.8 Hz), 138.1, 136.8, 136.3, 129.0, 128.7 (d, *J* = 8.6 Hz), 127.6, 126.9, 114.9 (d, *J* = 21.0 Hz), 110.5, 101.6, 94.1, 60.8, 60.7, 55.8, 49.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –114.68; IR (neat) 1636 (C=O), 1602 (C=C) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{21}FINO_4$•Na 568.0397, found 568.0387 $[M+Na]^+$.

Procedure for Suzuki–Miyaura coupling of 7 – Synthesis of 1-benzyl-4-(4-fluorophenyl)-5,6,7-trimethoxy-3-(4-methoxyphenyl)quinolin-2(1*H*)-one (9): To a solution of **7** (109.6 mg, 0.20 mmol) in dry THF (1.0 mL) and aq. Na_2CO_3 (1 M, 1 mL, 1 mmol) was added *p*-methoxyphenylboronic acid (91.7 mg, 0.60 mmol) and Pd catalyst **8** (8.95 mg, 0.01 mmol) at room temperature under an argon atmosphere. The mixture was degassed at –78 °C and stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature and diluted by AcOEt (5 mL). The whole mixture was extracted with AcOEt (3 × 10 mL). The combined organic layer was washed with brine (10

mL), and dried over $MgSO_4$. After concentration in vacuo, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford 3,4-diaryl-2-quinolone **9** (93.1 mg, 88%) as a white solid (mp 200.4–204.2 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.41–7.26 (m, 5 H), 7.03 (dd, *J* = 8.8, 5.6 Hz, 2 H), 6.95 (dt, *J* = 8.8, 2.4 Hz, 2 H), 6.87 (tt, *J* = 8.8, 2.8 Hz, 2 H), 6.70 (dt, *J* = 8.4, 2.4 Hz, 2 H), 6.65 (s, 1 H), 5.62 (br s, 2 H), 3.77 (s, 3 H), 3.73 (s, 6 H), 3.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0, 161.1 (d, *J* = 243.1 Hz), 158.0, 155.3, 151.8, 145.6, 138.2, 136.8, 136.6, 136.1 (d, *J* = 2.9 Hz), 131.8, 130.8, 130.0 (d, *J* = 7.6 Hz), 128.8, 128.3, 127.4, 127.0, 113.8 (d, *J* = 21.9 Hz), 113.0, 109.7, 94.3, 60.8, 60.7, 55.7, 55.0, 47.6; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –116.31; IR (neat) 1634 (C=O), 1605 (C=C) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{32}H_{28}FNO_5$•Na 548.1849, found 548.1846 $[M+Na]^+$.

Procedure for Mizoroki–Heck reaction of 7 – Synthesis of (*E*)-ethyl 3-(1-benzyl-4-(4-fluorophenyl)-5,6,7-trimethoxy-2-oxo-1,2-dihydroquinolin-3-yl)acrylate (10): To a solution of 3-iodo-2-quinolone **7** (110.3 mg, 0.20 mmol) in dry DMF (1.0 mL) was added triethylamine (70 μL, 0.50 mmol), Pd catalyst **8** (9.03 mg, 0.01 mmol) and ethyl acrylate (66 μL, 0.60 mmol) at room temperature under an argon atmosphere. The mixture was degassed at –78 °C and stirred at 85 °C for 12 h. The reaction mixture was cooled to room temperature and quenched by H_2O (5 mL). The whole mixture was extracted with AcOEt (3 × 10 mL). The combined organic layer was washed with H_2O (2 × 10 mL) and brine (10 mL), and dried over Na_2SO_4. After concentration in vacuo, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to afford 3-alkenyl-4-aryl-2-quinolone **10** (91.9 mg, 88%) as a yellow solid (mp 173.0–

177.6 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.40–7.27 (m, 6 H), 7.21–7.12 (m, 5 H), 6.57 (s, 1 H), 5.63 (br s, 2 H), 4.12 (q, *J* = 6.8 Hz, 2 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.22 (s, 3 H), 1.21 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 168.0, 161.9 (d, *J* = 245.0 Hz), 160.7, 156.8, 152.2, 149.9, 138.4, 138.3, 136.9, 136.4, 135.3 (d, *J* = 3.8 Hz), 129.2 (d, *J* = 7.6 Hz), 129.0, 127.5, 126.7, 123.0, 122.0, 114.9 (d, *J* = 21.0 Hz), 109.7, 94.0, 60.74, 60.70, 60.0, 55.8, 47.4, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –114.65; IR (neat) 1706 (C=O), 1647 (C=O), 1602 (C=C) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{28}FNO_6$•Na 540.1798, found 540.1793 $[M+Na]^+$.

Procedure for cyanation of 7 – Synthesis of 1-benzyl-4-(4-fluorophenyl)-5,6,7-trimethoxy-3-(cyano)quinolin-2(1*H*)-one (11): To a solution of **7** (109.2 mg, 0.20 mmol) in pyridine (1.0 mL) was added copper(I) cyanide (53.8 mg, 0.60 mmol) at room temperature under an argon atmosphere. The mixture was stirred at reflux for 3 h. The reaction mixture was cooled to room temperature and diluted with AcOEt (20 mL). The whole mixture was washed with 10% HCl (10 mL), 10% NaOH (10 mL), and brine (10 mL), and dried over $MgSO_4$. After concentration in vacuo, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to afford **11** (83.9 mg, 94%) as a yellow solid (mp 198.2–200.0 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.40–7.28 (m, 7 H), 7.18 (*t*, J = 8.6 Hz, 2 H), 6.59 (s, 1 H), 5.59 (br s, 2 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.6 (d, *J* = 246.0 Hz), 159.0, 158.8, 157.3, 152.3, 138.6, 138.4, 135.5, 134.1 (d, *J* = 3.8 Hz), 129.1, 128.6 (d, *J* = 7.7 Hz), 127.9, 126.9, 115.1 (d, *J* = 22.0 Hz), 108.6, 105.4, 94.4, 60.9 (2 C), 56.0, 47.5; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –112.81; IR (neat) 2225 (C≡N), 1649

(C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{21}FN_2O_4$•Na 467.1383, found 467.1396 $[M+Na]^+$.

Synthesis of 1-benzyl-4-(4-fluorophenyl)-5,6,7-trimethoxy-3-(phenylethynyl)quinolin-2(1*H*)-one (12): In a similar manner as above, **7** (109.6 mg, 0.20 mmol) was treated with phenylethynyl copper(I) (99.3 mg, 0.60 mmol) in pyridine (1.0 mL) at reflux for 3 h to afford **12** (94.4 mg, 90%) as a white solid (mp 231.6–233.8 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.38–7.12 (m, 14 H), 6.61 (s, 1 H), 5.64 (br s, 2 H), 3.76 (s, 3 H), 3.74 (s, 3 H), 3.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 161.9 (d, *J* = 244.1 Hz), 160.1, 156.2, 151.3, 150.9, 138.4, 136.7 (d, *J* = 3.9 Hz), 136.5, 136.4, 131.5, 129.4 (d, *J* = 8.6 Hz), 128.9, 128.1, 128.0, 127.5, 126.9, 123.2, 115.0, 114.3 (d, *J* = 21.9 Hz), 109.7, 98.9, 94.4, 85.7, 60.8, 60.7, 55.8, 47.7; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –115.48; IR (neat) 1635 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{26}FNO_4$•Na 542.1744, found 542.1755 $[M+Na]^+$.

Procedure for trifluoromethylation of 7 – Synthesis of 1-benzyl-4-(4-fluorophenyl)-5,6,7-trimethoxy-3-(trifluoromethyl)quinolin-2(1*H*)-one (13): The trifluoromethylation of **7** was performed according to the reported procedure.[19] To a solution of 3-iodo-2-quinolone **7** (108.9 mg, 0.20 mmol) in dry DMF (1.0 mL) was added CuI (190.3 mg, 1.00 mmol) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (126.2 μL, 1.00 mmol) at room temperature under an argon atmosphere. The mixture was degassed at –78 °C and stirred at 70 °C for 48 h. The reaction mixture was cooled to room temperature and insoluble materials were filtered off. The filtrate was concentrated in

vacuo, and the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 3:1) to afford 4-aryl-3-trifluoromethyl-2-quinolone **13** (83.5 mg, 86%) as a white solid (mp 206.3–211.1 °C): ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.40–7.19 (m, 7 H), 7.10 (tt, *J* = 8.4, 2.4 Hz, 2 H), 6.57 (s, 1 H), 5.60 (br s, 2 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 3.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0 (d, *J* = 244.1 Hz), 158.5, 157.7, 153.3, 150.4, 138.6, 137.8, 136.0, 134.1 (d, *J* = 3.9 Hz), 129.0, 128.4 (d, *J* = 5.7 Hz), 127.7, 126.9, 123.2 (q, *J* = 274.3 Hz), 117.5 (q, *J* = 26.7 Hz), 114.2 (d, *J* = 21.9 Hz), 108.6, 93.9, 60.8, 60.7, 55.9, 47.4; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –54.98, –114.99; IR (neat) 1653 (C=O), 1603 (C=C) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{21}F_4NO_4$•Na 510.1304, found 510.1296 $[M+Na]^+$.

Procedures for benzylation of 1 – Synthesis of 4-(4-fluorophenyl)-5,6,7-trimethoxy-1-(4-methoxybenzyl)quinolin-2(1*H*)-one (14a).

Method A: To a solution of **1** (66.7 mg, 0.20 mmol) in DMF (1.0 mL) was added sodium hydride (60% oil, 10.2 g, 0.24 mmol) at 0 °C under an argon atmosphere. After stirring at 0 °C for 1 h, *p*-methoxybenzyl chloride (33 μL, 0.24 mmol) was added. The reaction mixture stirred at room temperature for 3 h. The reaction was quenched with sat. NH_4Cl (10 mL) and the whole mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford quinoline **15a** (25.5 mg, 28%). Further elution (hexane/EtOAc = 3:1) afforded **14a** (48.4 mg, 53%).

Method B:[21] To a solution of **1** (66.0 mg, 0.20 mmol) in dioxane (1.0 mL) was

added Cs_2CO_3 (133.1 mg, 0.40 mmol) at room temperature under an argon atmosphere. After stirring at room temperature for 30 min, *p*-methoxybenzyl chloride (30 μL, 0.22 mmol) was added. The reaction mixture was stirred at room temperature for 3 h and then stirred under reflux for 12 h. After cooled to room temperature, the reaction was quenched with H_2O (10 mL) and the whole mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. After concentration *in vacuo*, the crude material was purified by flash column chromatography on silica gel (hexane/EtOAc = 5:1) to afford **15a** (9.6 mg, 11%). Further elution (hexane/EtOAc = 3:1) afforded **14a** (71.6 mg, 80%).

4-(4-Fluorophenyl)-5,6,7-trimethoxy-1-(4-methoxybenzyl)quinolin-2(1*H*)-one (14a): white solid (mp 154.5–155.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.32–7.22 (m, 4 H), 7.08 (t, *J* = 9 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 6.64 (s, 1 H), 6.44 (s, 1 H), 5.51 (br s, 2 H), 3.783 (s, 3 H), 3.779 (s, 3 H), 3.75 (s, 3 H), 3.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0 (d, *J* = 245.1 Hz), 161.8, 158.9, 155.8, 151.4, 149.1, 138.1, 137.4, 137.1 (d, *J* = 2.9 Hz), 129.0 (d, *J* = 7.7 Hz), 128.6, 128.1, 120.8, 114.3, 114.2 (d, *J* = 20.9 Hz), 109.3, 94.6, 61.0, 60.7, 55.8, 55.3, 46.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –115.18; IR (neat) 1649 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{24}FNO_5$•Na 472.1536, found 472.1544 $[M+Na]^+$.

4-(4-Fluorophenyl)-5,6,7-trimethoxy-2-(4-methoxybenzyloxy)quinoline (15a): white solid (mp 102.8–105.0 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ˚C) δ 7.45 (d, *J* = 8.8 Hz, 2 H), 7.31 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.16 (s, 1 H), 7.07 (t, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.59 (s, 1 H), 5.46 (s, 2 H), 4.02 (s, 3 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.27 (s,

3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0 (d, *J* = 244.1 Hz), 161.1, 159.4, 155.7, 149.3, 148.9, 145.4, 140.3, 137.5 (d, *J* = 3.8 Hz), 129.9, 129.8 (d, *J* =7.7 Hz), 129.4, 114.0 (d, *J* = 21.9 Hz), 113.9, 113.0, 103.9, 67.3, 61.1, 60.6, 56.0, 55.3; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –115.61; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{24}FNO_5$•Na 472.1536, found 472.1550 $[M+Na]^+$.

N-Benzylated 2-quinolones **14b**–**d** were also synthesized using Method B, except for using the corresponding benzylic bromides and stirring at 60 °C for 6 h.

1-(2,5-Dimethoxybenzyl)-4-(4-fluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (14b): 81.1 mg, 84%; white solid (mp 152.9–155.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.30 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.08 (t, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.76 (dd, *J* = 8.4, 2.8 Hz, 1 H), 6.70 (s, 1 H), 6.69 (d, *J* = 2.8 Hz, 1 H), 6.44 (s, 1 H), 5.58 (br s, 2 H), 3.92 (s, 3 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.68 (s, 3 H), 3.23 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.0 (d, *J* = 244.1 Hz), 162.0, 156.0, 154.2, 151.3, 150.7, 149.1, 138.1, 137.4, 137.2 (d, *J* = 3.8 Hz), 129.2 (d, *J* = 7.6 Hz), 125.9, 120.7, 114.6, 114.2 (d, *J* = 21.0 Hz), 112.6, 111.4, 109.2, 94.5, 60.9, 60.7, 56.3, 55.72, 55.67, 40.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –115.30; IR (neat) 1653 (C=O) cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{26}FNO_6$•Na 502.1642, found 502.1651 $[M+Na]^+$.

1-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-4-(4-fluorophenyl)-5,6,7-trimethoxyquinolin-2(1*H*)-one (14c): 81.5 mg, 87%; white solid (mp 162.2–163.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.29 (dd, *J* = 8.8, 5.6 Hz, 2 H), 7.08 (t, *J* = 8.8 Hz, 2 H), 6.87 (d, *J* = 8.4 Hz, 1 H), 6.83 (dd, *J* = 8.0, 1.6 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 6.77 (d, *J* = 1.6 Hz, 1 H), 6.64 (s, 1 H), 6.44 (s, 1 H), 5.94 (s, 2 H), 5.48 (br s, 2 H), 3.79 (s, 3 H), 3.76 (s, 3 H),

3.24 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.1 (d, J = 245.0 Hz), 161.7, 155.9, 151.4, 149.2, 148.3, 146.9, 138.1, 137.4, 137.1 (d, J = 3.8 Hz), 130.5, 129.1 (d, J = 7.7 Hz), 120.8, 120.0, 114.2 (d, J = 21.0 Hz), 109.3, 108.4, 107.4, 101.1, 94.6, 61.0, 60.8, 55.9, 46.5; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –115.15; IR (neat) 1651 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{26}H_{22}FNO_6$•Na 486.1329, found 486.1339 $[M+Na]^+$.

4-(4-Fluorophenyl)-5,6,7-trimethoxy-1-(3,4,5-trimethoxybenzyl)quinolin-2(1*H*)-one (14d): 81.5 mg, 79%; white solid (mp 175.5–177.2 °C); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 7.30 (dd, J = 8.8, 5.6 Hz, 2 H), 7.09 (t, J = 8.8 Hz, 2 H), 6.67 (s, 1 H), 6.56 (s, 2 H), 6.45 (s, 1 H), 5.49 (br s, 2 H), 3.83 (s, 3 H), 3.82 (s, 6 H), 3.80 (s, 3 H), 3.77 (s, 3 H), 3.26 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 162.1 (d, J = 244.1 Hz), 161.8, 155.9, 153.8, 151.5, 149.3, 138.2, 137.60, 137.55, 137.0 (d, J = 3.8 Hz), 132.5, 129.1 (d, J = 7.7 Hz), 120.7, 114.2 (d, J = 21.9 Hz), 109.3, 104.2, 94.6, 61.0, 60.9, 60.8, 56.3, 55.8, 47.2; ^{19}F NMR (376 MHz, $CDCl_3$, 25 °C) δ –115.02; IR (neat) 1652 (C=O) cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{28}FNO_7$•Na 532.1748, found 532.1753 $[M+Na]^+$.

ASSOCIATED CONTENT

Supporting Information

The Supprting Information is available free of charge on the ACS Publication website.

Temperature–time profile for microwave-heating experiments and ^{1}H and ^{13}C NMR charts (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: yamamoto-yoshi@ps.nagoya-u.ac.jp

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research is partially supported by the Platform Project for Supporting in Drug Discovery and Life Science Research (Platform for Drug Discovery, Information, and Structural Life Science) from the Ministry of Education, Culture, Sports, Science and Japan Agency for Medical Research and Development.

REFERENCES

(1) (a) El Abbdabi, N.; Weinger, B.; Lobstein, A.; Quirion, J. C.; Anton, R. *Planta Medica* **1989**, *55*, 603-604. (b) Kobayashi, Y.; Harayama, T. *Org. Lett.* **2009**, *11*, 1603-1606, and cited references.

(2) For selected examples, see: (a) Mederski, W. W. K. R.; Osswald, M.; Dorsch, D.; Christadler, M.; Schmitges, C.-J.; Wilm, C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1883-1886. (b) Hewawasam, P.; Fan, W.; Ding, M.; Flint, K.; Cook, D.; Goggins, G. D.; Myers, R. A.; Gribkoff, V. K.; Boissard, C. G.; Dworetzky, S. I.; Starrett, J. E., Jr.; Lodge, N. J. *J. Med. Chem.* **2003**, *46*, 2819-2822. (c) Ribeiro, N.; Tabaka, H.; Peluso, J.; Fetzer, L.; Nebigil, C.; Dumont, S.; Muller, C. D.; Désaubry, L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5523-5524. (d) Peifer, C.; Urich, R.; Schattel, V.; Abadleh,

M.; Röttig, M.; Kohlbacher, O.; Laufer, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1431-1435. (e) Wall, M. J.; Chen, J.; Meegalla, S.; Ballentine, S. K.; Wilson, K. J.; DesJarlais, R. L.; Schubert, C.; Chaikin, M. A.; Crysler, C.; Petrounia, I. P.; Donatelli, R. R.; Yurkow, E. J.; Boczon, L.; Mazzulla, M.; Player, M. R.; Patch, R. J.; Manthey, C. L.; Molloy, C.; Tomczuk, B.; Illig, C. R. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2097-2102. (f) Cheng, P.; Zhang, Q.; Ma, Y.-B.; Jiang, Z.-Y.; Zhang, X.-M.; Zhang, F.-X.; Chen, J.-J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3787-3789. (g) Kraus, J. M.; Tatipaka, H. B.; McGuffin, S. A.; Chennamaneni, N. K.; Karimi, M.; Arif, J.; Verlinde, C. L. M. J.; Buckner, F. S.; Gelb, M. H. *J. Med. Chem.* **2010**, *53*, 3887-3898.

(3) For selected examples, see: (a) Battistuzzi, G.; Bernini, R.; Cacchi, S.; De Salve, I.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297-302. (b) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. *J. Org. Chem.* **2010**, *75*, 3900-3903. (c) Shibuya, T.; Shibata, Y.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 3963. (d) Borhade, S. R.; Waghmode, S. B. *Can. J. Chem.* **2011**, *89*, 1355-1363. (e) Deng, Y.; Gong, W.; He, J.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 6692-6695. (f) Ryabukhin, D. S.; Gurskaya, L. Y.; Fukin, G. K.; Vasilyev, A. V. *Tetrahedron* **2014**, *70*, 6428-6443. (g) Zhang, Z.; Liao, L.-L.; Yan, S.-S.; Wang, L.; He, Y.-Q.; Ye, J.-H.; Li, J.; Zhi, Y.-G.; Yu, D.-G. *Angew. Chem. Int. Ed.* **2016**, *55*, 7068-7072.

(4) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964-1969. (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58. (c) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329-8351.

(5) (a) Wang, Z.; Wang, B.; Wu, J. *J. Comb. Chem.* **2007**, *9*, 811-817. (b) Wang, Z.; Wu, J. *Tetrahedron* **2008**, *64*, 1736-1742.

(6) Shimokawa, Y.; Nakakoshi, M.; Saito, S.; Suzuki, H.; Yokoyama, Y.; Ishigami, A.; Nishioka, H.; Tsubuki, M. *Heterocycles* **2012**, *85*, 1933-1940.

(7) Murayama, T.; Shibuya, M.; Yamamoto, Y. *Adv. Synth. Catal.* **2016**, *358*, 166-171.

(8) Yonemoto-Kobayashi, M.; Inamoto, K.; Tanaka, Y.; Kondo, Y. *Org. Biomol. Chem.* **2013**, *11*, 3773-3775.

(9) Baker, S. R.; Parsons, A. F.; Wilson, *Tetrahedron* **1998**, *39*, 331-332.

(10) Kitahara, Y.; Shimizu, M.; Kubo, A. *Heterocycles* **1990**, *31*, 2085-2090.

(11) Yamamoro, Y.; Kirai, N. *Heterocycles* **2010**, *80*, 269-279.

(12) Manikandan, R.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 3568-3571.

(13) Glasnov, T. N.; Stadlbauer, W.; Kappe, C. O. *J. Org. Chem.* **2005**, *70*, 3864-3870.

(14) Racys, D. T.; Sharif, S. A. I.; Pimlott, S. L.; Sutherland, A. *J. Org. Chem.* **2016**, *81*, 772-780.

(15) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

(16) Heck, R. F. *Org. React.* **1982**, *27*, 345-390.

(17) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23-41.

(18) Benjahad, A.; Oumouch, S.; Guillement, J.; Pasquier, E.; Mabire, D.; Andries, K.; Nguyen, C. H.; Grierson, D. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 712-716.

(19) Clarke, S. L.; McGlacken, G. P. *Tetrahedron* **2015**, *71*, 2906-2913.

(20) Dehmlow, E. V.; Bollhöfer, J.; Thye, G. *J. Chem. Res. (S)* **2001**, 113-115.

(21) Yamada, M.; Ookubo, A.; Minegishi, T.; Oomori, M. Jpn. Kokai Tokkyo Koho, 08020576, 1996.

(22) Nguyen, B. H.; Perkins, R. J.; Smith, J. A.; Moeller, K. D. *J. Org. Chem.* **2015**, *80*, 11953-11962.

(23) Darnbrough, S.; Mervic, M.; Condon, S. M.; Burns, C. J. *Synth. Commun.* **2001**, *31*, 3273-3280.

(24) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.*, **1997**, *62*, 2312-2313.