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Controlled derivatization of polyhalogenated quinolines utilizing selective cross-coupling reactions

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Abstract

Straightforward procedures for the derivatization of tri- and tetrahalogenated quinolines utilizing sequential selective Pd-catalyzed cross-coupling reactions are described. Taking advantage of intrinsic halide reactivity, substrate control, and appropriate reaction conditions, highly selective reactions at the quinoline 3-, 4-, and 6-position are possible.

In the course of a recent medicinal chemistry program, we needed to prepare a diverse range of 4-alkoxy-3,6-diarylquinolines of structure **1**. These compounds exhibit potent and selective agonism of the somatostatin receptor subtype 2 (sst_2), and are promising agents for the treatment of acromegaly,[1] diabetic retinopathy,[2] and proliferative diseases. In addition to furnishing the desired targets, we sought a route that would culminate with the formation of a biaryl in the final step. Such a route would take full advantage of the myriad structurally diverse aryl- and heteroaryl coupling partners (e.g., boronic acids/esters, stannanes, organozinc/Grignard reagents) which are commercially available or easily prepared, and would facilitate an iterative analogue library approach to the SAR studies of **1**. Ideally, termination of the synthesis with formation of either the 3- or 6-biaryl could be attained; as studies progressed, cross-coupling derivatization of the quinoline 4-position was also explored. Herein, we describe the development of a route which permits elaboration of the quinoline 3-, 4-, and 6-position via selective Pd-catalyzed reactions of polyhalogenated precursors. While it is possible to achieve regio- and chemoselectivity in cross-coupling reactions through variation of ligands and palladium sources, we discovered that useful selectivities in the reactions of tetrahalogenated quinolines of type **1** could be obtained with a single catalyst/ligand system simply by varying the reaction time and temperature (Fig. 1).

Several routes to substituted quinolines[3] and the related 3,6-diaryl-2-quinolones[4,5] have been described. While these routes provide efficient access to target 4-alkoxy-3,6-diarylquinolines, they are not conducive to parallel derivatization at the quinoline 3- and 6-position; in most cases the 3- or 6-aryl group is incorporated in the first step. For instance, in an initial route, cross-coupling substrates were prepared via the well-precedented Conrad–Limpach quinoline synthesis (Scheme 1).[6] In the first step, formylation of ethyl 3,5-dimethylphenylacetate (which ultimately forms the quinoline 3-aryl group) provided aldehyde **2**, which was condensed

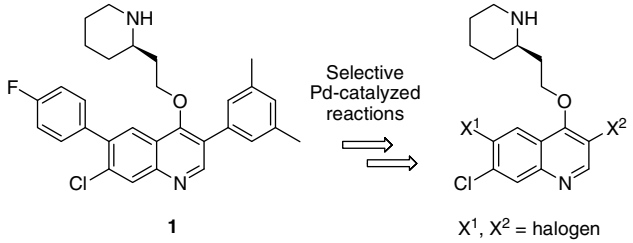

Fig. 1. Structure of 4-alkoxy-3,6-diarylquinoline sst_2 agonists.

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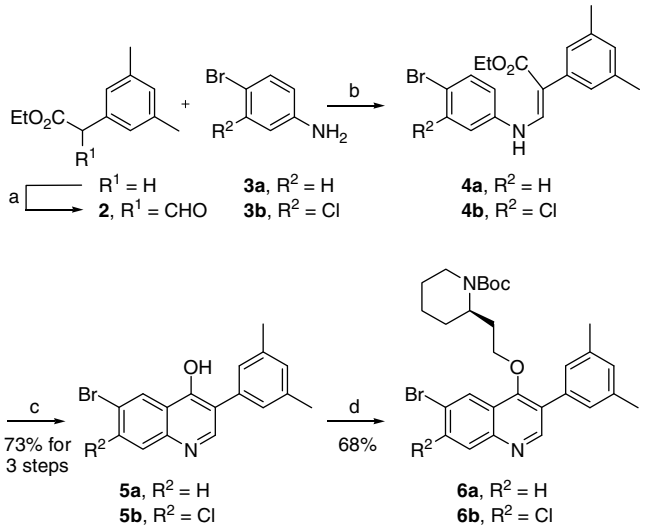
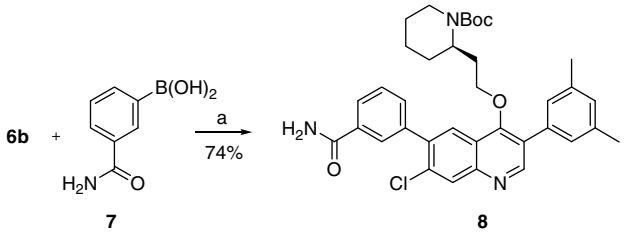


Scheme 1. Reagents and conditions: (a) NaH, ethyl formate, rt, 16 h; (b) THF, 120 °C; (c) diphenyl ether, 250 °C, 30 min; (d) DIAD, PPh_3, *tert*-butyl (2*R*)-2-(3-hydroxypropyl)piperidine-1-carboxylate, sonication.

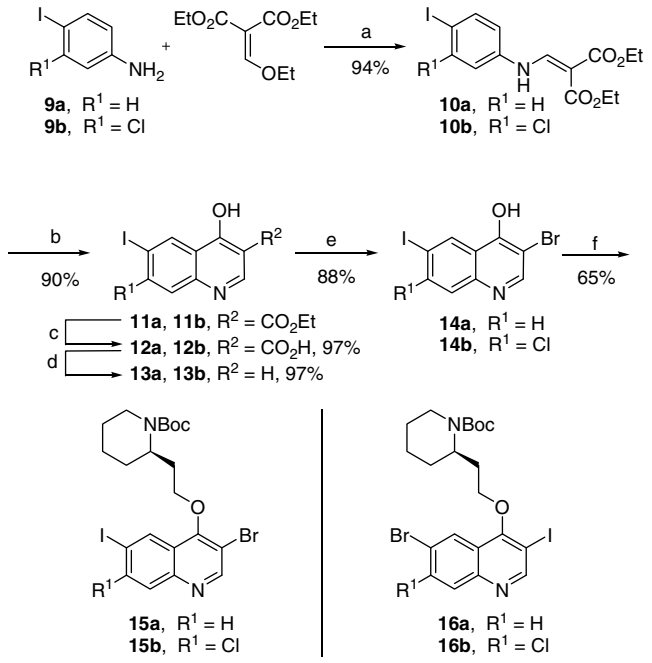
with either 4-bromoaniline (**3a**) or 3-chloro-4-bromoaniline (**3b**) to generate intermediate enamines **4** that were not isolated. Warming **4** in diphenyl ether (250 °C) induced rapid cyclization with evaporation of ethanol to provide 6-bromo-4-hydroxyquinolines (**5**, 73% for three steps).[7] Cyclization of **4b** produced hydroxyquinolines as a mixture of 7-chloro and 5-chloro regioisomers (84:16) which were separated in a subsequent step. Di- and trihalogenated hydroxyquinolines (vide infra) were insoluble in a range of solvents (including DMF and DMSO), and Mitsunobu reaction to form ethers **6** was only effective upon sonication of the reaction mixture (THF, 25 °C).

Cross-coupling reactions of **6a** and **6b** proceeded smoothly using a highly versatile set of conditions described previously ($Cl_2Pd(dppf)$, THF/1 M aq Cs_2CO_3, microwave, Scheme 2).[8] In the case of **6b**, selective coupling of the 6-bromide was observed with heating at 160 °C for 10 min; reaction at the 7-chloride was only observed under forcing conditions ($Pd(OAc)_2$, $NaHCO_3$, DMF, microwave, 200 °C).

While practical for late stage diversification of the quinoline 6-aryl group of **1**, the route described in Schemes 1 and 2 requires incorporation of the 3-aryl group in its first



Scheme 2. Reagents and conditions: (a) $Cl_2Pd(dppf)$, 3:1 THF/1 M aq Cs_2CO_3, 160 °C, 10 min microwave.



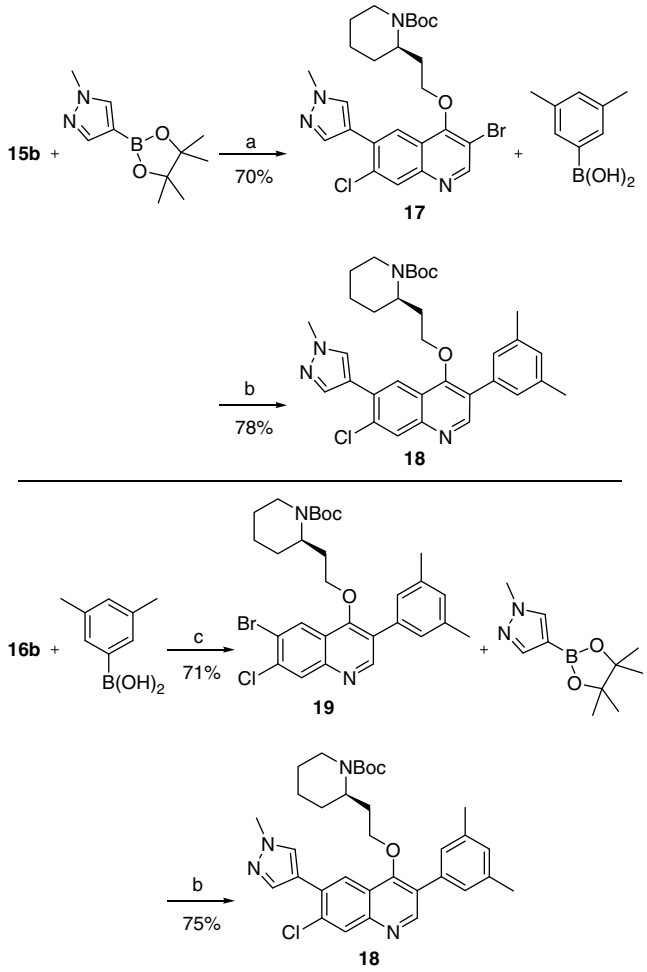
Scheme 3. Reagents and conditions: (a) 120 °C, neat, 1 h; (b) 250 °C, diphenyl ether, 1 h; (c) 10% aq NaOH; (d) 250 °C, diphenyl ether; (e) NBS, AcOH, 60 °C, 2 h; (f) DIAD, PPh_3, *tert*-butyl (2*R*)-2-(3-hydroxypropyl) piperidine-1-carboxylate, sonication.

step. Therefore, an improved synthesis was developed which allows for derivatization of either the 3- or 6-aryl group of **1** in the final step (Scheme 3). This route depends on the ability to distinguish among three halides (Cl, Br, I), and selectivity was expected to depend on both the relative intrinsic reactivity of the halide and the electronic effect of its position in the quinoline ring system. While at the outset it was not clear whether useful selectivities could be achieved, the approach was pursued because of its potential for building diversified target molecules from a common scaffold.

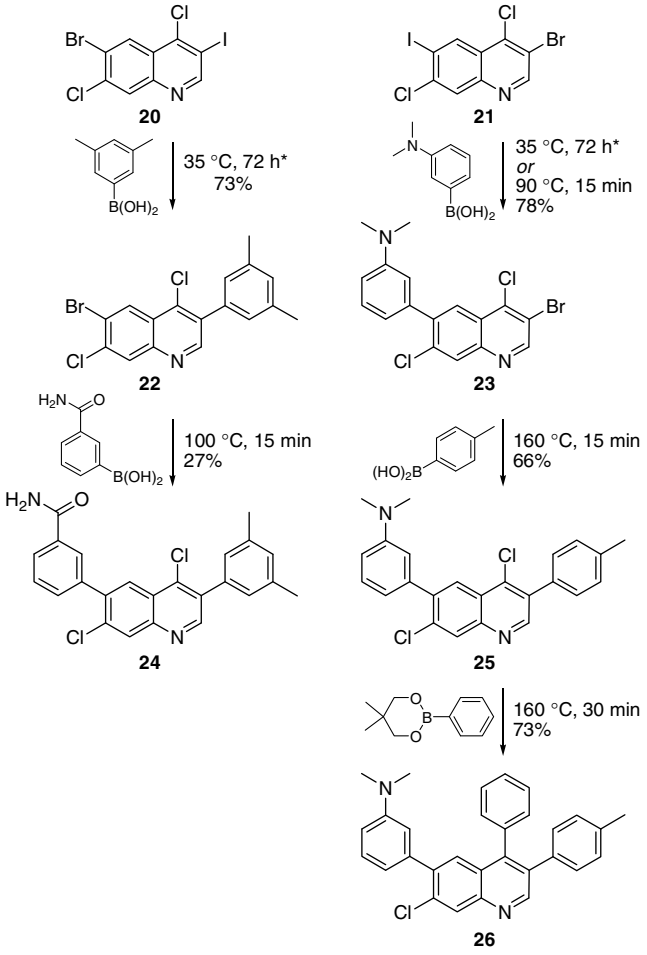
Condensation of 4-iodoaniline (**9a**) or 3-chloro-4-iodoaniline (**9b**) with diethylethoxymethylene malonate with evaporation of ethanol provided enamines **10**, which upon warming at high temperature cyclized to form hydroxyquinolines **11**. In this case, unsymmetrical substrate **10b** cyclized to form 7-chloro-3-ethoxycarbonyl-6-iodo-4-hydroxyquinoline exclusively (as shown for **11**; no 5-chloroquinoline was observed). Following saponification and thermal decarboxylation, **13** was brominated exclusively at the quinoline 3-position when stirred with *N*-bromosuccinimide in warm acetic acid to provide **14**. Ether **15** was then formed in 65% yield under Mitsunobu conditions (DIAD, PPh_3, *tert*-butyl (2*R*)-2-(3-hydroxypropyl) piperidine-1-carboxylate, sonication, 1 h).

Application of the same route using 4-bromoaniline starting materials, with NIS iodination of the intermediate 4-hydroxyquinolines, provided the complementary 6-bromo-4-chloro-3-iodoquinolines **16**.

Sequential, selective cross-coupling of 3-bromo-7-chloro-6-iodoquinoline **15b** was achieved using the



Scheme 4. Reagents and conditions: (a) 1 M aq Cs_2CO_3, THF, $Cl_2Pd(dppf)$, 90 °C, 30 min microwave; (b) 1 M aq Cs_2CO_3, THF, $Cl_2Pd(dppf)$, 140 °C, 10 min microwave; (c) 1 M aq Cs_2CO_3, THF, $Cl_2Pd(dppf)$, 80 °C, 30 min microwave.



Scheme 5. Reactions were heated under microwave conditions (cat. $Cl_2Pd(dppf)$, 1 M aq Cs_2CO_3, THF) except those indicated (*) which were heated conventionally.

identical $Cl_2Pd(dppf)$ catalyst simply by varying reaction time and temperature (Scheme 4). Coupling occurred first at the more reactive 6-iodo position (to form **17**) with microwave heating at 80 °C for 30 min (70%), followed by a second Suzuki reaction at the 3-bromide to form **18** upon heating at 140 °C for 10 min (78%).[9]

Complementary reactivity was observed for trihalide **16b**, where selective 3-arylation required slightly reduced temperature (vs **15b**, 80 °C) for 30 min to provide **19** in equivalent yield. Subsequent arylation in the quinoline 6-position proceeded in good yield under microwave irradiation at 140 °C for 10 min to form **18**. Together, these sequences (**15b**→**18** and **16b**→**18**) permitted the iterative synthesis of libraries of several hundreds of analogues of **1**. Importantly, regardless of whether parallel arylation was carried out in the quinoline 3- or 6-position, the diversity-incorporating step was at the end of the synthesis.[10] This avoided the need to isolate and carry forward hundreds of intermediates in parallel.

Encouraged by the successful discrimination among three halogens within substrates **15b** and **16b**, an investigation of cross-coupling reactions of tetrahalogenated quinolines was pursued (Scheme 5). Chlorination of hydroxyquinoline **14b** and its 6-bromo-3-iodo analogue ($POCl_3$, 93%) generated complementary bromodichloroiodoquinolines **20** and **21**.[11] Conditions for the initial Suzuki reactions were screened using conventional heating or an automated microwave synthesizer, and representative data for **21** are presented in Table 1. Because of the short reaction times resulting from microwave heating, rapid optimization of time, temperature, and stoichiometry was possible. Complete conversion of **21** to **23** with minimal appearance of product resulting from multiple cross-coupling was observed with prolonged warming at 35 °C (entry 8); alternatively, identical conversion and isolated yield could be achieved in dramatically reduced reaction times with microwave heating at 90 °C (entry 4). The microwave conditions are selective even in the presence of a twofold excess of boronic acid (entry 5).[12] Similar conditions were effective for the conversion of **20** to **22** (Scheme 5).

Differences in reactivity were observed for the second Suzuki reactions of **22** and **23** (Scheme 5). Cross-coupling

Table 1
Development of cross-coupling conditions

Entry	Boronic acid (equiv)	Reaction conditions	**21**:**23**: double arylation[a]
1	1.2	60 °C, 10 min	46:54:0
2	1.2	70 °C, 10 min	34:66:0
3	1.2	80 °C, 10 min	26:74:0
4	1.2	90 °C, 15 min	0:99:1[b]
5	2	90 °C, 10 min	0:87:13
6	1.2	100 °C, 10 min	0:82:18
7	1.2	120 °C, 10 min	0:77:23
8	1.2	35 °C, 72 h	—[b]

[a] Arylation of both the quinoline 3- and 6-position; ratios determined by LCMS analysis of reaction mixtures, ELSD integration.
[b] 78% isolated yield.

at the bromine-substituted carbon of **22** proceeded only in a low yield, and major side products from competing reaction at the quinoline 4-chloride were observed. In contrast, selective coupling occurred in the case of **23** (160 °C, 15 min, microwave) to form **25** in a moderate yield.

In the third sequential Suzuki reaction, the 4-chloride of **25** was converted to a phenyl substituent in good yield by heating with 5,5-dimethyl-2-phenyl-1,3,2-dioxaborinane at 160 °C for 30 min. Conversion of **21** to **26** represents the successful distinction among four halogens within a single quinoline ring system. Impressively, the same catalyst, base, and solvent combination (Cl_2Pd(dppf), aq Cs_2CO_3/THF) was effective in each of these transformations, and selectivity could be tuned by varying time and temperature.[13]

While not investigated in detail, the generation of **26** from **21** in one-pot, via sequential heating of a single reaction mixture with addition of the respective boronic acid/ester coupling partners was possible.[14] Three arylation cycles were completed using the optimal stepwise conditions to furnish, after purification of a relatively complex reaction mixture, **26** in 20% yield.

In summary, we have developed useful microwave-assisted protocols for selective, sequential cross-coupling of tri- and tetrahalogenated quinoline precursors.[15] Use of catalytic Cl_2Pd(dppf), aq Cs_2CO_3, and THF with microwave heating proved amenable to the selective couplings investigated, and with a variety of commercially available boronic acids and esters as coupling partners. Excellent regio- and chemoselectivity were observed in the course of our studies through careful manipulation of reaction temperature and time. These procedures were effectively utilized as part of an iterative analogue library approach to the identification of potent and selective sst_2 agonists.[16]

Acknowledgments

We thank Brian Eastman for early experiments, John Swestock for the preparation of **5a** and **5b**, and Joan Murphy and Charles W. Ross, III for high-resolution mass spectroscopy. Discussions with James J. Mulhearn prompted the investigation of a one-pot, sequential functionalization of **21**.

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7. All reported yields are for isolated, analytically pure material.
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9. Not surprisingly, double arylation of **15a** was also possible by heating at 160 °C for 10 min with an excess of arylboronic acid.
10. Deprotection (TFA) of the Boc-protected piperidine nitrogen was required in parallel, and was technically non-demanding.
11. 6-Bromo-4,7-dichloro-3-iodoquinoline (**20**): ^{1}H NMR ($CDCl_3$): 9.11 (s, 1H), 8.56 (s, 1H), 8.22 (s, 1H); 3-bromo-4,7-dichloro-6-iodoquinoline (**21**): ^{1}H NMR ($CDCl_3$): 8.93 (s, 1H), 8.78 (s, 1H), 8.19 (s, 1H); 6-bromo-4,7-dichloro-3-(3,5-dimethylphenyl)quinoline (**22**): TLC $R_f = 0.47$ (95:5 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): 8.83 (s, 1H), 8.64 (s, 1H), 8.26 (s, 1H), 7.11 (s, 3H), 2.40 (s, 6H); ^{13}C NMR ($CDCl_3$): 153.25, 147.11, 138.52, 138.48, 136.48, 135.66, 134.54, 130.58, 129.54, 127.63, 126.23, 123.07, 104.57, 21.57; HRMS: calcd for $C_{17}H_{12}BrCl_2N$ ($M+H^+$) 379.9603, found 379.9604.
12. 3-(3-Bromo-4,7-dichloroquinolin-6-yl)-*N*,*N*-dimethylbenzenamine (**23**): TLC $R_f = 0.45$ (95:5 EtOAc/hexanes); ^{1}H NMR ($CDCl_3$): 8.99 (s, 1H), 8.27 (s, 1H), 8.20 (s, 1H), 7.57–7.63 (m, 1H), 7.5 (s, 2H), 7.41–7.44 (m, 1H), 3.22 (s, 6H); ^{13}C NMR ($CDCl_3$): 152.9, 146.3, 145.5, 142.0, 140.3, 140.0, 135.5, 130.2, 130.1, 127.2, 126.7, 126.1, 119.4, 118.8, 118.2, 44.6; HRMS: calcd for $C_{17}H_{14}BrCl_2N_2$ ($M+H^+$) 394.9712, found 394.9716.
13. While further improvements in selectivity could be expected by screening various catalyst, ligand, and base combinations this work was limited to exploration of the Cl_2Pd(dppf)/Cs_2CO_3 system.
14. For each sequential Suzuki–Miyaura coupling step, 10 mol % of fresh Cl_2Pd(dppf) was added to the reaction mixture.

15. General procedure for Suzuki reactions: **21** (100 mg, 0.25 mmol), 3-dimethylaminophenylboronic acid (46 mg, 0.27 mmol), and $Cl_2Pd(dppf)$ (16 mg, 0.2 mmol) were combined and suspended in 2 mL THF and 0.5 mL of 1 M aq Cs_2CO_3 in a 2–5 mL Biotage microwave reaction vial containing a magnetic stir bar. The vial was capped and heated in a Biotage Optimizer reactor cavity for 15 min at 90 °C, after which the vessel was rapidly cooled to 40 °C by the unit. The organic phase was separated, evaporated under reduced pressure, and purified by flash chromatography (4–10% EtOAc/hexanes) to provide **23** (77 mg, 77%).
16. Manuscript in preparation.