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Divergent Route to Access Structurally Diverse 4-Quinolones via Mono or Sequential Cross-Couplings

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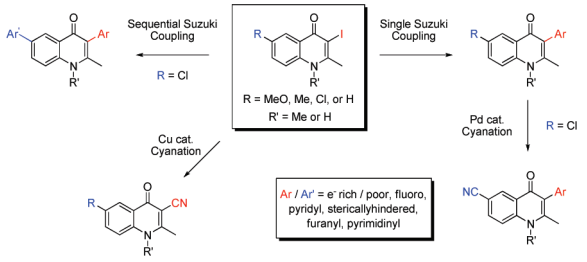

A divergent route was developed to access 3-iodo- and 6-chloro-3-iodo-4(1*H*)-quinolones for further elaboration via mono and/or sequential Suzuki−Miyaura cross-coupling to generate novel and medicinally important 4(1*H*)-quinolones. Copper- and palladium-catalyzed cyanations were used to functionalize the 4-quinolone core further.

Substituted 4-quinolones are relevant for various medicinal applications including inhibition of tubulin formation,[1] antimicrobial[2] and antiviral therapies,[3] antiallergy treatments,[4] and cancer chemotherapies[5] and are common scaffolds found in various natural products.[6] In the past decade, 4-quinolones have resurfaced as antimalarial agents.[7] Using *in vitro* activity assays against erythrocytic stages of multidrug-resistant isolates and clones of *P. falciparum*, Kyle, Manetsch, and Riscoe recently demonstrated that 3-substituted 4(1*H*)-quinolone derivatives display antimalarial activity at low to single-digit nanomolar concentrations.[7] Herein, we report a divergent synthetic protocol for the rapid preparation of functionalized 3-substituted 4(1*H*)- and 4(1*alkyl*)-quinolones.

Most routes to access 4-quinolones rely on traditional reactions such as the Gould−Jacobs,[8] Conrad−Limpach,[9] Niementowski,[10] or Camps cyclizations.[11] However, these transformations are limited by elevated reaction temperatures, unsatisfactory yields, and poor regioselectivities. Furthermore, several mild synthetic approaches focusing primarily on 2-substituted 4-quinolones have been developed utilizing transition metal catalysis[12] as well as base-promoted Camps cyclization of *N*-(ketoaryl)amides.[13] Among the entire repertoire of 4-quinolone syntheses, the Conrad−Limpach cyclization is the most prevalent reaction for the preparation of 3-substituted 4-quinolones involving 2-substituted-β-ketoesters and anilines as starting materials. Nevertheless, the cyclization step using sterically hindered and/or acid-sensitive 2-substituted β-ketoesters commonly generates 3-substituted-4-quinolones in poor yields and requires difficult purification protocols.

The need to access structurally diverse 3-aryl-4-quinolones, in conjunction with the lack of a contemporary synthetic approach to such compounds, motivated us to devise a reliable and divergent synthetic route (Scheme 1). The key step of our method involves substitution of the quinolone core at the 3-position using a Suzuki−Miyaura cross-coupling. Strikingly, our approach further demonstrates the utility of sequential cross-couplings with dihalogenated quinolones culminating in the synthesis of structurally diverse analogues. The quinolone intermediate is obtained by a combination of easily synthesized or commercially available anilines and ethyl acetoacetate cyclized through a high-yielding Conrad−Limpach reaction (Scheme 1). Subsequent regioselective halogenation of the quinolone core provides the Suzuki−Miyaura

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SCHEME 1. Sequential Pd-Catalyzed Cross-Coupling of Iodo-chloro Quinolones

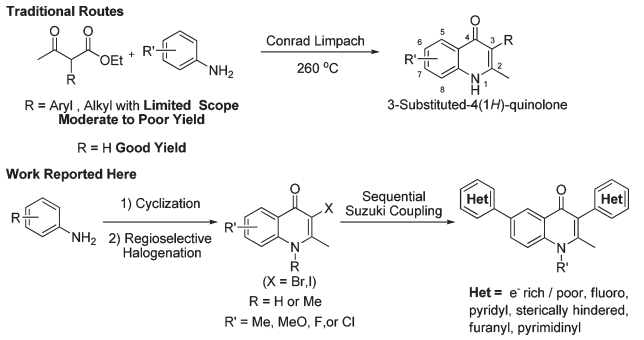
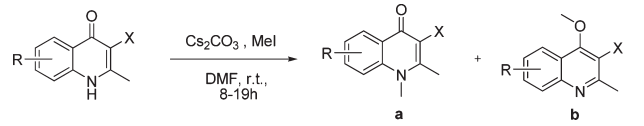


TABLE 1. Methylation of Halo-quinolones



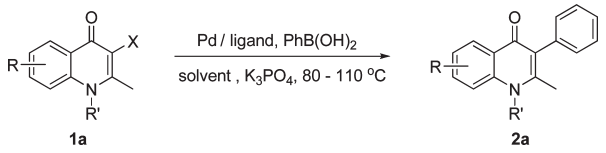
entry	R	X	time (h)	% yield	(**a**:**b**)
1	6-H	Br	8	99	1.67:1
2	6-H	I	12	95	2.37:1
3	6-F	Br	16	94	2.05:1
4	6-Cl	I	12	97	3.20:1
5	6-0 Me	Br	14	99	2.51:1
6	6-Me	I	19	85	1.95:1
7	5,7-diCl	I	15	90	12.0:1

coupling precursor.[14] These halides and their *N*-methyl analogues could be directly subjected to cross-coupling conditions.

4(1-*alkyl*)-Quinolones have also found utility in medicinal applications[15] and their preparations have been explored. Standard alkylation conditions were screened using the group 1 and silver carbonates at various temperatures. Heating of the reaction mixtures resulted in both lower selectivities and yields due to reduction of the halide substituent to the 3-H-4-quinolone. Likewise, the use of cold reaction conditions resulted in poor yields due to the decreased solubility of the quinolones at lower temperatures. Ultimately, the use of Cs_2CO_3 in DMF at room temperature provided excellent yields albeit with modest chemoselectivities (Table 1, entries 1−7).

Screening of appropriate Suzuki−Miyaura conditions applicable to our substituted quinolones commenced with a study of different catalyst systems and solvents. The choice to use SPHOS as the ligand and K_3PO_4 as the base was suggested by previous and extensive work of Buchwald[16] et al. Couplings using quinolones **1a** and the standard catalyst $Pd(PPh_3)_4$ furnished quinolone **2a** in good yields (Table 2, entry 1). However, reactions were completed in less time using a Pd/SPHOS system and resulted in higher yields of the 3-substituted quinolones (Table 2, entries 2−4). When applying the same conditions to a quinolone with an iodo- substituent rather than a bromo- substituent, an improvement in yield was obtained (Table 2, entry 5). The use of toluene as solvent for the

TABLE 2. Optimization of Cross-Coupling Conditions



entry	R	R′	X	Pd/ligand	solvent	% yield[a]
1	H	Me	Br	$Pd(PPh_3)_4$	toluene	85
2	H	Me	Br	$Pd_2(dba)_3$/SPHOS[c]	toluene	92
3	H	Me	Br	$Pd_2(dba)_3$/XPHOS[d]	toluene	90
4	H	Me	Br	$Pd(OAc)_2$/SPHOS	toluene	88
5	H	Me	I	$Pd_2(dba)_3$/SPHOS	toluene[e]	95
6	H	H	I	$Pd_2(dba)_3$/SPHOS	toluene	< 25
7	H	H	I	$Pd_2(dba)_3$/SPHOS	DMF[e]	72[b]
8	6-Cl	Me	I	$Pd_2(dba)_3$/SPHOS	2-butanol[e]	50[b]
9	6-Cl	Me	I	$Pd_2(dba)_3$/SPHOS	DMF[e]	85[b]

[a]Reaction conditions: 1a (0.4 mmol), Pd source (4 mol %), ligand (8 mol %), K_3PO_4 (2 equiv), $PhB(OH)_2$ (1.5 equiv), solvent (3 mL), 80 °C. [b]110 °C. [c]SPHOS (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl. [d]XPHOS (2-(dicyclohexylphosphino)-2′,4′,6′-tri-isopropyl-1,1′-biphenyl. [e]Solvent (1 mL).

N-methylated quinolone substrates was found to be superior, whereas the couplings with 4(1*H*)-quinolones required DMF for complete conversion, although resulting in modest yields (entry 6 and 7). Similarly, 6-chloro-*N*-methyl-quinolones required the use of DMF as a solvent, and 2-butanol was found to be suboptimal (entry 8 and 9).

Next, the substrate scope of the coupling reaction was studied in detail. Couplings with various phenylboronic acids with both *N*-methylated 3-bromo- and 3-iodo-quinolones (Table 3, entries 1 and 2) resulted in 92% and 95% yields of quinolones, respectively. DMF was required for the less soluble 4(1*H*)-quinolone (entry 3), providing a 72% yield. Halides were efficiently coupled with electron-rich boronic acids (entries 4−6) in a short amount of time. 4-Methoxyphenyl boronic acid was also reacted with *N*-methyl- and *N*-H-3-bromo-6-fluoro-quinolones (entries 7 and 8), furnishing the corresponding products in 95% and 73% yields, respectively. Sterically hindered boronic acids were coupled smoothly with electron-deficient and electron-neutral quinolones (entries 9 and 10). *meta*-Substituted arylboronic acids (entries 11−14) including 3-(dimethylcarbamoyl)phenylboronic acid (entries 13 and 14) provided yields of 95% and 65% for both the *N*-alkyl- and the *N*-H-quinolone. A fluorinated quinolone was cross-coupled with 4-fluorophenyl boronic acid (entries 15 and 16) in 81% and 73% yields.

Although furan-2-boronic acids have been reported to be problematic with the Pd/SPHOS catalyst/ligand system, Molander and co-workers realized these problematic couplings by the use of 2-furanyl organotrifluoroborates.[17] Strikingly, the substitution of *N*-methyl- and *N*-H-4-quinolones with furan-2-boronic acids provided the desired products in 97% and 75% yields, respectively (Table 3, entries 19 and 20). Finally, *E*-phenylethenylboronic acid (entry 25) was installed at the 3-position in excellent yields with a *trans*:*cis* ratio of 12:1. Conveniently, this set of conditions was effective for coupling our quinolones with all of the major subclasses of substrates including heteroaryl, both electron-rich and -deficient, alkenyl,

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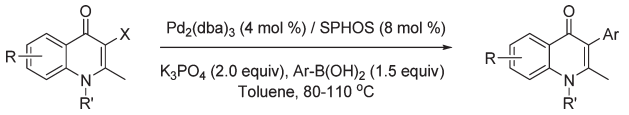
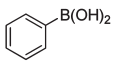
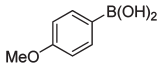
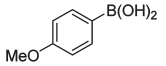
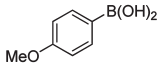
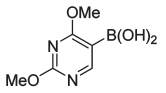
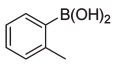
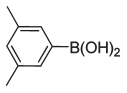
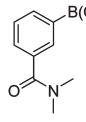
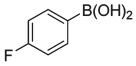
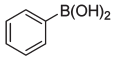
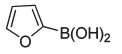
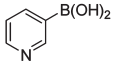
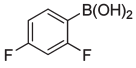
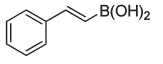
TABLE 3. Scope 3-Halo-4-quinolone Cross-Couplings



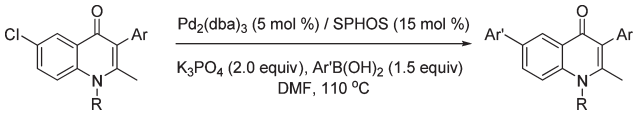
entry	R	R'	X	$ArB(OH)_2$	time (h)	% yield
1	H	Me	Br		0.75	92
2	H	Me	I		0.75	95
3	H	H	I		1.0	72[a]
4	H	Me	Br		2.0	89
5	6-Me	M e	I		0.5	99
6	6-Me	H	I		1	62[b]
7	6-F	Me	Br		1	95
8	6-F	H	Br		36	73[c]
9	6-Cl	Me	I		0.5	91[d]
10	H	Me	Br		1.0	83[e]
11	6-OMe	Me	Br		4.5	73[e]
12	6-OMe	H	Br		2.0	51[c]
13	6-Me	Me	I		36	95[c]
14	6-Me	H	I		37	65[b]
15	6-F	Me	Br		24	81[c]
16	6-F	H	Br		18	73[f]
17	6-Cl	Me	I		48	85[c]
18	6-Cl	H	I		16	68[a]
19	6-Cl	Me	I		0.5	97[d]
20	6-Cl	H	I		18	75[a]
21	6-Cl	Me	I		24	65[a]
22	6-Cl	H	I		44	51[b]
23	6-Cl	Me	I		16	90[c]
24	6-Cl	H	I		18	55[c]
25	6-Cl	Me	I		19	95

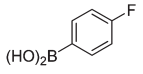
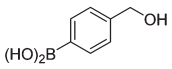
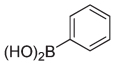
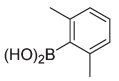
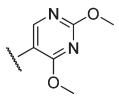
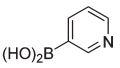
[a]DMF, 1.5 equiv of $ArB(OH)_2$, 110 °C. [b]2-Butanol, 1.5 equiv of $ArB(OH)_2$, 110 °C. [c]DMF, 3.5 equiv of $ArB(OH)_2$, 110 °C. [d]DMF, 2.0 equiv of $ArB(OH)_2$, 85 °C. [e]Toluene, 2.0 equiv of $ArB(OH)_2$. [f]DMF, 5 equiv of $ArB(OH)_2$, 110 °C.

fluorinated, and pyridyl, as well as sterically hindered substrates (Table 3).

6-Chloro-3-aryl-4-quinolones (Table 3, entries 9 and 17−24) were studied to highlight the divergent nature of this synthetic route further by taking advantage of the reactivity differences between the iodo and chloro substituents. The 3-position could be subjected to Suzuki−Miyaura coupling followed by a subsequent coupling with a different boronic acid at the 6-position, providing the capability of building complex 4-quinolones. 3-Phenyl-6-chloroquinolones were

TABLE 4. Scope of 6-Chloro-4-quinolone Cross-Couplings



entry	Ar	R	$Ar'B(OH)_2$	time (h)	% yield
1		Me		18	94[a]
2		H		20	72[a]
3		Me		17	70
4		H		24	73[a]
5		Me		2[b]	92[b,c]
6		H		26	41[c]
7		Me		1.5	91[b,c]
8		H		17	47[c]
9		Me		22	88[c]

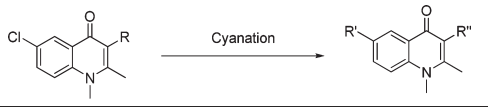
[a]3.5 equiv of $Ar'B(OH)_2$. [b]Toluene. [c]2 equiv of $Ar'B(OH)_2$. [d]100 °C.

coupled with 4-fluorophenylboronic acid smoothly in 94% yields for the *N*-methylated and in 72% yields with *N*-H-quinolone (Table 4, entries 1 and 2). 3-Phenyl-6-chloroquinolone was next coupled with 4-(hydroxymethyl)phenylboronic acid (entries 3 and 4) in good yields for both amino forms. 3-Furanyl-6-chloro quinolones reacted well in the *N*-methyl form with a 92% yield for phenylboronic acid (entry 5) and 91% for the sterically encumbered 2,5-dimethylphenylboronic acid (entry 7). The free *N*-H containing 3-furanyl-6-chloro quinolones only produced modest yields when coupled with phenyl and dimethylphenylboronic acids (entries 6 and 8) of 41% and 47%, respectively. 3-Pyrimidine-6-chloro-4-quinolone (entry 9) was coupled with 3-pyridylboronic acid in 88% yield to generate a 3-pyrimidine-6-pyridyl-4-quinolone heterocycle.

To build in additional avenues for diversity, we explored the possibilities of installing cyano groups at both the 3- and 6-positions (Table 5, entries 1 and 2). 6-Chloro-3-cyano-quinolones could provide an intermediate to diversify the benzenoid ring of the quinolone while enabling a potential transformation to a 3-carboxylate group similar to ciprofloxacin. An extension of the method developed by Eli Lilly using a Pd/dppf catalyst with Zn^0 as the in situ reductant[18] efficiently transformed the 6-chloro-4-quinolone to 3-furanyl-6-cyano quinolone (Table 5, entry 1) in high yields. The same conditions failed to catalyze the cyanation of 3-iodo-quinolone. Previous work shows that many palladium-catalyzed methods proceed with only low to moderate yields of the product.[19] Ultimately, switching to a copper iodide/DMEDA system[20] with sodium cyanide resulted in cyanation of the 3-position with excellent yields (Table 5, entry 2).

(18) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *41*, 3271–3273.
(19) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224–8228.
(20) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890–2891.

TABLE 5. Cyanation of 4-Quinolone



entry	R	R'	R''	CN source	M / L	time (h)	% yield
1		CN		$Zn(CN)_2$	$Pd_2(dba)_3$ / dppf	23	91
2	I	Cl	CN	NaCN	CuI / DMEDA	20	90

In summary, using the Pd/SPHOS catalyst/ligand system, we have designed and optimized a divergent synthetic route to structurally diverse 3-aryl-4-quinolones resulting in medicinally important heterocyclic scaffolds. A 6-chloro-3-iodo-quinolone was used as a core intermediate to diversify the quinolone scaffold via mono or sequential Suzuki–Miyaura cross-couplings including fluoro, pyridyl, sterically hindered, heteroaryl, electron-rich, and electron-poor substrates. In addition, iodo-4-quinolones were subjected to cyanations via Pd-catalysis, and chloro-4-quinolones were transformed by copper catalysis. Ongoing efforts at preparing 3-aryl-4-quinolones via this route led to the identification of several analogues displaying antimalarial activity in the nanomolar range.[21]

Experimental Section

Procedure for 3-Halo-4-quinolone Cross-Couplings. In a flame-dried Schlenk tube backfilled with argon (3×) a mixture of 3-iodo-1,2-dimethylquinolin-4(1*H*)-one (100 mg, 0.4 mmol), phenylboronic acid (97 mg, 0.59 mmol), K_3PO_4 (168 mg, 0.79 mmol), $Pd_2(dba)_3$ (14.5 mg, 0.016 mmol), and SPHOS (13 mg, 0.032 mmol) was heated to 80 °C in toluene (1 mL) for 45 min. The reaction was cooled to room temperature and then diluted with 20 mL of chloroform and 20 mL of methanol, and this mixture was brought to a boil and then filtered over a pad of Celite. The eluent was concentrated under reduced pressure, and the residual oil was purified via flash chromatography on silica gel (hexanes/EtOAc gradient) to provide the title compound in 95% yield (94 mg) as an off-white solid, mp = 208–210 °C. Characterization data for Table 3, entry 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (dd, J = 8.0, 1.5, 1H), 7.61 (dd, J = 9.4, 7.8, 1H), 7.48 (d, J = 8.6, 1H), 7.40–7.27 (m, 4H), 7.24–7.17 (m, 2H), 3.75 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.1, 148.5,141.6, 137.3, 132.14, 131.1, 128.5, 127.5, 127.2, 126.4, 125.3, 124.6, 123.3,115.3, 35.3, 20.2. HRMS (ESI) calcd for $C_{17}H_{15}NO$ $[M + H]^+$ 250.12264, found 250.12372.

Procedure for 6-Chloro-4-quinolone Cross-Couplings. In a flame-dried Schlenk tube backfilled with argon (3×), a mixture of 6-chloro-2-methyl-3-phenylquinolin-4(1*H*)-one (100 mg, 0.37 mmol), 4-(hydroxymethyl)phenylboronic acid (197 mg, 1.29 mmol), K_3PO_4 (158 mg,0.74 mmol), $Pd_2(dba)3$ (17 mg, 0.019 mmol), and SPHOS (23 mg, 0.056 mmol) was heated to 110 °C in DMF (1 mL) for 21 h. The reaction was cooled to room temperature and then diluted with 20 mL of chloroform and 20 mL of methanol. This mixture was brought to a boil and then filtered over a pad of Celite, an additional 10 mL of boiling DMF was then poured over the pad, and the combined eluent was concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (DCM/MeOH gradient) to provide the title compound in 73% yield (92 mg) as a light yellow solid, mp = 341–344 °C. Characterization data for Table 4, entry 4: ^{1}H NMR (400 MHz, DMSO) δ 11.73 (s, 1H), 8.32 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.66 (dd, J = 20.1, 8.2 Hz, 3H), 7.41 (dd, J = 14.9, 7.6 Hz, 4H), 7.29 (dd, J = 19.8, 7.2 Hz, 3H), 5.23 (s, 1H), 4.55 (s, 2H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.9, 146.5, 141.7, 138.6, 137.9, 136.2, 134.5, 131.0, 130.1, 127.8, 127.2, 126.5, 126.2, 124.6, 122.5, 121.0, 118.4, 62.6, 18.9. HRMS (ESI) calcd for $C_{23}H_{20}NO_2$ $[M + H]^+$ 342.14886, found 342.14981.

Procedure for 6-Chloro-4-quinolone Cross-Couplings. To a flame-dried Schlenk tube backfilled with argon (3×) was added a mixture of 6-chloro-3-iodo-1,2-dimethylquinolin-4(1*H*)-one (100 mg, 0.3 mmol), CuI (6 mg, 0.03 mmol), DMEDA (32 μL, 0.3 mmol), and sodium cyanide (18 mg, 0.36 mmol). The reaction was heated to 90 °C in toluene (1 mL) for 23 h. The reaction was cooled to room temperature, diluted with 20 mL of chloroform, filtered through a pad of Celite, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (EtOAC/MeOH 5%) to provide 6-chloro-1,2-dimethyl-4-oxo-1,4-dihydroquinoline-3-carbonitrile in 90% yield (63 mgs) as a light brown solid, mp = 255–256 °C. Characterization data for Table 5, entry 2: ^{1}H NMR (400 MHz, DMSO) δ 8.06 (d, J = 2.4 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.86 (dd, J = 9.2, 2.4 Hz, 1H), 3.82 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 172.7, 159.9, 139.4, 133.3, 130.1, 126.0, 124.1, 120.4, 116.8, 96.0, 36.5, 21.0.

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Supporting Information Available: Detailed experimental procedures including ^{1}H, ^{13}C, and ^{19}F NMR, HRMS, and melting points. This material is available free of charge via the Internet at http://pubs.acs.org.

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