JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

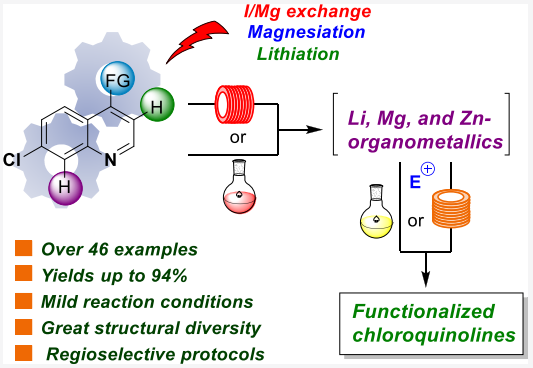
Synthesis of 7-Chloroquinoline Derivatives Using Mixed Lithium-Magnesium Reagents

Valter E. Murie,[⊥] Paula V. Nicolino,[⊥] Thiago dos Santos, Guido Gambacorta, Rodolfo H. V. Nishimura, Icaro S. Perovani, Luciana C. Furtado, Leticia V. Costa-Lotufo, Anderson Moraes de Oliveira, Ricardo Vessecchi, Ian R. Baxendale,* and Giuliano C. Clososki*

Cite This: J. Org. Chem. 2021, 86, 13402−13419 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: We have prepared a library of functionalized quinolines through the magnesiation of 7-chloroquinolines under mild conditions, employing both batch and continuous flow conditions. The preparation involved the generation of mixed lithium-magnesium intermediates, which were reacted with different electrophiles. Mixed lithium-zinc reagents allowed the synthesis of halogenated and arylated derivatives. Some of the synthesized 4-carbinol quinolines have shown interesting antiproliferative properties, their hydroxyl group being a suitable amino group bioisostere. We also report a two-step approach for optically active derivatives.



INTRODUCTION

The benzo-fused *N*-heterocycle quinoline is a privileged scaffold in medicinal chemistry being a constituent of several therapeutics displaying activity against different human cancer cell lines as well as other disease conditions.[1] In this context, 4-anilinoquinolines (e.g., bosutinib (**1**)) show high inhibitory activity for the epidermal growth factor receptor (EGFR), a highly expressed receptor in solid tumors.[2−4] Additionally, analogous 4-phenoxyquinoline derivatives, including some important anticancer pharmaceutical compounds such as foretinib (**2a**), cabozantinib (**2b**), and lenvatinib (**3**) (Figure 1), have been reported as antiproliferative compounds.[5−8] Interestingly, Charris and co-workers reported that quinolin-4-ylsulfonyl acrylate derivatives (**4**) based on the parent chloroquine structure are bioactive substances against malaria and cancer.[9] Moreover, the historical antimalarial alkaloid, quinine (**5**), and the synthetic therapeutic agent for chloroquine-resistant malaria, mefloquine (**6**), are further examples of bioactive carbinol derivatives.[10,11] Recently, de Souza and co-workers reported molecular modifications at the C4 position on the quinoline core to synthesize bioactive mefloquine-based analogues against *Mycobacterium tuberculosis*.[12]

Substituted quinolines can be synthesized by using classic cyclization reactions such as Doebner−von Miller, Combes, Conrad−Limpach−Knorr, Friedlander syntheses, and others,[13−18] whereas aryl(quinolin-4-yl)methanols can be prepared through the reaction of quinoline-4-carboxaldehydes with aromatic organometallic reagents;[19−24] quinolines bearing different functional groups at the C4 position are more commonly accessed from halogenated substrates by exploiting the reactivity of the corresponding lithium,[25−27] magnesium,[28] and zinc[29] organometallic intermediates. For example, Mongin and co-workers have explored a Br/Mg exchange reaction promoted by a tributylmagnesium ate complex to prepare 4-substituted quinolines.[30,31]

Over the past few years, numerous functionalized heterocycles have been prepared by using Turbo Grignard reagents, a class of mixed magnesium-lithium organometallic reagents, which enhance the rate of bromo- and iodo-magnesium exchange.[32,33] Knochel and co-workers employed this type of reagents in the regioselective functionalization of 2,4-dibromoquinoline derivatives because *i*-PrMgCl·LiCl preferably reacts with a halogen located at the C4 position.[34] Furthermore, Linington and co-workers have synthesized a collection of (quinoline-4-yl)carbinols via bromo-magnesium exchange reactions but this required using an excess of *i*-PrMgCl·LiCl, at −78 °C for a halogen-metal exchange step and extended reaction times (12 h) between the organomagnesium intermediate and the electrophile.[35]

Received: June 28, 2021
Published: September 23, 2021

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

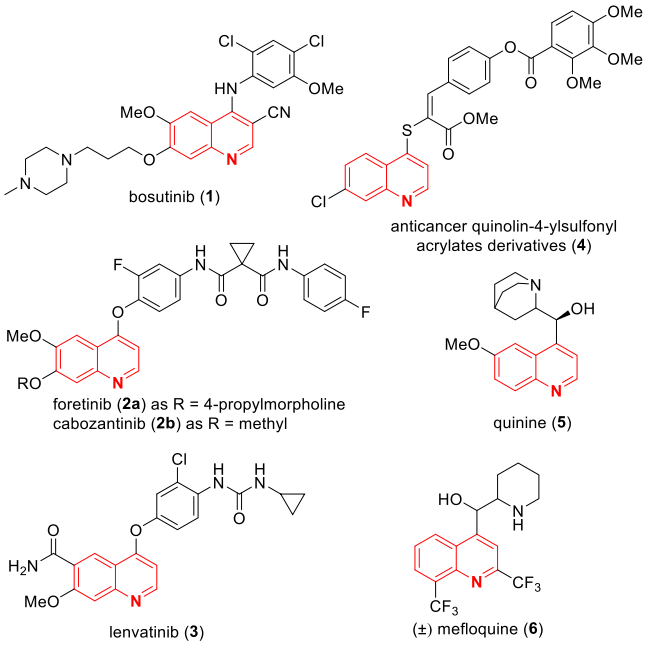
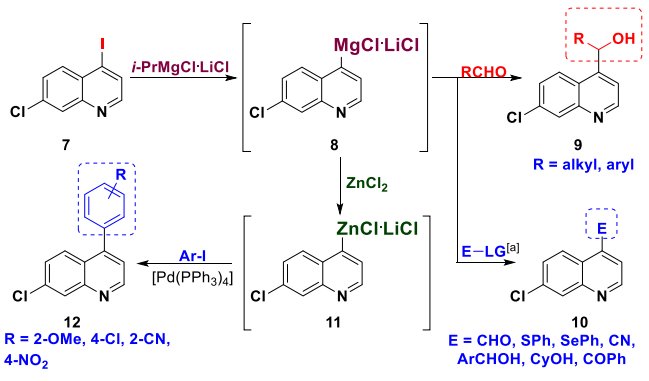


Figure 1. Some examples of bioactive quinolines bearing functional groups at the C4 position.

Chloro-substituted quinolines are important intermediates in medicinal chemistry.[36] For instance, 4,7-dichloroquinoline is a valuable precursor to the antimalarial chloroquine.[37,38] Given our interest in developing selective strategies to functionalize aromatic and heteroaromatic substrates,[39−42] we recently sort to prepare some novel di- and tri-functionalized quinolines by using regioselective metalation strategies.[43] Herein, we report the preparation of a library of functional quinolines through the fast and efficient magnesiation of halogenated substrates under mild conditions. We have shown that iodo-magnesium exchange of 7-chloro-4-iodoquinoline (**7**) with *i*-PrMgCl·LiCl is highly efficient and selectively yield exclusively organomagnesium species **8**. Subsequent quenching of **8** with different electrophiles yields the corresponding 4-functionalized quinoline derivatives of type **9** or **10**, while transmetalation of **8** with zinc chloride enables access to Negishi-arylated derivatives of type **12** (Scheme 1). To aid synthesis, we have demonstrated that magnesiations at C4 or C8 positions of 7-chloroquinolines can be efficiently conducted under continuous flow conditions, giving easy access to scalable quantities of materials.

Scheme 1. General Strategy toward 4-Subtituted 7-Chloroquinolines via Organomagnesium Reagent 8



[a]LG: leaving group.

RESULTS AND DISCUSSION

We initiated this work by first performing a methodological study to identify the best reaction condition to promote efficient iodo-magnesium exchange from 7-chloro-4-iodoquinoline (**7**) with *i*-PrMgCl·LiCl. Interestingly, GC−MS analysis of reaction aliquots quenched with water showed that full conversion of the starting material into the organomagnesium reagent occurred within 10 min by using 1.1 equiv of the Turbo Grignard reagent in THF at room temperature. In contrast, quenching of the reaction with benzaldehyde (1.1 equiv) afforded a 4:1 mixture of the expected alcohol **9a** (64% yield) and corresponding ketone **10a** (16% yield), respectively. Formation of ketone **10a** could be rationalized by a magnesium variant of the Oppenauer oxidation reaction (Scheme 2).[44−46]

We optimized the reaction selectivity and increased the yield of **9a** by performing both the iodo-magnesium exchange and sequential reaction of organomagnesium **8** with benzaldehyde (1 equiv) at 0 °C. Under these conditions, generation of **9a** was favored over ketone **10a** (**9a**:**10a** = 93:7 ratio), allowing isolation of the desired alcohol in 74% yield (Scheme 3). We therefore applied the optimized conditions to prepare a library of quinoline-4-carbinol derivatives in good overall yields (Scheme 3). Quenching of intermediate **8** with different monosubstituted benzaldehydes bearing electron-donating or electron-withdrawing groups at the ortho, meta, or para positions of the aromatic ring afforded the expected derivatives (**9a−r**) in yields ranging from 61 to 91%. It is worth mentioning that methoxy, nitro, and fluorine groups at the meta position of the benzene moiety have been associated with antiproliferative activity on 4-anilinoquinolines.[47] Moreover, the use of disubstituted benzaldehydes as electrophiles produced diaryl alcohols **9s** and **9t** in 82 and 74% yield, respectively. The reaction between intermediate **8** and heteroaromatic carboxaldehydes afforded the diheteroaryl alcohols **9u−9y** in high yields, from 70 to 93%. Similarly, the quenching of the organomagnesium **8** with aliphatic aldehydes like isobutyraldehyde and cyclohexane carboxaldehyde also gave good isolated yields of the alcohol derivatives **9z** and **9aa** in 61 and 87%, respectively. In these reactions, we did not detect the presence of the corresponding Oppenauer oxidation ketone derivatives in the crude reaction.[44]

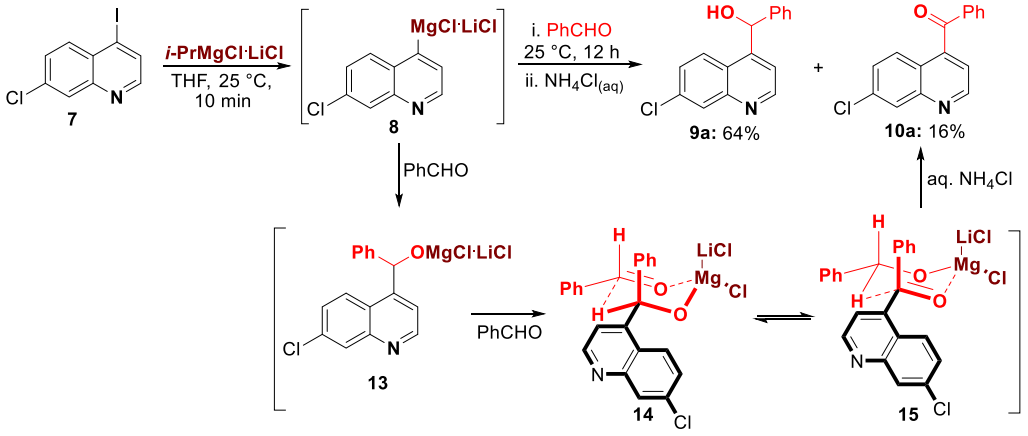
To expand the range of chemistry and to generate valuable reactive functional groups, the reaction of organomagnesium reagent **8** with *trans*-cinnamaldehyde was tested and afforded the allyl alcohol **16** in 92% yield, which was further oxidized with Dess−Martin periodinane[48] (DMP) to chalcone **17** in 82% yield.

In a complementary approach, we showed that a quinoline metalation approach[43] could be used to prepare the 3-substituted chalcone derivative **20**. Thus, after C3 regioselective metalation of 4,7-dichloroquinoline **18** with LDA at −70 °C, reaction of the corresponding organolithium intermediate with *trans*-cinnamaldehyde furnished the allyl alcohol **19** in 50% yield, which was further oxidized with DMP to chalcone **20** in 63% yield (Scheme 4).

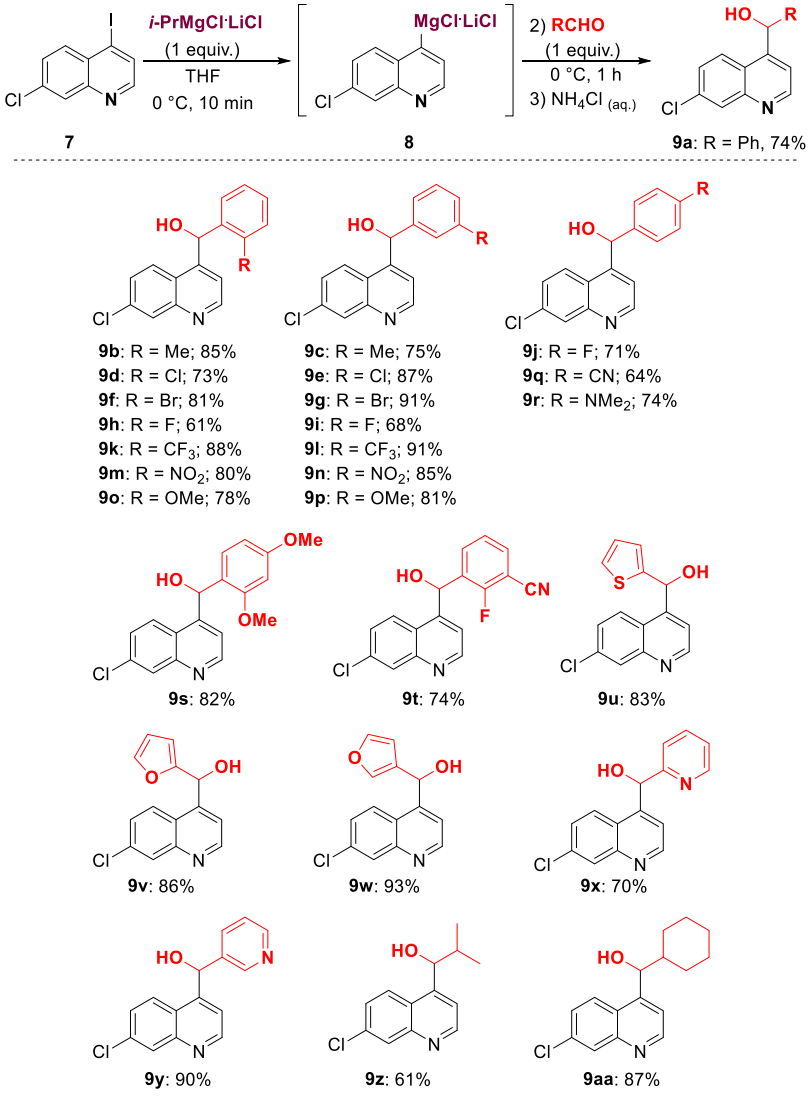
We next turned our attention to examining the reactivity of organomagnesium **8** with additional electrophiles (Scheme 5). Interestingly, quenching compound **8** with cyclohexanone gave the expected tertiary alcohol **10b** in 51% yield. Additionally,

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

Scheme 2. Iodo-magnesium Exchange Reaction Using 7-Chloro-4-iodoquinoline (7) and Benzaldehyde as an Electrophile



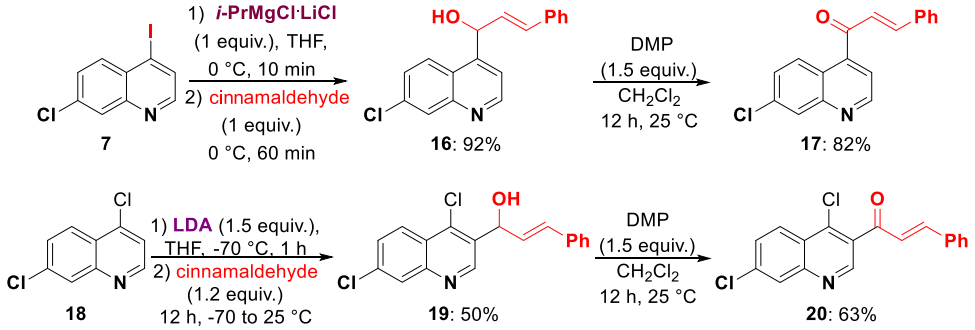
Scheme 3. Iodo-magnesium Exchange of 7 Followed by Reaction with an Aldehyde



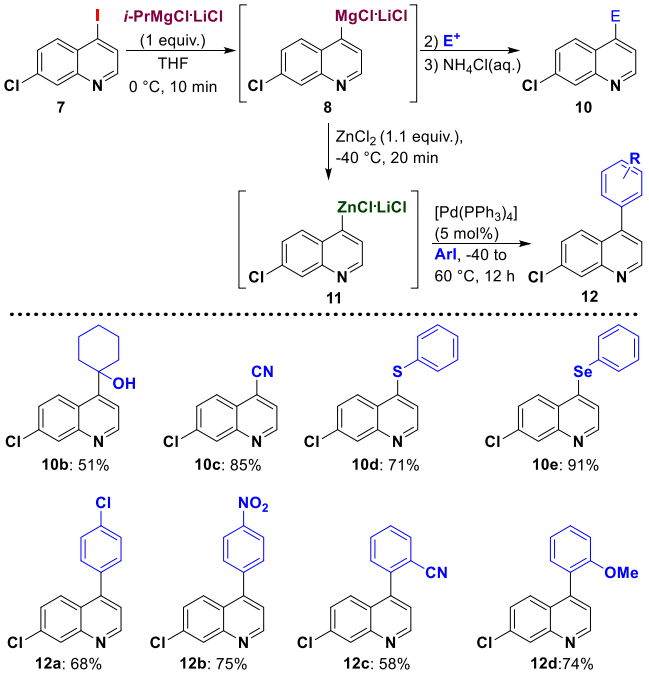
when we used tosyl cyanide as the electrophile, the 7-chloroquinoline-4-carbonitrile derivative **10c** was isolated in 85% yield. Similarly, reaction of **8** with diphenyl disulfide and diphenyl diselenide afforded the expected chalcogens **10d** and **10e** in 71 and 91% yield, respectively. Palladium-catalyzed cross-coupling reactions are important synthetic tools to further functionalize heterocycles.[49−52] Notably, transmetalation of organomagnesium **8** with $ZnCl_2$ occurred smoothly at −40 °C to generate the corresponding organozinc reagent **11** within 20 min. Further reaction of **11** with aryl iodides bearing electron-withdrawing and electron-donating groups in the

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

Scheme 4. Synthesis of Allyl Alcohol Derivatives and Subsequent Oxidation to Chalcones



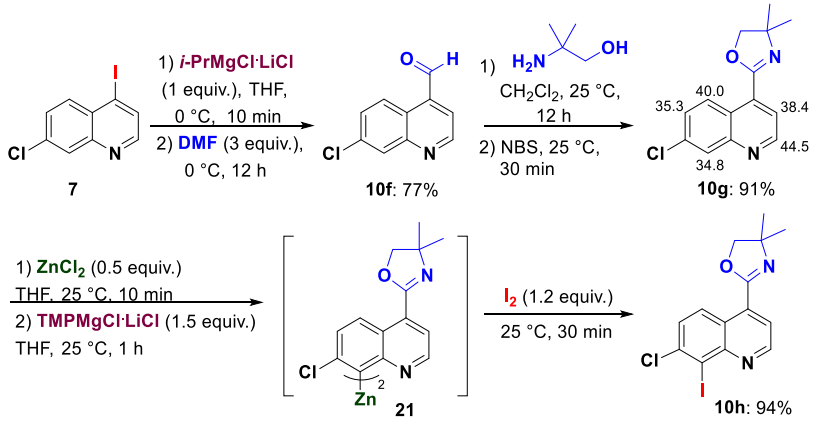
Scheme 5. Turbo Grignard-Mediated Preparation of 4-Substituted 7-Chloroquinoline Derivatives



presence of 5 mol % $Pd(PPh_3)_4$ generated the expected arylated derivatives **12a−d** in yields ranging from 58 to 75%.

We also demonstrated the synthetic versatility of the methodology through the synthesis of 7-chloroquinoline-4-carbaldehyde **10f**. Reacting intermediate **8** with dimethylformamide (DMF, 1.1 equiv) afforded the desired aldehyde in 18% yield, and overnight stirring of intermediate **8** with an excess of DMF (3 equiv) gave **10f** in an improved 77% isolated yield. 2-Oxazolines are important intermediates in organic synthesis and are largely used as protecting groups for carboxylic acids[53−55] and in directed ortho metalation (DoM) reactions, allowing regioselective functionalization of aromatic and heteroaromatic rings.[56−58] To explore this chemistry in the synthesis of new functionalized quinolines, we reacted aldehyde **10f** with 2-amino-2-methylpropan-1-ol, to generate the expected oxazoline, which was further oxidized with *N*-bromosuccinimide (NBS) to give the 4-quinolinyl oxazoline **10g** in 91% isolated yield. With **10g** in hands, we studied its magnesiation with TMPMgCl·LiCl.[59] Interestingly, despite the powerful metalation directing effect of the 2-oxazoline group,[60−62] metalation exclusively occurred at the C8 ring position to yield the iodide **10h** in 50% through iodine quenching. Similarly, application of the *in situ*-trapping metalation strategy[63] through addition of TMPMgCl·LiCl to **10g** in the presence of $ZnCl_2$ (0.5 equiv) led to the full conversion of the starting material within 1 h at room temperature. Further reaction with iodine allowed compound **10h** to be isolated in 94% yield (Scheme 6). To rationalize the regioselective metalation of **10g**, we conducted a computational study to determine the pK_a values of the aromatic hydrogens using the B3LYP/6-311++G(d,p) level[64,65] in Gaussian 03.[66] We computed the pK_a values by employing hypothetical reactions between the heterocycle and pyridine (reference) in THF, as described in the literature.[67,68] As expected, H-8 was the most acidic (pK_a: 34.8), being much more acidic than H-3 (pK_a: 38.4). Moreover, coordination of

Scheme 6. Synthesis of the Tri-functionalized Quinoline Derivative 10h Using Selective Magnesiation Strategies



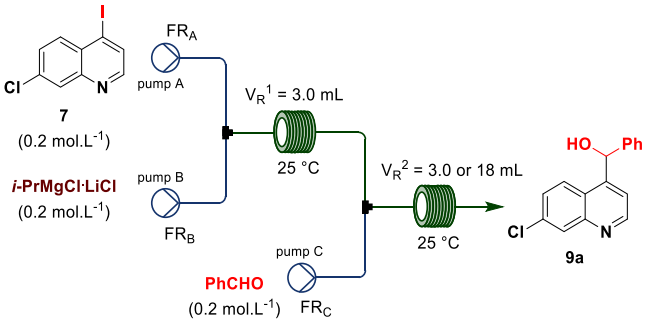
https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

the quinoline nitrogen with $ZnCl_2$ should significantly affect the pK_a of the adjacent hydrogens,[69] favoring selective deprotonation of H-8 (See the SI).

Over the past two decades, continuous flow processes have been highlighted as a powerful tool to synthesize natural products,[70] active pharmaceutical ingredients (APIs),[71−73] and fragrances.[74] Indeed, a number of quinoline derivatives have been obtained under flow conditions[75] through chlorination,[76] trihalomethylation,[77] and Suzuki−Miyaura arylation.[78] Moreover, microreactor technology has proved its value for the functionalization of several heteroarenes using organometallic intermediates.[79−82]

Given the fast kinetics of the iodo-magnesium exchange, we envisioned that the improved mixing promoted by a microreactor would enhance reaction times for the magnesiation of 7-chloro-4-iodoquinoline **7** with *i*-PrMgCl·LiCl and the subsequent reaction of the intermediate and electrophile. Consequently, we set up a flow system composed of three pumps (Syrris syringe pumps), T-mixer connections, and two flow coil reactors to perform this reaction using benzaldehyde as a model electrophile (Scheme 7).

Scheme 7. Magnesiation of 7 with *i*-PrMgCl·LiCl Followed by Benzaldehyde Quenching under Flow Conditions



By combining streams of the Turbo Grignard and substrate **7** at a T-mixer, the iodine-magnesium exchange took place inside the first coil reactor (3 mL) in residence times of between 30 and 75 s at room temperature, which was advantageous when compared to the batch process (10 min at 0 °C). Furthermore, according to our previously optimized batch results, 1 h of reaction between intermediate **8** and the aldehyde is crucial in achieving high yields of the alcohol **9a**. To our delight, quenching the organomagnesium **8** with benzaldehyde added through an additional input flow and passing the newly combined stream through a second coil reactor (3 mL) afforded **9a** in 95% conversion after 50 s (Table 1, entry 6). A reaction concentration of 0.2 mol·L^{-1} was shown to be optimal as diluted solutions decreased the conversion, and a more concentrated reactions led to reactor fouling and eventual clogging (Table 1, entries 8 and 9). We note that mixing is key as changing from a Y-mixer to a T-mixer, which induces more turbulent mixing, improved the yield (Table 1, entries 6 and 7). Consequently, compound **9a** was isolated in 86% isolated yield.

Thus, by applying a flow rate of 3.0 mL·min^{-1}, the synthesis of various aryl(7-chloroquinolin-4-yl)methanol derivatives could be feasible in a reaction time of 50 s (Scheme 8 and Table 2). In contrast, using the same flow conditions for cyclohexanone and DMF as the electrophiles, compounds **10b** and **10f** were isolated in low yields (28 and 22%, respectively).

Table 1. Magnesiation of 7-Chloro-4-iodoquinoline Using *i*-PrMgCl·LiCl Followed by Reaction with Benzaldehyde[f]

entry	type of mixer[e]	V_R^2 (mL)	flow rate (mL·min^{-1})	R_T (min)	NMR conversion[a] (%)
1	T	18	1.2	6.25	81.5
2	T	18	1.5	5	94.3
3	T	18	3	2.5	92.9
4	T	3	1.2	2.08	81.0
5	T	3	1.5	1.67	76.9
6	T	3	3	0.83	94.7 (86)[b]
7	Y	3	3	0.83	84.3
8	T	3	3	0.83	80.9[c]
9	T	3	3	0.83	clogged[d]
10	T	3	6	0.42	55.5

[a]Calculated via ^{1}HNMR analysis using dimethyl sulfone as an internal standard. [b]Isolated yield. [c]Concentration: 0.1 mmol·mL^{-1}. [d]Concentration: 0.4 mmol·mL^{-1}. [e]PEEK mixers (internal diameter, I.D. = 0.020 in.). [f]All the experiments were carried out at 0.5 mmol scale.

Scheme 8. Magnesiation of 7 Followed by the Reaction with Electrophiles under Flow Conditions

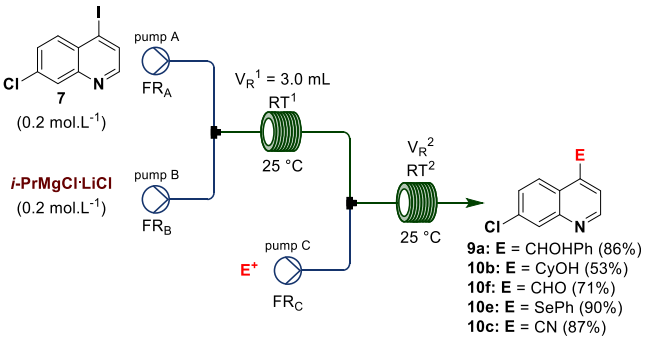


Table 2. Flow Setup for Each Electrophile

electrophile solution (mol·L^{-1})[a]	$FR_A = FR_B = FR_C$ (mL·min^{-1})[b]	RT_1 (s)[c]	RT_2 (min)[d]	V_R^2 (mL)[e]
PhCHO (0.2)	3.0	30	0.33	3
cyclohexanone (1.2)	1.2	75	5	18
DMF (1.2)	1.2	75	5	18
TsCN (0.3)	3.0	30	2	18
PhSeSePh (0.4)	3.0	30	2	18

[a]Concentration. [b]FR: flow rate each pump. [c]RT_1: residence time of the halogen-metal exchange step. [d]RT_2: residence time of reaction between organomagnesium intermediate **8** and the electrophile. [e]V_R^2: reactor volume of the second coil.

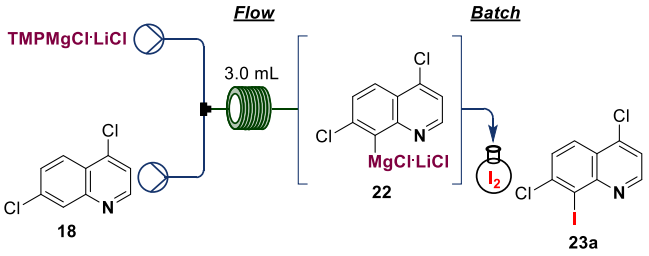
Therefore, modifications regarding the electrophile concentration, volume of the second coil, and flow rate, the latter two generating different residence times, were investigated.[81,83] According to results, which are shown in Table 1, longer residence times may be used as an interesting alternative to afford quinoline derivatives in high conversions from less reactive electrophiles (Table 1, entries 1−3). Thus, an improved yield (37%) was obtained from a more concentrated solution of cyclohexanone (1.2 mol·L^{-1}, 6 equiv), larger coil reactor (18 mL), and high residence time (2.5 min). By decreasing the flow rate of all pumps (1.2 mL·min^{-1}) and raising the total residence time in both coil reactors (1.25 and 5 min, respectively), tertiary alcohol **10b** could be isolated in 53% yield, which is similar to that obtained in batch. Application of the same reaction conditions also allowed the

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

preparation of 4-formyl quinoline **10f** in 71% yield. By keeping the coil reactor volumes at 3 and 18 mL, respectively, with each input flow rate set at 3.0 mL·min^{-1}, equating to a residence time of 2.5 min, diphenyl diselenide (0.4 mol·L^{-1}, 2 equiv) and *p*-toluenesulfonyl cyanide (0.32 mol·L^{-1}, 1.6 equiv) furnished products **10c** and **10e** in yields of 90 and 87%, respectively (Scheme 8).

Having demonstrated the beneficial use of continuous flow microreactors in the functionalization of quinolines, we turned our attention to investigate the magnesiation reactions using TMPMgCl·LiCl also in continuous flow since this strategy has proven to be an interesting approach to functionalize the C8 position of 7-chloroquinolines.[43] Synthetic studies were conducted using a Vapourtec E-series system equipped with three peristaltic pumps, T- or Y-mixers, and coil reactors (3 mL). First, aiming to determine the best conditions for the functionalization of 4,7-dichoroquinoline (**18**), which is an important drug intermediate,[84−86] we pumped anhydrous solutions of this substrate and TMPMgCl·LiCl (1.1−2 equiv) in THF with the in-flow-generated organomagnesium intermediate **22** being dispensed into an iodine stock solution as a batch quench (Scheme 9).

Scheme 9. Regioselective Magnesiation of 18 under Flow Conditions



As shown in Table 3, conversion of **18** into the expected iodide **23a** reached 90% when the reaction was performed using 1.1 equiv of TMPMgCl·LiCl and a 1 min residence time (Table 2, entry 3). Moreover, when the amount of base was increased to 1.5 equiv, maintaining the 1 min residence time, the conversion peaked at 96.1% (Table 3, entry 8). Longer residence times did not improve the final outcomes (Table 3, entry 10). Considering the mixer types employed in the flow setup, we found that the turbulent flow promoted by the T-mixer has advantages over the Y-mixer. Thus, using the optimized flow setup, 4,7-dichoro-8-iodoquinoline **23a** could be prepared in 92% isolated yield, which is an 11% improvement to that obtained in batch, coupled with the simplified scaling considering the continuous operation, which could be utilized in flow.[43]

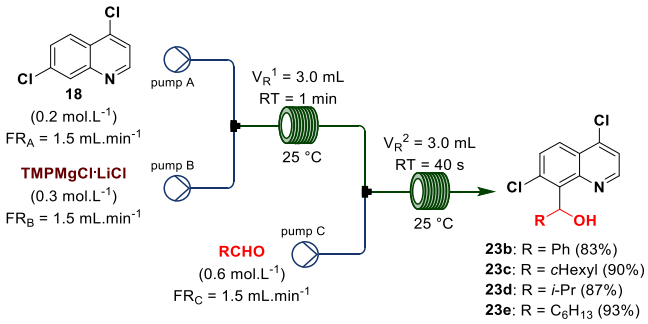
Table 3. Regioselective Magnesiation of 4,7-Dichloroquinoline Using TMPMgCl·LiCl Followed by the Reaction with Iodine[d]

entry	type of mixer[c]	base (equiv.)	flow rate (mL·min^{-1})	R_T (min)	NMR conversion[a] (%)
1	Y	1.1	3	0.5	77.5
2	T	1.1	3	0.5	72.6
3	T	1.1	1.5	1	90.0
4	Y	1.1	1.5	1	82.8
5	T	1.2	1.5	1	78.5
6	Y	1.5	3	0.5	88
7	T	1.5	3	0.5	86.9
8	T	1.5	1.5	1	96.1 (92)[b]
9	Y	1.5	1.5	1	87.6
10	T	1.5	1.5	2[c]	84.8
11	Y	2.0	3	0.5	87.2
12	Y	2.0	1.5	1	85.6

[a]Calculated via ^{1}HNMR analysis using dimethyl fumarate as an internal standard. [b]Isolated yield. [c]A coil reactor of 6 mL was employed to have a residence time of 2 min. R_T: residence time of the metalation step. PEEK mixers (internal diameter, I.D. = 0.020 in). [d]All the experiments were carried out at a 1 mmol scale.

Returning to the previous concept of generate and quench in flow, we added a second coil reactor (3 mL) to the system and demonstrated the ability to quench intermediate **22** with benzaldehyde. Different concentrations (0.24 mol·L^{-1}, 1.2 equiv and 0.6 mol·L^{-1}, 3 equiv) gave conversions of 63.2 and 93.9%, respectively (Scheme 10). By keeping the same flow rate (1.5 mL·min^{-1}) and using coil reactors of 3 or 10 mL, we achieved conversions of 93.9 and 96.1%, respectively, equating to residence times of 40 and 133 s. Despite the option of using a longer residence time, which might allow a higher yield, we opted for a fast process (higher throughput) and consequently a residence time of 40 s (Scheme 10). Thus, in a total of 100 s, product **23b** could be isolated after purification in 83% yield, therefore presenting several advantages over the batch process.[43]

Scheme 10. Magnesiation of Substrate 18 Followed by the Reaction with Different Aldehydes under Flow Conditions



Of particular note is then even for enolizable aldehydes, mixing the organomagnesium intermediate **22** in, compounds **23c−e** were rapidly prepared in good yields (87−93%, Scheme 10). As noted with the previous system, certain electrophiles have reduced reactivity, requiring longer reaction times. However, by maintaining the same flow rates but substituting a larger volume (18 mL) coil reactor, a residence time of 4 min was attained for the second step, as such compound **23f** was prepared in 54% yield from substrate **18** and diphenyl diselenide (0.4 mol·L^{-1}, 2 equiv) (Table 4). The reaction of **22** with DMF or 1,2-dibromotetrachloroethane as electrophiles required a further decreasing in the flow rate to 1.2 mL·min^{-1}, affording products **23g** and **23h** in yields up to 94%, which are much better than those obtained in batch (44 and 42%, respectively)[43] (Scheme 11 and Table 4). Therefore, both metalation and halogen-metal exchange reactions under continuous flow conditions may be successfully used to prepare 4- and 8-substituted quinolines in a fast process and in good yields.

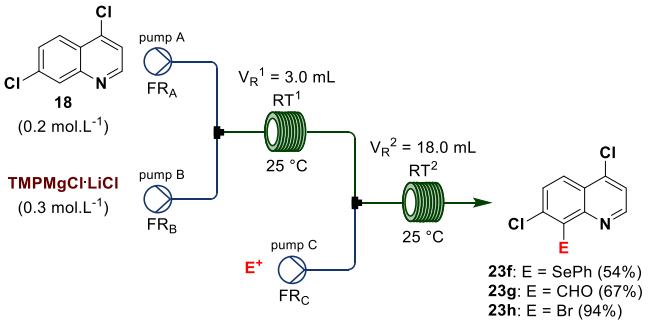
https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

Table 4. Flow Setup for each Electrophile

electrophile solution ($mol \cdot L^{-1}$)[a]	$FR_A = FR_B = FR_C$ ($mL \cdot min^{-1}$)[b]	RT_1 (s)[c]	RT_2 (min)[d]
PhSeSePh (0.4)	1.5	60	4
DMF (1.2)	1.2	75	5
$C_2Br_2Cl_4$ (1.2)	1.2	75	5

[a]Concentration. [b]FR: flow rate each pump. [c]RT_1: residence time of the metalation step. [d]RT_2: residence time of the reaction between organomagnesium intermediate **22** and the electrophile.

Scheme 11. Magnesiation of Substrate 18 Followed by the Reaction with Different Electrophiles under Flow Conditions



Finally, to illustrate the importance of the developed quinoline functionalization methodologies for the medicinal chemistry applications, we screened the antiproliferative activity of the synthesized racemic compounds **9a–aa** and **16** against the cancer cell lines HOG (human oligodendroglioma), HCT116 (colorectal carcinoma), and T98G (human glioblastoma). At 50 μM, **9j**, **9l**, and **9aa** inhibited >75% of tumor growth for both glioma cell types (see the SI for details). Screening of all the alcohol derivatives against A549 (lung carcinoma) and HCT116 (colon carcinoma) showed that **9e**, **9g**, **9l**, **9aa**, and **16** were promising molecules (Table 5). By

Table 5. Antiproliferative Activity of Promising Quinolinic Alcohol Derivatives

		IC_{50} (μM)	
entry	compound	A549	HCT116
1	**9e**	16.3	21.94
2	**9g**	19.13	20.09
3	**9l**	15.43	14.7
4	**9aa**	12.51	10.76
5	**16**	14.95	11.03
6	doxorubicin	0.05	1.568

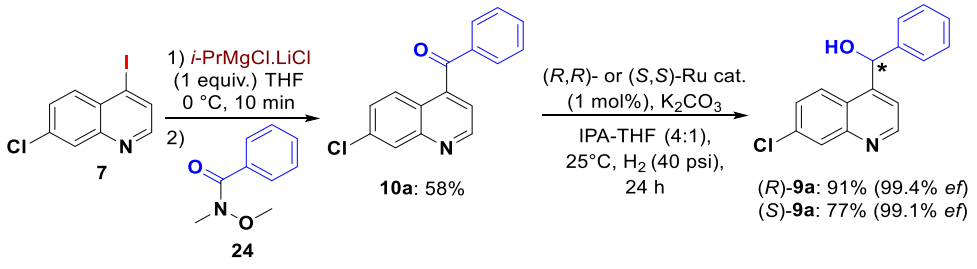
using doxorubicin as the reference drug, the IC_{50} values for each compound were less than 22 μM. According to the biological results, **9aa** (IC_{50} = 12.51 and 10.76 μM, respectively) displayed the best activity profile under the tested experimental conditions, which makes it a potential pattern for further molecular modifications. Interestingly, **9e**, **9g**, and **9l** are meta-substituted derivatives, which may be seen as an essential feature in novel molecular designs for medicinal chemistry investigation. Therefore, the synthesized carbinol derivatives **9a–aa** and **16** displayed interesting antiproliferative properties.

Considering the identified antiproliferative activity of 4-carbinol quinolines of type **9** and the importance of specific chirality for drug selectivity, we further used the developed iodo-magnesium exchange reaction in a straightforward two-stage process to illustrate how chiral compounds can be rapidly prepared (Scheme 12). Thus, following *i*-PrMgCl·LiCl-mediated magnesiation of **7**, reaction quenching with the Weinreb amide **24** gave the acetophenone derivative **10a** in 58% yield. A ruthenium-based enantioselective reduction[87,88] of **10a** allowed us to isolate the optically active alcohols in good yields and high enantiomeric fraction (>99%). As indicated, such a strategy would allow rapid access to each enantiomer for individual biological screening.

CONCLUSIONS

In summary, we have described the preparation of a series of novel functionalized quinolines by using organometallic intermediates under batch and flow conditions. Meanwhile, with 7-chloroquinoline-based mixed magnesium-lithium reagents that reacted with aldehydes and other electrophiles to give the expected products under mild conditions, we were able to use mixed zinc-lithium reagents to prepare C4-arylated or C8-halogenated derivatives. Moreover, lithium and mixed magnesium-lithium amides appeared as interesting organometallic partners to increase the structural complexity of substituted quinolines. The use of continuous flow microreactors enabled a precise control of both chloroquinoline magnesiations and reactions of the corresponding organomagnesium intermediates with several electrophiles, allowing faster and more efficient reactions when compared to the respective batch processes. The library of synthesized quinoline derivatives may be seen as an important contribution to medicinal chemistry due to the large application of this privileged scaffold, as illustrated by the antiproliferative activity of some synthesized derivatives. In this context, aiming at further biological studies, we have also developed a two-step approach for optically active 4-carbinol quinolines. The scope of the developed methodologies and their applicability toward

Scheme 12. Two-Step Approach for Optically Active 4-Carbinol Quinolines



https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402–13419

the synthesis of other biologically active molecules are currently being investigated in our laboratories.

EXPERIMENTAL SECTION

General Considerations. All solvents were purified according to standard procedures.[89] The starting materials such as 7-chloro-4-iodoquinoline, Turbo Grignard (1.3 mol·L^{-1} in THF), electrophiles, 4,7-dichloroquinoline, *n*-butyllithium solution (2.5 mol·L^{-1} in hexanes), diisopropylamine, and 2,2,6,6-tetramethylpiperidine were purchased from Sigma-Aldrich Corp. THF was continuously refluxed and freshly distilled from sodium and benzophenone under a nitrogen atmosphere. All water-sensitive reactions were carried out with dry solvents under anhydrous conditions and a nitrogen atmosphere. The reactions were monitored by TLC on a Fluka Analytical silica gel (silica gel matrix, with a fluorescent indicator of 254 nm) viewed by using UV light and gas chromatography on a Shimadzu GC-2014 with a capillary column (DB17MS, 30 m × 0.25 mm), nitrogen gas as the mobile phase, and flame ionization detector. Silica gel (particle size 0.040−0.063 nm) from Sigma Aldrich was used as a stationary phase for flash chromatography. NMR analyses were recorded with a Bruker DRX 400 and 700 (at 400 and 700 MHz for protons and 100 and 176 MHz for carbon-13, respectively) using chloroform, dimethyl sulfoxide, or methanol as the deuterium solvent. The chemical shifts are reported as δ units in parts per million (ppm) relative to the solvent residual peak ($CDCl_3$ δH: 7.26 ppm; δC: 77.2 ppm, DMS-d_6 δH: 2.50 ppm; δC: 39.5 ppm, and MeOD-d_4 δH: 3.31 ppm; δC: 49.0 ppm) or the internal reference (TMS δH: 0.00 ppm). IR spectra were obtained using an IR 400 (PerkinElmer) spectrophotometer with an attenuated total reflectance device (zinc selenide crystal) from 600 to 4000 cm^{-1} with a 4 cm^{-1} resolution. Gas chromatography−mass spectrometry (GC−MS) was performed in a Shimadzu GC (model: 2010) coupled to a Shimadzu QP 2010 Ultra MS operated in the electron impact ionization mode (70 eV) using the column DB-5MS, helium as carrier gas, a column flow of 1.2 mL·min^{-1}, and a pressure of 68.1 kPa. High-resolution mass spectra were obtained with a Bruker Daltonics (model: microTOF QII − ESI-TOF Mass Spectrometer). HPLC analyses were performed in a Shimadzu LC-20AP constituted of two gradient pumps equipped with a DAD detector and automatic injector. HPLC chiral analyses were carried out on a column Chiralpak AD-H (150 × 4.6 mm, 5 μm, Daicel, Tokyo, Japan) using MeOH as the mobile phase. The column temperature, flow rate, and injection volume were set at 30 °C, 0.4 mL·min^{-1}, and 10 μL, respectively. The detection was carried out at 278 nm. The specific rotation for each enantiomer was obtained using a P-2000 Digital Polarimeter of Jasco. The melting points of synthesized compounds were obtained using the equipment from Buchi, model-560 (for more details, see the SI).

Typical Procedure 1 (TP1). *Halogen/Metal Exchange Reaction between 7-Chloro-4-iodoquinoline and i-PrMgCl·LiCl Followed by the Reaction with Different Electrophiles.* To a dry nitrogen-flushed round-bottom flask (10 mL) under magnetic stirring containing a solution of 7-chloro-4-iodoquinoline (7) (144.7 mg, 0.5 mmol, 1.0 equiv) in anhydrous THF (2.0 mL) was added dropwise *i*-PrMgCl·LiCl (0.42 mL, 1.2 mol·L^{-1}, 0.5 mmol, 1.0 equiv) at 0 °C. After 10 min, the appropriate electrophile (0.5 mmol, 1.0 equiv) was added and the reaction mixture was kept under magnetic stirring at 0 °C for 1 h (except when DMF and *N*-methoxy-*N*-methylbenzamide were used as the electrophiles, and in those cases, the reaction mixture was kept at 0 °C for 12 h). The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (20 mL), and the products were extracted with EtOAc (3 × 10 mL). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using a mixture of hexanes and EtOAc as an eluent.

*(7-Chloroquinolin-4-yl)(phenyl)methanol (**9a**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (171.0 mg, 0.59 mmol) and benzaldehyde (0.06 mL, 0.59 mmol) afforded **9a** (118.0 mg, 74%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 138−140 °C; IR (ATR, cm^{-1}): 3139, 1487, 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.81 (d, J^3 = 4.5 Hz, 1H), 8.02 (d, J^4 = 2.2 Hz, 1H), 7.85 (d, J^3 = 9.1 Hz, 1H), 7.69 (d, J^3 = 4.5 Hz, 1H), 7.37 (dd, J^3 = 9.1 Hz, J^4 = 2.2 Hz, 1H), 7.34−7.27 (m, 5H), 6.43 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.4, 148.9, 148.8, 141.9, 135.2, 129.1 (2 × C), 129.0, 128.6, 127.7, 127.3 (2 × C), 125.5, 124.2, 118.8, 72.9; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{13}{}^{35}ClNO$: 270.0680, found: 270.0676 (Δ = −1.5 ppm).

*(7-Chloroquinolin-4-yl)(phenyl)methanone (**10a**).* CAS number: 169957-11-3. Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (219.0 mg, 0.76 mmol) and benzaldehyde (0.07 mL, 0.75 mmol) afforded **10a** (8.1 mg, 4%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 106−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.04 (d, J^3 = 4.4 Hz, 1H), 8.25 (d, J^4 = 2.1 Hz, 1H), 7.85−7.81 (m, 3H), 7.68−7.64 (m, 1H), 7.52−7.47 (m, 3H), 7.43 (d, J^3 = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 195.4, 150.2, 148.5, 145.0, 136.6, 136.4, 134.6, 130.4 (2 × C), 129.1, 129.0 (2 × C), 128.6, 126.9, 123.6, 119.9; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{11}{}^{35}ClNO$: 268.0524, found: 268.0518 (Δ = −2.2 ppm).

*(7-Chloroquinolin-4-yl)(2-methylphenyl)methanol (**9b**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (261.0 mg, 0.90 mmol) and 2-methylbenzaldehyde (0.1 mL, 0.90 mmol) afforded **9b** (218.2 mg, 85%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 164−166 °C; IR (ATR, cm^{-1}): 3099, 3074, 1491, 822; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, J^3 = 4.5 Hz, 1H), 8.06 (d, J^4 = 2.2 Hz, 1H), 7.69 (d, J^3 = 9.0 Hz, 1H), 7.54 (d, J^3 = 4.5 Hz, 1H), 7.39 (dd, J^3 = 9.0, J^4 = 2.2 Hz, 1H), 7.27−7.21 (m, 2H), 7.10 (ddt, J^3 = 7.0, J^4 = 2.2 Hz, 1H), 7.02 (d, J^3 = 7.5 Hz, 1H), 6.62 (s, 1H), 2.46 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.4, 148.8, 148.7, 139.7, 136.1, 135.2, 131.2, 129.1, 128.8, 127.9, 127.2, 126.8, 125.3, 124.5, 119.2, 69.6, 19.3; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{17}H_{15}{}^{35}ClNO$: 284.0837, found: 284.0830 (Δ = −2.4 ppm).

*(7-Chloroquinolin-4-yl)(3-methylphenyl)methanol (**9c**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (226.0 mg, 0.78 mmol) and 3-methylbenzaldehyde (0.09 mL, 0.78 mmol) afforded **9c** (166.6 mg, 75%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 162−164 °C; IR (ATR, cm^{-1}): 3122, 3061, 1499, 867; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.85 (d, J^3 = 4.5 Hz, 1H), 8.04 (d, J^4 = 2.2 Hz, 1H), 7.85 (d, J^3 = 9.0 Hz, 1H), 7.71 (d, J^3 = 4.5 Hz, 1H), 7.38 (dd, J^3 = 9.0, J^4 = 2.2 Hz, 1H), 7.22 (t, J^3 = 7.5 Hz, 1H), 7.14−7.10 (m, 3H), 6.39 (s, 1H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.5, 148.8, 141.9, 138.9 (2 × C), 135.1, 129.5, 129.0 (2 × C), 128.0, 127.7, 125.2, 124.5, 124.3, 118.8, 73.0, 21.6; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{17}H_{15}{}^{35}ClNO$: 284.0837, found: 284.0833 (Δ = −1.4 ppm).

*(2-Chlorophenyl)(7-chloroquinolin-4-yl)methanol (**9d**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (260.0 mg, 0.90 mmol) and 2-chlorobenzaldehyde (0.1 mL, 0.90 mmol) afforded **9d** (199.1 mg, 73%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 174−176 °C; ^{1}H NMR (400 MHz, MeOD-d_4) δ: 8.86 (d, J^3 = 4.6 Hz, 1H), 8.07 (d, J^3 = 9.1 Hz, 1H), 8.04 (d, J^4 = 2.1 Hz, 1H), 7.58−7.54 (m, 2H), 7.48−7.45 (m, 1H), 7.37−7.26 (m, 3H), 6.85 (s, 1H); ^{13}C{^{1}H} NMR (100 MHz, MeOD-d_4) δ: 152.5, 151.2, 149.4, 140.9, 136.5, 134.2, 130.8, 130.7. 130.1, 128.8, 128.8, 128.5, 127.0, 126.0, 120.6, 69.2; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{16}H_{12}{}^{35}Cl_2NO$: 304.0290, found: 304.0285 (Δ = −1.6 ppm).

*(3-Chlorophenyl)(7-chloroquinolin-4-yl)methanol (**9e**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (248.0 mg, 0.85 mmol) and 3-chlorobenzaldehyde (0.09 mL, 0.85 mmol) afforded **9e** (225.8 mg, 87%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 206−209 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.97 (d, J^3 = 4.5 Hz, 1H), 8.24 (d, J^3 = 9.1 Hz, 1H), 8.08 (d, J^4 = 2.2 Hz, 1H), 7.74 (d, J^3 = 4.5 Hz, 1H), 7.60 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.49 (s, 1H), 7.35−7.28 (m, 3H), 6.52 (d, J^3 = 4.5 Hz, 1H), 6.44 (d, J^3 = 4.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 151.8, 149.5, 148.4, 145.8,

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

133.7, 133.0, 130.3, 128.2, 127.3, 127.0, 126.7, 126.6, 125.5, 123.8, 119.3, 70.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}Cl_2NO$: 304.0290, found: 304.0298 (Δ = 2.6 ppm).

*(2-Bromophenyl)(7-chloroquinolin-4-yl)methanol (**9f**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (225.0 mg, 0.78 mmol) and 2-bromobenzaldehyde (0.1 mL, 0.90 mmol) afforded **9f** (220.4 mg, 81%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 198−200 °C; IR (ATR, cm^{-1}): 3102, 3070, 1430, 834; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.94 (d, J^3 = 4.5 Hz, 1H), 8.12 (d, J^4 = 2.1 Hz, 1H), 7.75 (d, J^3 = 9.0 Hz, 1H), 7.67−7.64 (m, 1H), 7.62 (dd, J^3 = 4.5, J^4 = 0.7 Hz, 1H), 7.44 (dd, J^3 = 9.0, J^4 = 2.1 Hz, 1H), 7.26−7.18 (m, 2H), 7.11−7.08 (m, 2H), 6.85 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.8, 148.6, 148.4, 141.5, 133.8, 132.8, 129.9, 129.3, 128.3, 128.1, 127.4, 126.1, 124.5, 122.7, 119.4, 69.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{79}Br^{35}ClNO$: 347.9785, found: 347.9773 (Δ = −3.4 ppm).

*(3-Bromophenyl)(7-chloroquinolin-4-yl)methanol (**9g**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (265.0 mg, 0.91 mmol) and 3-bromobenzaldehyde (0.1 mL, 0.91 mmol) afforded **9g** (290.3 mg, 91%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 191−194 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.96 (d, J^3 = 4.5 Hz, 1H), 8.23 (d, J^3 = 9.1 Hz, 1H), 8.07 (d, J^4 = 2.2 Hz, 1H), 7.73 (d, J^3 = 4.5 Hz, 1H), 7.63−7.62 (m, 1H), 7.60 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.45−7.42 (m, 1H), 7.36−7.34 (m, 1H), 7.28−7.24 (m, 1H), 6.51 (d, J^3 = 4.4 Hz, 1H), 6.43 (d, J^3 = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.9, 149.5, 148.4, 146.1, 133.7, 133.6, 130.3, 129.5, 128.2, 127.0, 126.8, 125.9, 123.8, 121.7, 119.3, 70.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{79}Br^{35}ClNO$: 347.9785, found: 347.9772 (Δ = −3.7 ppm).

*(7-Chloroquinolin-4-yl)(2-fluorophenyl)methanol (**9h**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (296.0 mg, 1.02 mmol) and 2-fluorobenzaldehyde (0.11 mL, 1.02 mmol) afforded **9h** (179.8 mg, 61%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 144−145 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.83 (d, J^3 = 4.5 Hz, 1H), 8.02 (d, J^4 = 2.2 Hz, 1H), 7.86 (d, J^3 = 9.0 Hz, 1H), 7.72 (d, J^3 = 4.5 Hz, 1H), 7.41 (dd, J^3 = 9.0, J^4 = 2.2 Hz, 1H), 7.31−7.26 (m, 1H), 7.20 (td, J^3 = 7.7, J^4 = 1.8 Hz, 1H), 7.11−7.05 (m, 2H), 6.80 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 160.1 (d, J^1 = 247.4 Hz, 1C), 151.4, 148.7, 148.1, 135.3, 130.5 (d, J^3 = 8.6 Hz, 1C), 129.1, 129.0, 128.8 (d, J^3 = 2.9 Hz, 1C), 127.9, 125.0, 124.9 (d, J^4 = 3.3 Hz, 1C), 124.1, 118.8, 115.9 (d, J^2 = 21.9 Hz, 1C), 65.8 (d, J^3 = 4.0 Hz, 1C); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClFNO$: 288.0586, found: 288.0578 (Δ = −2.8 ppm).

*(7-Chloroquinolin-4-yl)(3-fluorophenyl)methanol (**9i**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (198.0 mg, 0.68 mmol) and 3-fluorobenzaldehyde (0.07 mL, 0.68 mmol) afforded **9i** (133.6 mg, 68%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 165−167 °C; IR (ATR, cm^{-1}): 3119, 1438, 870, 749; ^1H NMR (400 MHz, MeOD-d_4) δ: 8.91 (d, J^3 = 4.6 Hz, 1H), 8.14 (d, J^3 = 9.1 Hz, 1H), 8.03 (d, J^4 = 2.1 Hz, 1H), 7.77 (d, J^3 = 4.6 Hz, 1H), 7.52 (dd, J^3 = 9.1, J^4 = 2.1 Hz, 1H), 7.35−7.30 (m, 1H), 7.19−7.16 (m, 1H), 7.02−6.97 (m, 1H), 6.47 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, MeOD-d_4) δ: 164.3 (d, J^1 = 245.2 Hz, 1C), 152.5, 151.9, 149.5, 146.7 (d, J^3 = 6.8 Hz, 1C), 136.5, 131.5 (d, J^3 = 8.1 Hz, 1C), 128.7, 128.6, 127.6, 125.7, 124.1 (d, J^4 = 2.9 Hz, 1C), 120.5, 115.6 (d, J^2 = 21.2 Hz, 1C), 115.0 (d, J^2 = 22.5 Hz, 1C), 72.6 (d, J^4 = 1.2 Hz, 1C); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClFNO$: 288.0586, found: 288.0584 (Δ = −0.7 ppm).

*(7-Chloroquinolin-4-yl)(4-fluorophenyl)methanol (**9j**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (287.0 mg, 0.99 mmol) and 4-fluorobenzaldehyde (0.1 mL, 0.99 mmol) afforded **9j** (203.0 mg, 71%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 152−154 °C; IR (ATR, cm^{-1}): 3115, 1604, 765; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.82 (d, J^3 = 4.5 Hz, 1H), 8.03 (d, J^4 = 2.2 Hz, 1H), 7.82 (d, J^3 = 9.0 Hz, 1H), 7.67 (d, J^3 = 4.5 Hz, 1H), 7.39 (dd, J^3 = 9.0, J^4 = 2.2 Hz, 1H), 7.34−7.29 (m, 2H), 7.04−6.98 (m, 2H), 6.42 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 163.9 (d, J^1 = 248.0 Hz, 1C), 151.4, 148.8, 148.7, 137.8 (d, J^4 = 3.1 Hz, 1C), 135.3, 129.2, 129.1 (d, J^3 = 6.4 Hz, 2 × C), 127.9, 125.4, 124.1, 118.8, 116.1 (d, J^2 = 21.4 Hz, 2 × C), 72.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClFNO$: 288.0586, found: 288.0589 (Δ = 1.0 ppm).

*(7-Chloroquinolin-4-yl)(2-(trifluoromethyl)phenyl)methanol (**9k**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (272.0 mg, 0.94 mmol) and 2-(trifluoromethyl)benzaldehyde (0.12 mL, 0.94 mmol) afforded **9k** (278.5 mg, 88%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 187−190 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.91 (d, J^3 = 4.5 Hz, 1H), 8.12 (d, J^4 = 2.2 Hz, 1H), 8.07 (d, J^3 = 9.1 Hz, 1H), 7.82 (d, J^3 = 7.7 Hz, 1H), 7.72−7.66 (m, 2H), 7.60−7.56 (m, 2H), 7.21 (d, J^3 = 4.5 Hz, 1H), 6.69 (d, J^3 = 6.0 Hz, 1H), 6.58 (d, J^3 = 6.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.7, 148.7, 148.4, 140.6, 133.8, 132.9, 129.5, 128.5, 128.3, 127.4, 126.4 (q, J^2 = 30.0 Hz, 1C), 126.1 (q, J^3 = 5.8 Hz, 1C), 125.9, 124.4 (q, J^1 = 274.7 Hz, 1C), 124.3, 119.7, 66.4 (d, J^4 = 1.7 Hz, 1C); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}{}^{35}ClF_3NO$: 338.0554, found: 388.0550 (Δ = −1.2 ppm).

*(7-Chloroquinolin-4-yl)(3-(trifluoromethyl)phenyl)methanol (**9l**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (283.0 mg, 0.98 mmol) and 3-(trifluoromethyl)benzaldehyde (0.13 mL, 0.98 mmol) afforded **9l** (298.8 mg, 91%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 161−163 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.98 (d, J^3 = 4.5 Hz, 1H), 8.27 (d, J^3 = 9.1 Hz, 1H), 8.08 (d, J^4 = 2.2 Hz, 1H), 7.84 (s, 1H), 7.73 (d, J^3 = 4.5 Hz, 1H), 7.64−7.59 (m, 3H), 7.55−7.51 (m, 1H), 6.61 (d, J^3 = 4.5 Hz, 1H), 6.56 (d, J^3 = 4.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.9, 149.4, 148.5, 144.7, 133.8, 130.9, 129.5, 129.1 (q, J^2 = 31.5 Hz, 1C), 128.2, 127.0, 126.7124.2 (q, J^3 = 3.7 Hz, 1C), 124.1 (q, J^1 = 272.6 Hz, 1C), 123.8, 123.2 (q, J^3 = 3.9 Hz, 1C), 119.4, 70.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}{}^{35}ClF_3NO$: 338.0554, found: 338.0549 (Δ = −1.5 ppm).

*(7-Chloroquinolin-4-yl)(2-nitrophenyl)methanol (**9m**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (269.0 mg, 0.93 mmol) and 2-nitrobenzaldehyde (140.4 mg, 0.93 mmol) afforded **9m** (233.9 mg, 80%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 195−197 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.86 (d, J^3 = 4.5 Hz, 1H), 8.27 (d, J^3 = 9.1 Hz, 1H), 8.13 (d, J^4 = 2.2 Hz, 1H), 8.07 (dd, J^3 = 8.1 Hz, J^4 = 1.1 Hz, 1H), 7.79 (ddd, J^3 = 7.8 Hz, J^4 = 1.1 Hz, J^4 = 0.6 Hz, 1H), 7.73−7.68 (m, 2H), 7.66−7.61 (m, 1H), 7.10 (d, J^3 = 4.5 Hz, 1H), 7.00 (d, J^3 = 6.2 Hz, 1H), 6.67 (d, J^3 = 6.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.8, 148.4, 148.1, 147.8, 137.1, 133.9, 133.7, 129.3, 129.2, 128.2, 127.4, 126.4, 124.7, 124.6, 119.2, 66.3; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClN_2O_3$: 315.0531, found: 315.0525 (Δ = −1.9 ppm).

*(7-Chloroquinolin-4-yl)(3-nitrophenyl)methanol (**9n**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (262.0 mg, 0.90 mmol) and 3-nitrobenzaldehyde (136.7 mg, 0.90 mmol) afforded **9n** (242.2 mg, 85%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 198−200 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 8.98 (d, J^3 = 4.4 Hz, 1H), 8.34−8.33 (m, 1H), 8.28 (d, J^3 = 9.1 Hz, 1H), 8.11 (ddd, J^3 = 8.2 Hz, J^4 = 2.3 Hz, J^4 = 0.9 Hz, 1H), 8.08 (d, J^4 = 2.2 Hz, 1H), 7.80 (d, J^3 = 7.8 Hz, 1H), 7.75 (d, J^3 = 4.4 Hz, 1H), 7.62−7.58 (m, 2H), 6.73 (d, J^3 = 4.5 Hz, 1H), 6.61 (d, J^3 = 4.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.9, 149.1, 148.5, 147.8, 145.6, 133.8, 133.4, 130.0, 128.3, 127.1, 126.8, 123.8, 122.4, 121.3, 119.6, 70.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}ClN_2O_3$: 315.0531, found: 315.0537 (Δ = 1.9 ppm).

*(7-Chloroquinolin-4-yl)(2-methoxyphenyl)methanol (**9o**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (350.0 mg, 1.21 mmol) and 2-methoxybenzaldehyde (164.6 mg, 1.21 mmol) afforded **9o** (283.7 mg, 78%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 170−171 °C; ^1H NMR (400 MHz, DMSO-d_6) δ:

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

8.91 (d, J^3 = 4.5 Hz, 1H), 8.16 (d, J^3 = 9.0 Hz, 1H), 8.06 (d, J^4 = 2.2 Hz, 1H), 7.61 (dd, J^3 = 9.0, J^4 = 2.2 Hz, 1H), 7.58 (d, J^3 = 4.5 Hz, 1H), 7.28−7.23 (m, 2H), 7.04−7.01 (m, 1H), 6.90 (td, J^3 = 7.5 Hz, J^4 = 0.9 Hz, 1H), 6.68 (d, J^3 = 5.0 Hz, 1H), 6.12 (d, J^3 = 5.0 Hz, 1H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 155.7, 151.7, 150.5, 148.2, 133.5, 131.0, 128.9, 128.1, 127.7, 126.9, 126.2, 124.3, 120.5, 119.0, 111.1, 64.2, 55.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}{}^{35}ClNO_2$: 300.0786, found: 300.0782 (Δ = −1.3 ppm).

*(7-Chloroquinolin-4-yl)(3-methoxyphenyl)methanol (**9p**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (277.0 mg, 0.95 mmol) and 3-methoxybenzaldehyde (0.11 mL, 0.95 mmol) afforded **9p** (231.1 mg, 81%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 168−169 °C; IR (ATR, cm^{-1}): 3115, 1483, 774; ^1H NMR (400 MHz, MeOD-d_4) δ: 8.89 (d, J^3 = 4.6 Hz, 1H), 8.12 (d, J^3 = 9.1 Hz, 1H), 8.01 (d, J^4 = 2.2 Hz, 1H), 7.78 (d, J^3 = 4.6 Hz, 1H), 7.48 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.21 (t, J^3 = 7.9 Hz, 1H), 6.98 (t, J^4 = 2.1 Hz, 1H), 6.92 (d, J^3 = 7.9 Hz, 1H), 6.82 (dd, J^3 = 7.9, J^4 = 2.1 Hz, 1H), 6.42 (s, 1H), 3.73 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, MeOD-d_4) δ: 161.4, 152.4, 152.3, 149.4, 145.3, 136.4, 130.7, 128.6, 128.4, 127.6, 125.8, 120.6, 120.3, 114.2, 114.2, 73.1, 55.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{15}{}^{35}ClNO_2$: 300.0786, found: 300.0784 (Δ = −0.7 ppm).

*4-((7-Chloroquinolin-4-yl)(hydroxy)methyl)benzonitrile (**9q**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (386.0 mg, 1.33 mmol) and 4-formylbenzonitrile (174.8 mg, 1.33 mmol) afforded **9q** (253.2 mg, 64%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 181−183 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.97 (d, J^3 = 4.5 Hz, 1H), 8.24 (d, J^3 = 9.1 Hz, 1H), 8.08 (d, J^4 = 2.2 Hz, 1H), 7.78 (d, J^3 = 8.3 Hz, 2H), 7.71 (d, J^3 = 4.5 Hz, 1H), 7.62−7.57 (m, 3H), 6.65 (d, J^3 = 4.5 Hz, 1H), 6.52 (d, J^3 = 4.5 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.8, 149.2, 148.7, 148.5, 133.8, 132.3 (2 × C), 128.2, 127.7 (2 × C), 127.0, 126.8, 123.8, 119.6, 118.7, 110.1, 70.4; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{12}{}^{35}ClN_2O$: 295.0633, found: 295.0645 (Δ = 4.0 ppm).

*(7-Chloroquinolin-4-yl)(4-(dimethylamino)phenyl)methanol (**9r**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (306.0 mg, 1.06 mmol) and 4-(dimethylamino)benzaldehyde (157.7 mg, 1.06 mmol) afforded **9r** (246.1 mg, 74%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 196−198 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.95 (d, J^3 = 4.5 Hz, 1H), 8.14 (d, J^3 = 9.1 Hz, 1H), 8.04 (d, J^4 = 2.2 Hz, 1H), 7.78 (d, J^3 = 4.5 Hz, 1H), 7.53 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.15 (d, J^3 = 8.7 Hz, 2H), 6.62 (t, J^3 = 8.7 Hz, 2H), 6.30 (d, J^3 = 4.2 Hz, 1H), 6.05 (d, J^3 = 4.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.7, 151.0, 149.7, 148.3, 133.4, 130.8, 128.1, 127.9 (2 × C), 126.8, 126.6, 123.9, 118.6, 112.1 (2), 70.6, 40.0 (2 × C); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}{}^{35}ClN_2O$: 313.1102, found: 313.1108 (Δ = 1.9 ppm).

*(7-Chloroquinolin-4-yl)(2,4-dimethoxyphenyl)methanol (**9s**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (259.0 mg, 0.89 mmol) and 2,4-dimethoxybenzaldehyde (148.6 mg, 1.21 mmol) afforded **9s** (242.9 mg, 82%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 194−196 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.92 (d, J^3 = 4.5 Hz, 1H), 8.06 (m, 2H), 7.63 (d, J^3 = 4.5 Hz, 1H), 7.59 (dd, J^3 = 9.0, J^4 = 2.3 Hz, 1H), 7.04 (d, J^3 = 8.5 Hz, 1H), 6.58−6.60 (m, 2H), 6.45 (dd, J^3 = 8.5, J^4 = 2.4 Hz, 1H), 5.98 (d, J^3 = 4.9 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 160.0, 156.8, 151.7, 150.8, 148.2, 133.5, 128.6, 128.1, 126.9, 126.2, 124.2, 123.5, 118.8, 105.1, 98.3, 63.9, 55.6, 55.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}{}^{35}ClNO_3$: 330.0891, found: 330.0889 (Δ = −0.6 ppm).

3-((7-Chloroquinolin-4-yl)(hydroxy)(methyl)-2-fluorobenzonitrile (9t)). Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (302.0 mg, 1.04 mmol) and 2-fluoro-3-formilbenzonitrile (155.4 mg, 1.04 mmol) afforded **9t** (240.3 mg, 74%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 194−196 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.97 (d, J^3 = 4.5 Hz, 1H), 8.13−8.10 (m, 2H), 7.88 (ddd, J^3 = 7.7, J^3 = 7.7, J^4 = 1.4 Hz, 1H), 7.65−7.62 (m, 2H), 7.40 (t, J^3 = 7.7 Hz, 1H), 6.75 (d, J^3 = 5.0 Hz, 1H), 6.69 (d, J^3 = 5.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 159.8 (d, J^1 = 257.3 Hz, 1C), 151.9, 148.4, 147.7, 134.4 (d, J^3 = 4.6 Hz, 1C), 133.9, 133.5, 131.3 (d, J^2 = 12.4 Hz, 1C), 128.3, 127.4, 126.0, 125.7 (d, J^3 = 3.6 Hz, 1C), 123.7, 119.5, 113.9, 100.4 (d, J^2 = 15.3 Hz, 1C), 64.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{11}{}^{35}ClFNO_2$: 313.0538, found: 313.0540 (Δ = 0.6 ppm).

*(7-Chloroquinolin-4-yl)(thiofen-2-yl)methanol (**9u**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (258.0 mg, 0.89 mmol) and thiophene-2-carboxaldehyde (0.08 mL, 0.89 mmol) afforded **9u** (203.7 mg, 83%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 180−182 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.98 (d, J^3 = 4.5 Hz, 1H), 8.27 (d, J^3 = 9.1 Hz, 1H), 8.09 (d, J^4 = 2.2 Hz, 1H), 7.77 (d, J^3 = 4.5 Hz, 1H), 7.59 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.41 (dd, J^3 = 4.8, J^4 = 1.5 Hz, 1H), 6.92−6.89 (m, 2H), 6.69−6.65 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.9, 149.9, 148.4, 147.1, 133.7, 128.2, 126.9, 126.7, 126.6, 125.6, 125.1, 123.7, 118.5, 67.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}{}^{35}ClNOS$: 276,0244, found: 276.0253 (Δ = 3.2 ppm).

*(7-Chloroquinolin-4-yl)(furan-2-yl)methanol (**9v**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (292.0 mg, 1.01 mmol) and furan-2-carboxaldehyde (0.08 mL, 1.01 mmol) afforded **9v** (226.6 mg, 86%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 139−141 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.97 (d, J^3 = 4.5 Hz, 1H), 8.17 (d, J^3 = 9.1 Hz, 1H), 8.09 (d, J^4 = 2.2 Hz, 1H), 7.76 (d, J^3 = 4.5 Hz, 1H), 7.59 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.55 (dd, J^3 = 1.8, J^4 = 0.9 Hz, 1H), 6.47−6.45 (m, 2H), 6.37 (dd, J^3 = 3.2, J^3 = 1.8 Hz, 1H), 6.25 (d, J^3 = 3.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 155.4, 151.8, 148.2, 147.7, 142.6, 133.6, 128.1, 126.9, 126.4, 123.9, 119.2, 110.4, 107.6, 64.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}{}^{35}ClNO_2$: 260.0473, found: 260.0462 (Δ = −4.2 ppm).

*(7-Chloroquinolin-4-yl)(furan-3-yl)methanol (**9w**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (284.0 mg, 0.98 mmol) and furan-3-carboxaldehyde (0.08 mL, 0.98 mmol) afforded **9w** (237.2 mg, 93%) as a light yellow oil after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.95 (d, J^3 = 4.5 Hz, 1H), 8.26 (d, J^3 = 9.1 Hz, 1H), 8.08 (d, J^4 = 2.2 Hz, 1H), 7.74 (d, J^3 = 4.5 Hz, 1H), 7.60−7.57 (m, 2H), 7.54 (t, J^3 = 1.6 Hz, 1H), 6.38 (d, J^3 = 4.6 Hz, 1H), 6.34 (m, 1H), 6.22 (d, J^3 = 4.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.8, 149.9, 148.4, 143.4, 140.0, 133.6, 128.4, 128.1, 126.8, 126.6, 123.8, 118.8, 109.7, 63.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}{}^{35}ClNO_2$: 260.0473, found: 260.0463 (Δ = −3.8 ppm).

*(7-Chloroquinolin-4-yl)(pyridin-2-yl)methanol (**9x**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (367.0 mg, 1.27 mmol) and pyridine-2-carbaldehyde (0.12 mL, 1.27 mmol) afforded **9x** (239.9 mg, 70%) as a colorless oil after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.86 (d, J^3 = 4.5 Hz, 1H), 8.60 (d, J^3 = 4.6 Hz, 1H), 8.09 (d, J^4 = 2.2 Hz, 1H), 8.07 (d, J^3 = 9.0 Hz, 1H), 7.60 (td, J^3 = 7.7, J^4 = 1.7 Hz, 1H), 7.50 (d, J^3 = 4.5 Hz, 1H), 7.37 (dd, J^3 = 9.0, J^3 = 2.2 Hz, 1H), 7.24 (ddd, J^3 = 7.1, J^3 = 5.0, J^4 = 0.3 Hz, 1H), 6.39 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 159.5, 151.4, 149.2, 148.5, 148.1, 137.4, 135.2, 129.1, 127.8, 125.9, 124.8, 123.2, 121.4, 120.0, 72.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}{}^{35}ClNO_2$: 271.0633, found: 271.0628 (Δ = −1.8 ppm).

*(7-Chloroquinolin-4-yl)(pyridin-3-yl)methanol (**9y**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (308.0 mg, 1.06 mmol) and pyridine-3-carbaldehyde (0.10 mL, 1.06 mmol) afforded **9y** (259.7 mg, 90%) as a colorless crystal after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 100−102 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.98 (d, J^3 = 4.5 Hz, 1H), 8.68 (d, J^4 = 1.6 Hz, 1H), 8.44 (dd, J^3 = 4.7, J^4 = 1.4 Hz, 1H), 8.21 (d, J^3 = 9.0 Hz, 1H), 8.07 (d, J^4 = 2.2 Hz, 1H), 7.79 (d, J^3 = 4.5

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

Hz, 1H), 7.70 (ddd, J^3 = 7.9, J^4 = 1.8, J^4 = 1.8 Hz, 3H), 7.58 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.31 (dd, J^3 = 7.9, J^3 = 4.8 Hz, 1H), 6.55 (d, J^3 = 4.4 Hz, 1H), 6.51 (d, J^3 = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.9, 149.4, 148.7, 148.4 (2 × C), 138.7, 134.5, 133.8, 128.3, 127.1, 126.6, 123.7, 123.6, 119.2, 68.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{12}{}^{35}ClN_2O$: 271.0633, found: 271.0629 (Δ = −1.5 ppm).

*1-(7-Chloroquinolin-4-yl)-2-methylpropan-1-ol (**9z**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (231.0 mg, 0.80 mmol) and isobutyraldehyde (0.07 mL, 0.80 mmol) afforded **9z** (93.7 mg, 61%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 113−114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.76 (d, J^3 = 4.5 Hz, 1H), 8.03 (d, J^4 = 2.2 Hz, 1H), 7.97 (d, J^3 = 9.1 Hz, 1H), 7.48 (d, J^3 = 4.5 Hz, 1H), 7.45 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 5.15 (d, J^3 = 5.4 Hz, 1H), 2.21−2.09 (m, 1H), 0.97 (d, J^3 = 6.7 Hz, 3H), 0.95 (d, J^3 = 6.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 151.0, 150.2, 148.7, 135.1, 129.0, 127.4, 125.1, 124.4, 119.0, 75.2, 34.7, 20.1, 17.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{13}H_{15}{}^{35}ClNO$: 236.0837, found: 236.0833 (Δ = −1.7 ppm).

*(7-Chloroquinolin-4-yl)(cyclohexyl)methanol (**9aa**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (239.0 mg, 0.82 mmol) and cyclohexane carboxaldehyde (0.10 mL, 0.82 mmol) afforded **9aa** (198.5 mg, 87%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 141−143 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.88 (d, J^3 = 4.5 Hz, 1H), 8.29 (d, J^3 = 9.1 Hz, 1H), 8.07 (d, J^4 = 2.2 Hz, 1H), 7.62 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 7.55 (d, J^3 = 4.5 Hz, 1H), 5.57 (d, J^3 = 4.4 Hz, 1H), 5.05 (t, J^3 = 4.4 Hz, 1H), 1.67−1.54 (m, 5H), 1.36−1.33 (m, 1H), 1.21−1.04 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.2, 150.9, 148.3, 133.5, 128.2, 126.6, 126.6, 124.4, 119.6, 72.9, 44.2, 29.6, 27.3, 25.9, 25.8, 25.5; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{19}{}^{35}ClNO$: 276.1150, found: 276.1152 (Δ = 0.7 ppm).

*(7-Chloroquinolin-4-yl)(phenyl)methanone (**10a**).* CAS number: 169957-11-3. The Weinreb amide, *N*-methoxy-*N*-methylbenzamide (**24**), was obtained as colorless oil (2.289 g, 13.87 mmol) in 92% isolated yield from *N*-methoxy-*N*-methylamine hydrochloride (1.463 g, 15 mmol), benzoyl chloride (1.74 mL, 15 mmol), and triethylamine (4.2 mL, 30 mmol) in DCM (30 mL) according to the reported procedure in the literature.[90] Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (179.0 mg, 0.62 mmol) and *N*-methoxy-*N*-methylbenzamide (0.20 mL, 1.24 mmol) afforded **10a** (96.0 mg, 58%) as a white solid after chromatographic purification using EtOAc/hexanes (1:9) as an eluent; m.p.: 106−109 °C; ^1H NMR(400 MHz, $CDCl_3$) δ: 9.04 (d, J = 4.4 Hz, 1H), 8.25 (d, J = 2.1 Hz, 1H), 7.85−7.81 (m, 3H), 7.68−7.64 (m, 1H), 7.52−7.47 (m, 3H), 7.43 (d, J = 4.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 195.4, 150.2, 148.5, 145.0, 136.6, 136.4, 134.6, 130.4 (2 × C), 129.1, 129.0 (2 × C), 128.6, 126.9, 123.6, 119.9; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{11}{}^{35}ClNO$: 268.0524, found: 268.0518 (Δ = −2.2 ppm).

*1-(7-Chloroquinoline-4-yl)cyclohena-1-ol (**10b**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (175.0 mg, 0.60 mmol) and cyclohexanone (0.06 mL, 0.60 mmol) afforded **10b** (81.0 mg, 51%) as a white solid after chromatographic purification using EtOAc/hexanes (1:9) as an eluent; m.p.: 134−136 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.84 (d, J^3 = 9.3 Hz, 1H), 8.68 (d, J^3 = 4.7 Hz, 1H), 8.02 (d, J^4 = 2.3 Hz, 1H), 7.44 (dd, J = 9.3, J^3 = 2.3 Hz, 1H), 7.34 (d, J^3 = 4.7 Hz, 1H), 2.53 (s, 1H), 2.17−2.11 (m, 2H), 1.98−1.71 (m, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 154.0, 150.9, 150.1, 134.6, 129.2, 129.1, 126.6, 125.0, 117.4, 74.2, 38.1 (2 × C), 25.6, 22.0 (2 × C); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{17}{}^{35}ClNO$: 262.7565, found: 262.7567 (Δ = 0.8 ppm).

*7-Chloroquinoline-4-carbonitrile (**10c**).* CAS number: 13337-75-2. Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (168.0 mg, 0.58 mmol) and *p*-toluenesulfoyl cyanide (115.7 mg, 0.64 mmol) afforded **10c** (93.0 mg, 85%) as a white solid after chromatographic purification using EtOAc/hexanes (1:9) as an eluent; m.p.: 171−172 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.05 (d, J^3 = 4.3 Hz, 1H), 8.21 (d, J^4 = 2.0 Hz, 1H), 8.14 (d, J^3 = 8.9 Hz, 1H), 7.74−7.71 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 150.7, 148.6, 137.6, 130.5, 129.5, 126.4, 125.0, 124.3, 118.9, 115.3; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_6{}^{35}ClN_2$: 189.0214, found: 189.0222 (Δ = 4.2 ppm).

*7-Chloro-4-(phenylthio)quinoline (**10d**).* CAS number: 1025-43-0. Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (173.0 mg, 0.60 mmol) and 1,2-diphenyldisulfide (131.0 mg, 0.60 mmol) afforded **10d** (116.0 mg, 71%) as a pale white solid after chromatographic purification using EtOAc/hexanes (1:19) as an eluent; m.p.: 85−87 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.55 (d, J^3 = 4.8 Hz, 1H), 8.14 (d, J^4 = 8.9 Hz, 1H), 8.06 (d, J^3 = 2.1 Hz, 1H), 7.59−7.57 (m, 2H), 7.53 (dd, J^3 = 8.9 Hz, J^4 = 2.1 Hz, 1H), 7.50−7.41 (m, 3H), 6.72 (d, J^3 = 4.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 150.6, 149.2, 148.3, 135.9, 135.5 (2 × C), 130.3 (2 × C), 130.0, 129.2, 129.0, 127.6, 125.1, 124.5, 118.0; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}{}^{35}ClNS$: 272.0295, found: 272.0299 (Δ = 1.5 ppm).

*7-Chloro-4-(phenylselanyl)quinoline (**10e**).* CAS number: 1415931-33-7. Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (283.0 mg, 0.98 mmol) and 1,2-diphenyldiselenide (329.5 mg, 1.05 mmol) afforded **10e** (284.2 mg, 91%) as a pale yellow solid after chromatographic purification using EtOAc/hexanes (1:19) as an eluent; m.p.: 93−95 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.53 (d, J^3 = 4.7 Hz, 1H), 8.08 (d, J^4 = 2.1 Hz, 1H), 8.02 (d, J^3 = 9.0 Hz, 1H), 7.68−7.65 (m, 2H), 7.53 (dd, J^3 = 9.0, J^4 = 2.1 Hz, 1H), 7.50−7.41 (m, 3H), 6.99 (d, J^3 = 4.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 150.6, 148.4, 146.2, 136.4 (2 × C), 135.9, 130.3 (2 × C), 129.7, 129.1, 127.8, 126.9, 126.5, 126.3, 122.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}{}^{35}ClNSe$: 319.9740, found: 319.9729 (Δ = −3.4 ppm).

*7-Chloroquinoline-4-carbaldehyde (**10f**).* CAS number: 35714-48-8. Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (318.0 mg, 1.10 mmol) and DMF (0.25 mL, 3.29 mmol) afforded **10f** (162.0 mg, 77%) as a white solid after chromatographic purification using EtOAc/hexanes (1:9) as an eluent; m.p.: 112−113 °C; ^1H NMR (400 MHz, $CDCl_3$) δ: 10.45 (s, 1H), 9.21 (d, J^3 = 4.2 Hz, 1H), 8.99 (d, J^3 = 9.1 Hz, 1H), 8.20 (d, J^4 = 2.1 Hz, 1H), 7.79 (d, J^3 = 4.2 Hz, 1H), 7.67 (dd, J^3 = 9.1, J^4 = 2.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ: 192.7, 151.7, 149.8, 136.9, 136.5, 130.4, 129.1, 126.3, 126.2, 122.2; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{10}H_7{}^{35}ClNO$: 192.0211, found: 192.0217 (Δ = 3.1 ppm).

*(E)-1-(7-Chloroquinolin-4-yl)-3-phenylprop-2-en-1-ol (**16**).* Following the general procedure **TP1**, 7-chloro-4-iodoquinoline (7) (320.0 mg, 1.10 mmol) and *trans*-cinnamaldehyde (0.14 mL, 1.10 mmol) afforded **16** (301.0 mg, 92%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 142−146 °C; ^1H NMR (400 MHz, DMSO-d_6) δ: 8.94 (d, J^3 = 4.5 Hz, 1H), 8.40 (d, J^3 = 9.1 Hz, 1H), 8.09 (d, J^4 = 2.2 Hz, 1H), 7.70 (d, J^3 = 4.5 Hz, 1H), 7.65 (dd, J^3 = 9.1 Hz, J^4 = 2.2 Hz, 1H), 7.42−7.39 (m, 2H), 7.30−7.27 (m, 2H), 7.23−7.19 (m, 1H), 6.80 (d, J^3 = 15.9 Hz, 1H), 6.49 (dd, J^3 = 15.9, J^3 = 6.2 Hz, 1H), 6.15 (d, J^3 = 4.3 Hz, 1H), 6.01−5.99 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ: 151.9, 149.7, 148.4, 136.2, 133.7, 131.5, 130.0, 128.6 (2 × C), 128.2, 127.7, 126.9, 126.7, 126.4 (2 × C), 124.0, 118.8, 69.6; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{15}{}^{35}ClNO$: 296.0837, found: 296.0829 (Δ = −2.7 ppm).

Lithiation of 4,7-Dichloroquinoline Using LDA and trans-Cinnamaldehyde as an Electrophile. To a dry nitrogen-flushed round-bottom flask (10 mL) under magnetic stirring containing a solution of diisopropylamine (0.44 mL, 3.15 mmol) in dry THF (1 mL), *n*-butyllithium (1.22 mL, 2.86 mmol, 2.5 mol·L^{-1} in hexanes) was added dropwise at −70 °C. After 10 min, the reaction mixture was allowed to warm to 0 °C and kept under magnetic stirring at the same temperature for 20 min. Then, the reaction flask was cooled to −70 °C, and a solution of 4,7-dichloroquinoline (378.0 mg, 1.91 mmol) in dry THF (3.5 mL) was added dropwise to the reaction mixture. The system was kept under magnetic stirring at −70 °C for 60 min. To the mixture was added *trans*-cinnamaldehyde (0.29 mL, 2.29 mmol), and the reaction mixture was kept under magnetic

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

stirring for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The product was extracted with EtOAc (3 × 15 mL), the organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by column chromatography using a mixture of hexanes and EtOAc (4:1) as an eluent to afford (*E*)-1-(4,7-dichloroquinolin-3-yl)-3-phenylprop-2-en-1-ol (**19**) (315.0 mg, 50%) as a pale yellow solid; m.p.: 137−139 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.10 (s, 1H), 8.23 (d, J = 9.0 Hz, 2H), 8.15 (d, J = 2.1 Hz, 1H), 7.78 (dd, J = 9.0, J = 2.1 Hz, 1H), 7.46−7.44 (m, 1H), 7.31−7.28 (m, 2H), 7.24−7.20 (m, 1H), 6.75 (d, J = 15.8 Hz, 1H), 6.51 (dd, J = 15.8, J = 6.1 Hz 1H), 6.27 (s, 1H), 5.84 (d, J = 6.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ: 151.4, 147.8, 138.0, 136.2, 134.9, 134.4, 130.2, 129.9, 128.8, 128.0, 127.8, 126.5, 126.0, 123.9, 69.1; HRMS (ESI) m/z: ([M + H]$^+$ calcd for $C_{18}H_{14}{}^{35}Cl_2NO$: 330,0447, found: 330.0444 (Δ = −0.9 ppm)).

Typical Procedure 2 (TP2). *Oxidation Reaction of Carbinol Derivatives Using a Dess−Martin Reagent.* To a dry flask (100 mL) containing a solution of the appropriate alcohol (2.48 mmol) in anhydrous dichloromethane (49.6 mL) at room temperature was added slowly DMP (1.5793 g, 3.72 mmol), and the reaction mixture was kept under magnetic stirring for 12 h. The crude was then concentrated under reduced pressure, and the residue was solubilized in diethyl ether (30 mL). The etheric solution was washed with an aqueous solution (15 mL) of a 1:1 mixture of $Na_2S_2O_3$ (10%):saturated $NaHCO_3$. Then, the organic phase was washed with water (10 mL) and brine (10 mL). The all-aqueous phases were extracted with diethyl ether (20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using a mixture of hexanes and EtOAc as an eluent.

*(7-Chloroquinolin-4-yl)(phenyl)methanone (**10a**).* CAS number: 169957-11-3. Following the general procedure **TP2**, the alcohol **9a** (669.0 mg, 2.48 mmol) and DMP (1.5793 g, 3.72 mmol) afforded **10a** (590.2 mg, 89%) as a white solid after chromatographic purification using EtOAc/hexanes (1:9) as an eluent; m.p.: 106−109 °C; spectroscopic data were reported previously.

*(E)-1-(7-Chloroquinolin-4-yl)-3-phenylprop-2-en-1-one (**17**).* Following the general procedure **TP2**, alcohol **16** (301.0 mg, 1.02 mmol) and DMP (647.5 mg, 1.52 mmol) afforded **17** (246.0 mg, 82%) as a white solid after chromatographic purification using EtOAc/hexanes (1:9) as an eluent; m.p.: 117−119 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.04 (d, J^3 = 4.3 Hz, 1H), 8.19 (d, J^4 = 2.1 Hz, 1H), 8.07 (d, J^3 = 9.0 Hz, 1H), 7.57−7.51 (m, 5H), 7.45−7.39 (m, 3H), 7.21 (d, J^3 = 16.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 194.1, 150.9, 149.4, 148.4, 144.6, 136.2, 134.0, 131.6, 129.3 (2 × C), 129.1, 129.0, 128.9 (2 × C), 126.9, 126.0, 123.1, 119.5; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{15}{}^{35}ClNO$: 294.0680, found: 294.0674 (Δ = −2.0 ppm).

*(E)-1-(4,7-Dichloroquinolin-3-yl)-3-phenylprop-2-en-1-one (**20**).* Following the general procedure **TP2**, alcohol **19** (175.0 mg, 0.53 mmol) and DMP (337.4 mg, 0.79 mmol) afforded **20** (110.0 mg, 63%) as a white solid after chromatographic purification using EtOAc/hexanes (1:9) as an eluent; m.p.: 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (s, 1H), 8.30 (d, J = 9.0 Hz, 2H), 8.18 (d, J = 2.0 Hz, 1H), 7.69 (dd, J^3 = 9.0 Hz, J^4 = 2.0 Hz, 1H), 7.61−7.54 (m, 3H), 7.46−7.40 (m, 3H), 7.25 (d, J = 16.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 191.6, 150.1, 149.7, 147.4, 140.4, 138.0, 134.2, 131.9, 131.5, 129.7, 129.3 (2 × C), 129.0, 128.9 (2 × C), 126.4, 126.1, 124.5; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{14}{}^{35}Cl_2NO$: 328.0290, found: 328.0284 (Δ = −1.8 ppm).

Typical Procedure 3 (TP3). *Halogen/Metal Exchange Reaction between 7-Chloro-4-iodoquinoline and i-PrMgCl·LiCl Followed by the Negishi Cross-coupling Reactions.* To a dry nitrogen-flushed round-bottom flask (10 mL) under magnetic stirring containing a solution of 7-chloro-4-iodoquinoline (**7**) (144.7 mg, 0.5 mmol, 1.0 equiv) in anhydrous THF (2.0 mL) at 0 °C was added dropwise *i*-PrMgCl·LiCl (0.42 mL, 1.2 mol·L^{-1}, 0.5 mmol, 1.0 equiv). After 10 min, the reaction mixture was cooled to −40 °C and an anhydrous THF solution of $ZnCl_2$ (0.52 mL, 1.0 mol·L^{-1}) was added. The flask was kept at this temperature for 20 min. Then, a solution of $Pd(PPh_3)_4$ (27.9 mg, 5 mol %) in THF (1.0 mL) and another with the appropriate electrophile (0.6 mmol) in THF (1.0 mL) were added at −40 °C. After that, the temperature was warmed to 60 °C and the reaction mixture was kept under stirring for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution, and the products were extracted with EtOAc (3 × 10 mL). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using a mixture of hexanes/EtOAc as an eluent.

*7-Chloro-4-(4-chlorophenyl)quinoline (**12a**).* CAS number: 1318249-22-7. Following the general procedure **TP3**, 7-chloro-4-iodoquinoline (**7**) (232.0 mg, 0.80 mmol) and 1-chloro-4-iodobenzene (210.2 mg, 0.88 mmol) afforded **12a** (149.0 mg, 68%) as a pale yellow solid after chromatographic purification using EtOAc/hexane (1:4) as an eluent ; m.p.: 103−105 °C; IR (ATR, cm^{-1}): 1597, 1418, 1010, 773; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (d, J = 4.4 Hz, 1H), 8.17 (d, J = 2.1 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.46 (dd, J^3 = 9.0, J^4 = 2.1 Hz, 1H), 7.42 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.1, 149.3, 147.4, 136.0, 135.6, 135.1, 130.9 (2 × C), 129.2 (2 × C), 129.0, 128.0, 127.1, 125.1, 121.5; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_9{}^{35}Cl_2N$: 274.0185, found: 274.0193 (Δ = 2.9 ppm).

*7-Chloro-4-(4-nitrophenyl)quinoline (**12b**).* CAS number: 192063-50-6. Following the general procedure **TP3**, 7-chloro-4-iodoquinoline (**7**) (286.0 mg, 0.99 mmol) and 1-iodo-4-nitrobenzene (268.4 mg, 1.08 mmol) afforded **12b** (210.0 mg, 75%) as a white solid after chromatographic purification using EtOAc/hexane (1:9) as an eluent; m.p.: 170−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.99 (d, J = 4.4 Hz, 1H), 8.41 (dl, J = 8.7 Hz, 2H), 8.19 (d, J = 2.1 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.67 (dl, J = 8.7 Hz, 2H), 7.50 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.35 (d, J = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.1, 149.2, 148.2, 146.1, 144.1, 136.0, 130.6 (2 × C), 129.2, 128.5, 126.5, 124.5, 124.1 (2 × C), 121.4; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{10}{}^{35}ClN_2O_2$: 285.0425, found: 285.0426 (Δ = 0.3 ppm).

*2-(7-Chloroquinolin-4-yl)benzonitrile (**12c**).* Following the general procedure **TP3**, 7-chloro-4-iodoquinoline (**7**) (193.0 mg, 0.67 mmol) and 2-iodobenzonitrile (183,0 mg, 0,80 mmol) afforded **12c** (102.0 mg, 58%) as a yellow solid after chromatographic purification using EtOAc/hexane (1:4) as an eluent ; m.p.: 166−168 °C; IR (ATR, cm^{-1}): 2230, 1583, 1482; 828; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.03 (d, J = 4.4 Hz, 1H), 8.23−8.20 (m, 1H), 7.89 (dd, J^3 = 7.8, J^4 = 0.9 Hz, 1H), 7.77 (ddd, J^3 = 7.7, J^3 = 7.7, J^4 = 1.4 Hz, 1H), 7.64 (ddd, J^3 = 7.7, J^3 = 7.7, J^4 = 1.4 Hz, 1H), 7.53−7.48 (m, 3H), 7.40 (d, J = 4.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.0, 149.1, 144.4, 141.0, 136.0, 133.7, 132.9, 130.9, 129.3, 129.2, 128.5, 126.6, 124.9, 122.1, 117.3, 113.1; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{10}{}^{35}ClN_2$: 265.0527, found: 265.0535 (Δ = 3.0 ppm).

*7-Chloro-4-(2-methoxyphenyl)quinoline (**12d**).* CAS number: 1663480-67-8. Following the general procedure **TP3**, 7-chloro-4-iodoquinoline (**7**) (172.0 mg, 0.59 mmol) and 1-iodo-2-methoxybenzene (0.08 mL, 0.65 mmol) afforded **12d** (118.0 mg, 74%) as a yellow oil after chromatographic purification using EtOAc/hexane (1:4) as an eluent; IR (ATR, cm^{-1}): 1601, 1486, 1238, 749; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.94 (d, J = 4.4 Hz, 1H), 8.15 (d, J = 2.1 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.51−7.46 (m, 1H), 7.39 (dd, J^3 = 9.0 Hz, J^4 = 2.1 Hz, 1H), 7.32 (d, J = 4.4 Hz, 1H), 7.27−7.22 (m, 1H), 7.11 (ddd, J^3 = 7.5, J^3 = 7.5, J^4 = 1.0 Hz, 1H), 7.07 (d, J = 8.3 Hz, 1H), 7.53−7.48 (m, 3H), 3.71 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 156.8, 151.1, 148.9, 146.1, 135.1, 131.3, 130.4, 128.6, 128.0, 127.3, 126.4, 126.1, 122.4, 120.9, 111.3, 55.6; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{13}{}^{35}ClNO$: 270.0680, found: 270.0692 (Δ = 4.4 ppm).

*Synthesis of 2-(7-Chloroquinolin-4-yl)-4,4-dimethyl-4,5-dihydrooxazole (**10g**).* To a nitrogen-flushed round-bottom flask (100 mL) containing molecular sieves 4A (1.3 g) and a solution of 2-amino-2-methylpropan-1-ol (0.08 mL, 0.84 mmol) in anhydrous dichloromethane (6 mL) was added 7-chloroquinoline-4-carboxalde-

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

hyde (**10f**) (162.0 mg, 0.84 mmol), and the reaction mixture was kept under magnetic stirring at 25 °C for 12 h. To the mixture was added *N*-bromosuccinimide (NBS) (180.0 mg, 1.01 mmol), and the reaction mixture was kept under stirring for 30 min until the medium turned red. Then, the reaction mixture was filtered and washed with saturated aqueous $NaHCO_3$ solution (4 × 70 mL) and water (70 mL). The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography using hexanes/EtOAc (4:1) as an eluent to afford compound **10g** (200.0 mg, 91%) as a needle white solid; m.p.: 78−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.10 (d, J^3 = 9.1 Hz, 1H), 8.97 (d, J^3 = 4.5 Hz, 1H), 8.13 (d, J^4 = 2.2 Hz, 1H), 7.86 (d, J^3 = 4.5 Hz, 1H), 7.57 (dd, J^3 = 9.1, J^4 = 2.2 Hz, 1H), 4.17 (s, 2H), 1.48 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 159.9, 151.0, 149.4, 135.7, 132.8, 128.8, 128.8, 128.3, 123.9, 121.9, 78.6, 69.1, 28.6 (2 × C); HRMS (ESI/Q-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{13}{}^{35}ClN_2NaO$: 283.0609, found: 283.0617 (Δ = 2.8 ppm).

*Magnesiation of 2-(7-Chloroquinolin-4-yl)-4,4-dimethyl-4,5-dihydrooxazole (**10h**) Using TMPMgCl·LiCl and Iodine as an Electrophile.* In a dry nitrogen-flushed round-bottom flask (10 mL) containing a solution of 2-(7-chloroquinolin-4-yl)-4,4-dimethyl-4,5-dihydrooxazole (**10g**) (74.0 mg, 0.28 mmol) in anhydrous THF (1.5 mL), an anhydrous solution of $ZnCl_2$ (0.14 mL, 0.14 mmol, 1.0 mol·L^{-1} in THF) in THF was added and the reactional flask was kept under magnetic stirring at 25 °C for 10 min. Then, TMPMgCl·LiCl (0.49 mL, 0.42 mmol, 0.87 mol·L^{-1} in THF) was added dropwise and the reaction mixture was stirred at 25 °C for 1 h. After this time, a solution of iodine (86.0 mg, 0.34 mmol) in THF (1 mL) was added and the system was kept under stirring for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution. The product was extracted with EtOAc (3 × 15 mL), the organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude was purified by column chromatography using a mixture of hexanes and EtOAc as an eluent to afford compound **10h** (103.0 mg, 94%) as a white solid; m.p.: 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.14 (d, J = 9.1 Hz, 1H), 9.04 (d, J = 4.5 Hz, 1H), 7.90 (d, J = 4.5 Hz, 1H), 7.65 (d, J = 9.1 Hz, 1H), 4.17 (s, 2H), 1.47 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 159.5, 151.6, 149.3, 141.9, 133.5, 128.8, 128.2, 124.1, 122.5, 108.2, 78.7, 69.3, 28.6 (2 × C); HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{13}{}^{35}ClIN_2O$: 386.9756, found: 386.9753 (Δ = −0.8 ppm).

Typical Procedure 4 (TP4). *Enantioselective Reduction of Ketone Derivatives.* To a dry round-bottom flask (25 mL) containing a solution of ketone **10a** (276.0 mg, 1.03 mmol) in a mixture of THF−IPA (3 mL, THF:IPA (1:4)) were added K_2CO_3 (34.5 mg, 0.25 mmol) and the appropriate ruthenium catalyst **C1** or **C2** (12 mg, 0.01 mmol). The reaction mixture was degassed under high vacuum and purged with nitrogen. Then, the reaction flask was kept under hydrogen (40 psi) at room temperature for 24 h. After the reaction time, the solvent was removed under reduced pressure and the crude was purified by chromatographic column using flash silica and hexanes/EtOAc (4:1) as an eluent. Following the general procedure **TP4**, the ketone **10a** (276.0 mg, 1.03 mmol) and the ruthenium catalyst *trans*-$RuCl_2$[(*S*)-xylbinap][(*S*)-daipen] (12.0 mg, 0.01 mmol) afforded (*S*)-(7-chloroquinolin-4-yl)(phenyl)methanol ($[\alpha]_D{}^{26}$ = −40.6 (*c* = 0.20, MeOH)) (215.0 mg, 0.80 mmol, 77%, 99.1% enantiomeric fraction) as a white solid after chromatographic purification using hexanes/EtOAc (4:1) as an eluent. Following **TP4**, the ketone **10a** (267.0 mg, 1.00 mmol) and the ruthenium catalyst *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] (12.0 mg, 0.01 mmol) afforded (*R*)-(7-chloroquinolin-4-yl)(phenyl)methanol ($[\alpha]_D{}^{26}$ = 40.1 (*c* = 0.20, MeOH)) (247.0 mg, 0.91 mmol, 91%, 99.4% enantiomeric fraction) as a white solid after chromatographic purification using hexanes/EtOAc (4:1) as an eluent (see the SI).

Enantioseparation from the Racemic Mixture. The separation of compounds **9a** was carried out on a chromatographic system acquired from Shimadzu (Kyoto, Japan). The equipment was equipped with two solvent delivery pumps models LC-20AT and LC-20 AD, one column oven model CTO-20A, one diode array detector model SPD-M20A, and one SIL-10AF automatic injector. The system was controlled by using a CBM-20A controller. The software used for data acquisition and processing was LC Solution version 1.25 SP5, also from Shimadzu. Acceptable enantioseparation of compound **10a** (resolution: >1.5) was performed by using a chiral stationary phase based on amylose 3,5-(tris-dimethylphenylcarbamate). The chiral separation was accomplished on a Chiralpak AD-H column (150 × 4.6 mm, 5 μm, Daicel, Tokyo, Japan), and methanol (100%) was used as the mobile phase (see the SI, Figure S1). The column temperature, flow rate, and injection volume were set at 30 °C, 0.4 mL min^{-1}, and 10 μL, respectively. The detection was carried out at 278 nm. After the enantioselective hydrogenation of compound **10a**, the products were analyzed using the chromatographic method previously described. Figure S2 (see the SI) represents the resulting products obtained. The enantiomeric fraction (EF) of each product was calculated according to Equation S1. The enantiomeric fraction obtained in each enantioselective synthesis was higher than 99% (w/w) (see the SI).

Cytotoxicity Assay. *Lung Carcinoma (A549) and Colon Adenocarcinoma (HCT-116).* Compounds **9a**−**aa** and **16** were prepared as 10 mM stock solutions in DMSO. DMSO and doxorubicin were used as negative and positive controls, respectively. The cancer cells were seeded into a 96-well microplate at an appropriate density (A549: 1 × 10^4 cells/mL and HCT-116: 5 × 10^4 cells/mL) and cultured for 24 h. After, the cells were treated with 0.0032, 0.016, 0.08, 0.4, 2.0, 10.0, and 50.0 μM of concentration for each compound and incubated for 72 h. Then, the supernatant was substituted by a culture medium (150 μL) containing MTT and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (0.5 mg/mL), and the cells were incubated for an additional 3 h. The supernatant was removed, and the microplate was dried for at least 3 h. The precipitated formazan was dissolved in DMSO (150 μL), and the absorbance intensity was measured at 570 nm using a multi-well scanning spectrophotometer (Multiskan FC, Fisher Scientific, USA).[90] All experiments were conducted in triplicate (see the SI).

General Remarks on Flow Chemistry. Dimethyl fumarate was used as an internal standard to calculate the conversion by ^{1}H NMR analysis. All flasks were dried inside the oven for 12 h, and after that time, the same flasks were dried using a heat gun (650 °C) under high vacuum and backfilled with anhydrous nitrogen after cooling. All flasks with rubber septa containing reagents in THF solution were kept under an inert atmosphere. Syringes, which were used to transfer reagents and solvents, were purged with nitrogen three times prior to use. Batch quenching reactions were carried out with magnetic stirring. Flow reactions were performed on commercially available flow systems. A Vapourtec E-series Integrated Flow Chemistry System with 3rd Pump Kit, Organometallic Kit, and Collection Valve Kit or an equipment using two Syrris Asia Flow Chemistry Syringe Pump, three set of Asia Red Syringes (2.5 mL/5 mL), three manual injection valve 2-position-6-port, and homemade coiled tubular reactors and injection loop were used. Coiled tubular reactors were made from PEEK (I.D. = 0.75 mm, O.D. = 1.6 mm) and sample loops from PTFE (I.D. = 0.75 mm, O.D. = 1.6 mm). Two T-pieces (I.D. = 0.5 mm) were used as mixers. Prior to performing reactions, the systems were dried by flushing with dry THF (flow rate of all pumps: 1.0 mL·min^{-1}; run time: 30 min).

Typical Procedure 5 (TP5). *Halogen-Metal Exchange Reaction Followed by the Reaction with Benzaldehyde Using the Syrris Asia Flow Chemistry System.* The following solutions were prepared in anhydrous THF: 7-chloro-4-iodoquinoline (**7**) (0.20 mol·L^{-1}, 1.0 equiv), *i*-PrMgCl·LiCl (0.20 mol·L^{-1}, 1.0 equiv), and the appropriate electrophile. Injection loop A (2.5 or 5 mL) was loaded with 7-chloro-4-iodoquinoline (0.2 mol·L^{-1}, 1.0 mmol), loop B (2.5 or 5 mL) was loaded with *i*-PrMgCl·LiCl (0.2 mol·L^{-1}, 1.0 mmol), and loop C (2.5 or 5 mL) was loaded with the electrophile solution in THF. The solutions were simultaneously injected into separate THF streams (pumps A and B, flow rates: FR_A = FR_B = 1.2 or 3.0 mL·min^{-1}) and mixed in a T-mixer. The combined streams passed a PEEK reactor tube (volume: V_R = 3 mL; residence time: RT = 30 s or 1.25 min). After the respective residence time, the electrophile was injected into separate THF stream (pump C, flow rate: FR_C = 1.2 or 3.0 mL·

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

min^{-1}) and mixed with the organomagnesium intermediate **8** generated from the first coiled reactor in a T-mixer. The second combined streams passed a PEEK reactor tube (volume: V_R = 3 or 18 mL; residence time: RT = 20 s, 2 min, or 5 min). After that, the reaction mixture was quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the organic phases were dried with $MgSO_4$ and filtrated. The solvent was removed under reduced pressure, and the crude was purified by flash column chromatography using hexanes/EtOAc as an eluent.

*(7-Chloroquinolin-4-yl)(phenyl)methanol (**9a**).* Following the general procedure **TP5**, 7-cloro-4-iodoquinoline (**7**) (289.5 mg, 0.2 mol·L^{-1}, 1.0 mmol) and benzaldehyde (0.1 mL, 0.2 mol·L^{-1}, 1.0 mmol) afforded **9a** (231.0 mg, 86%) as a white solid. Spectroscopic data matched that reported previously. Flow setup: flow rates (FR_A = FR_B = FR_C = 3.0 mL·min^{-1}), injection loops (loop A = loop B = loop C = 5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 30 s), and second coil reactor (volume: V_R = 3 mL; residence time: RT = 20 s).

*1-(7-Chloroquinoline-4-yl)cyclohena-1-ol (**10b**).* Following the general procedure **TP5**, 7-chloro-4-iodoquinoline (**7**) (144.7 mg, 0.2 mol·L^{-1}, 0.5 mmol) and cyclohexanone (0.3 mL, 1.2 mol·L^{-1}, 3.0 mmol) afforded **10b** (70.0 mg, 53%) as a white solid. Spectroscopic data matched that reported previously. Flow setup: flow rates (FR_A = FR_B = FR_C = 1.2 mL·min^{-1}), injection loops (loop A = loop B = loop C = 2.5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 1.25 min), and second coil reactor (volume: V_R = 18 mL; residence time: RT = 5 min).

*7-Chloroquinoline-4-carbonitrile (**10c**).* CAS number: 13337-75-2. Following the general procedure **TP5**, 7-chloro-4-iodoquinoline (**7**) (144.7 mg, 0.2 mol·L^{-1}, 0.5 mmol) and *p*-toluenesulfonyl cyanide (143.0 mg, 0.3 mol·L^{-1}, 0.75 mmol) afforded **10b** (82.0 mg, 87%) as a white solid. Spectroscopic data matched that reported previously. Flow setup: flow rates (FR_A = FR_B = FR_C = 3.0 mL·min^{-1}), injection loops (loop A = loop B = loop C = 2.5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 30 s), and second coil reactor (volume: V_R = 18 mL; residence time: RT = 2 min).

*7-Chloro-4-(phenylselanyl)quinoline (**10e**).* CAS number: 1415931-33-7. Following the general procedure **TP5**, 7-chloro-4-iodoquinoline (**7**) (144.7 mg, 0.2 mol·L^{-1}, 0.5 mmol) and 1,2-diphenyldiselenide (312.1 mg, 0.4 mol·L^{-1}, 1.0 mmol) afforded **10b** (144.0 mg, 90%) as a white solid. Spectroscopic data matched that reported previously. Flow setup: flow rates (FR_A = FR_B = FR_C = 3.0 mL·min^{-1}), injection loops (loop A = loop B = loop C = 2.5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 30 s), and second coil reactor (volume: V_R = 18 mL; residence time: RT = 2 min).

*7-Chloroquinoline-4-carbaldehyde (**10f**).* CAS number: 35714-48-8. Following the general procedure **TP5**, 7-chloro-4-iodoquinoline (**7**) (144.7 mg, 0.2 mol·L^{-1}, 0.5 mmol) and DMF (0.2 mL, 1.2 mol·L^{-1}, 3.0 mmol) afforded **10b** (68.0 mg, 71%) as a white solid. Spectroscopic data matched that reported previously. Flow setup: flow rates (FR_A = FR_B = FR_C = 1.2 mL·min^{-1}), injection loops (loop A = loop B = loop C = 2.5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 1.25 min), and second coil reactor (volume: V_R = 18 mL; residence time: RT = 5 min).

Typical Procedure 6 (TP6). *Metalation Step Using the Vapourtec E-Series Integrated Flow Chemistry System and Iodine as an Electrophile.* The following solutions were prepared: 4,7-dichloroquinoline (**18**) solution in THF (0.20 mol·L^{-1}, 1.0 equiv) and TMPMgCl·LiCl (0.30 mol·L^{-1}, 1.5 equiv). The solutions were pumped from their flasks through a suction needle at flow rate A (FR_A = 1.5 mL·min^{-1}) and flow rate B (FR_B = FR_A) for 3 min and 20 s. The solutions were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The combined stream passed through a PEEK reactor tube (volume: V_R = 3.0 mL; residence time RT = 1.0 min) and was subsequently injected in a flask containing iodine (304.8 mg, 1.2 equiv). The reaction mixture was quenched with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous phase was extracted with EtOAc, and the organic phases were dried with Na_2SO_4 and filtrated. The solvent was removed under reduced pressure, and the crude was purified by flash column chromatographic separation using hexanes/EtOAc (9:1) as an eluent.

Following the general procedure **TP6**, 4,7-dichloroquinoline (**18**) (198.0 mg, 0.2 mol·L^{-1}, 1 mmol) and iodine (304.8 mg, 1.2 mmol) afforded 4,7-dichloro-8-iodoquinoline (**23a**) (298.0 mg, 92%) (CAS number: 2169765-08-4) as a white solid after chromatographic purification with hexanes/EtOAc (1:9) as an eluent; m.p.: 136−142 °C; IR (ATR, cm^{-1}): 1579, 1388, 844; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.88 (d, J = 4.7 Hz, 1H), 8.18 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 4.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ: 151.5, 149.6, 143.0, 142.8, 128.7, 125.6, 124.8, 121.9, 108.0. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_9H_5N^{35}Cl_2I$: 323.6644, found: 323.6634 (Δ = −3.1 ppm).

Typical Procedure 7 (TP7). *Metalation Followed by the Reaction with Aldehydes Using the Vapourtec E-Series Integrated Flow Chemistry System.* The following solutions were prepared in anhydrous THF: 7-chloro-4-iodoquinoline (**18**) (0.20 mol·L^{-1}, 1.0 equiv), TMPMgCl·LiCl (0.30 mol·L^{-1}, 1.5 equiv), and the appropriate electrophile (0.60 mol·L^{-1}, 3.0 equiv). First of all, 4,7-dichloroquinoline (**18**) and TMPMgCl·LiCl solutions were pumped from their flasks through a suction needle at flow rate A (FR_A = 1.5 mL·min^{-1}) and flow rate B (FR_B = FR_A) for 3 min and 20 s from pumps A and B, respectively. The solutions were mixed in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). After 1 min, the respective electrophile solution was pumped from its flask at the same flow rate (FR_C = FR_A) and mixed with the organomagnesium intermediate generated from the first coiled reactor in a T-mixer (PFA or PTFE, I.D. = 0.5 mm). The second combined streams passed through a PEEK reactor tube (volume: V_R = 3.0 mL; residence time: RT = 40 s). The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the organic phases were dried with Na_2SO_4 and filtrated. The solvent was removed under reduced pressure, and the crude was purified by flash column chromatography using hexanes/EtOAc as an eluent.

*(4,7-Dichloroquinolin-8-yl)(phenyl)methanol (**23b**).* CAS number: 2169765-11-9. Following the general procedure **TP7**, 4,7-dichloroquinoline (**18**) (198.0 mg, 0.2 mol·L^{-1}, 1 mmol) and benzaldehyde (0.3 mL, 0.6 mol·L^{-1}, 3 mmol) afforded compound **23b** (252.5 mg, 83%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 125−132 °C; IR (ATR, cm^{-1}): 3376, 1449, 832; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.68 (d, J = 4.8 Hz, 1H), 8.15 (d, J = 9.1 Hz, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 4.8 Hz, 1H), 7.48−7.41 (m, 2H), 7.30−7.22 (m, 2H), 7.23−7.15 (m, 1H), 6.68 (s, 1H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ: 148.6, 147.9, 144.2, 143.8, 136.9, 135.6, 129.8, 128.3 (2 × C), 127.2, 126.3, 126.2 (2 × C), 124.7, 121.5, 74.3; HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}{}^{35}Cl_2NO$: 304.0296, found: 304.0284 (Δ = −3.9 ppm).

*Cyclohexyl(4,7-dichloroquinolin-8-yl)methanol (**23c**).* Following the general procedure **TP7**, 4,7-dichloroquinoline (**18**) (198.0 mg, 0.2 mol·L^{-1}, 1 mmol) and cyclohexanecarbaldehyde (0.36 mL, 0.6 mol·L^{-1}, 3 mmol) afforded compound **23c** (279.2 mg, 90%) as a crystal after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 168−175 °C; IR (ATR, cm^{-1}): 3394, 2850, 1079, 843, 802; ^1H NMR (700 MHz, $CDCl_3$) δ: 8.71 (d, J = 4.7 Hz, 1H), 8.08 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.51 (d, J = 4.7 Hz, 1H), 5.22 (d, J = 8.0 Hz, 1H), 2.20−2.12 (m, 1H), 2.04 (dtt, J = 11.6, 7.6, 3.5 Hz, 1H), 1.84−1.71 (m, 1H), 1.68−1.54 (m, 2H), 1.34−1.11 (m, 5H), 1.04 (tdd, J = 12.9, 9.3, 3.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (176 MHz, $CDCl_3$) δ: 148.2, 148.2, 144.0, 137.5, 135.7, 129.7, 126.1, 124.0, 121.4, 78.0, 45.7, 29.7, 29.6, 26.5, 26.4, 26.2. HRMS (ESI/Q-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{18}{}^{35}Cl_2NO$: 310.0765, found: 310.0771 (Δ = 1.9 ppm). Crystal data for $C_{16}H_{17}Cl_2NO$ (M = 310.20 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 10.4145(5) Å, b = 10.1079(5) Å, c = 13.6710(7) Å, β = 91.857(2)°, V = 1438.37(12) $Å^3$, Z = 4, T = 120 K, μ(MoKα) = 0.446 mm^{-1}, D_{calc} = 1.432 g/cm^3, 33,825 reflections measured (5.012° ≤ 2Θ ≤ 63.008°), 4777 unique

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

(R_{int} = 0.0424, R_{sigma} = 0.0307), which were used in all calculations. The final R_1 was 0.0338 ($I > 2\sigma(I)$), and wR_2 was 0.0866 (all data).

*1-(4,7-Dichloroquinolin-8-yl)-2-methylpropan-1-ol (**23d**).* Following the general procedure **TP7**, 4,7-dichloroquinoline (**18**) (198.0 mg, 0.2 mol·L^{-1}, 1 mmol) and isobutyraldehyde (0.27 mL, 0.6 mol·L^{-1}, 3 mmol) afforded compound **23d** (235.0 mg, 87%) as a white solid after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; m.p.: 83−86 °C; IR (ATR, cm^{-1}): 3311, 3073, 1034, 820; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (d, J = 4.8 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 4.8 Hz, 1H), 5.18 (d, J = 7.9 Hz, 1H), 2.37 (t, J = 7.9, 6.9 Hz, 1H), 1.15 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ: 148.2, 148.2, 143.9, 137.7, 135.7, 129.7, 126.1, 124.0, 121.4, 78.8, 36.1, 19.5, 19.2; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{13}H_{14}{}^{35}Cl_2NO$: 270.0452, found: 270.0450 (Δ = −0.7 ppm).

*1-(4,7-Dichloroquinolin-8-yl)heptan-1-ol (**23e**).* Following the general procedure **TP7**, 4,7-dichloroquinoline (**18**) (198.0 mg, 0.2 mol·L^{-1}, 1 mmol) and 1-heptanal (0.42 mL, 0.6 mol·L^{-1}, 3 mmol) afforded compound **23e** (290.4 mg, 93%) as colorless oil after chromatographic purification using EtOAc/hexanes (1:4) as an eluent; IR (ATR, cm^{-1}): 3376, 2926, 821, 635; ^{1}H NMR (700 MHz, $CDCl_3$) δ: 8.72 (d, J = 4.8 Hz, 1H), 8.09 (d, J = 9.0 Hz, 1H), 7.61 (d, J = 9.0 Hz, 1H), 7.54 (d, J = 4.7 Hz, 1H), 5.48 (dd, J = 9.1, 4.8 Hz, 1H), 2.09−2.02 (m, 1H), 1.87−1.79 (m, 1H), 1.71−1.61 (m, 1H), 1.49−1.41 (m, 1H), 1.41−1.22 (m, 8H), 0.95−0.84 (m, 3H); ^{13}C{^{1}H} NMR (176 MHz, $CDCl_3$) δ: 148.1, 144.2, 138.4, 134.6, 129.8, 126.2, 123.9, 121.4, 73.5, 68.1, 38.9, 31.9, 29.3, 26.2, 22.7, 14.2; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{20}{}^{35}Cl_2NO$: 312.0922, found: 312.0912 (Δ = −3.2 ppm).

Typical Procedure 8 (TP8). *Metalation Reaction Followed by the Reaction with Different Electrophiles Using the Syrris Asia Flow Chemistry System.* The following solutions were prepared in anhydrous THF: 4,7-dichloroquinoline (**18**) (0.20 mol·L^{-1}, 1.0 equiv), TMPMgCl·LiCl (0.30 mol·L^{-1}, 1.5 equiv), and the appropriate electrophile. Injection loop A (2.5 mL) was loaded with 4,7-dichloroquinoline (**18**) (0.2 mol·L^{-1}, 0.5 mmol), loop B (2.5 mL) was loaded with TMPMgCl·LiCl (0.3 mol·L^{-1}, 0.75 mmol), and loop C was loaded with the electrophile solution. The solutions were simultaneously injected into separate THF streams (pumps A and B, flow rates: FR_A = FR_B = 1.2 or 1.5 mL·min^{-1}) and mixed in a T-mixer (PEEK, I.D. = 0.5 mm). The combined streams passed a PEEK reactor tube (volume: V_R = 3 mL; residence time: RT = 1 or 1.25 min). After the respective residence time, the electrophile was injected into separate THF stream (pump C, flow rate: FR_C = 1.2 or 1.5 mL·min^{-1}) and mixed with the organomagnesium intermediate **22** generated from the first coiled reactor in a T-mixer (PEEK, I.D. = 0.5 mm). The second combined streams passed through a PEEK reactor tube (volume: V_R = 18 mL; residence time: RT = 2 or 5 min). The reaction mixture was then quenched with a saturated aqueous NH_4Cl solution. The aqueous phase was extracted with EtOAc (3 × 30 mL), and the organic phases were dried with $MgSO_4$ and filtrated. The solvent was removed under reduced pressure, and the crude was purified by flash column chromatography using hexanes/EtOAc as an eluent.

*4,7-Dichloro-8-(phenylselanyl)quinoline (**23f**).* Following the general procedure **TP8**, 4,7-dichloroquinoline (**18**) (99.0 mg, 0.2 mol·L^{-1}, 0.5 mmol) and diphenyl diselenide (312.1 mg, 0.4 mol·L^{-1}, 1 mmol) afforded compound **23f** (95.3 mg, 54%) as a white solid after chromatographic purification using EtOAc/hexanes (1:19) as an eluent; m.p.: 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.87 (d, J = 4.6 Hz, 1H), 8.23 (d, J = 8.9 Hz, 1H), 7.71 (d, J = 8.9 Hz, 1H), 7.52 (d, J = 4.6 Hz, 1H), 7.34−7.31 (m, 2H), 7.17−7.14 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.1, 150.4, 143.4, 143.2, 132.2, 131.4 (2 × C), 129.7, 129.1 (2 × C), 128.4, 126.8, 126.2, 125.6, 121.7; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{15}H_{10}{}^{35}Cl_2NSe$: 353.9350, found: 353.9364 (Δ = 3.9 ppm). Flow setup: flow rates (FR_A = FR_B = FR_C = 1.5 mL·min^{-1}), injection loops (loops A−C = 2.5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 1 min), and second coil reactor (volume: V_R = 18 mL; residence time: RT = 4 min).

*4,7-Dichloroquinoline-8-carbaldehyde (**23g**).* CAS number: 2169765-16-4. Following the general procedure **TP8**, 4,7-dichloroquinoline (**18**) (99.0 mg, 0.2 mol·L^{-1}, 0.5 mmol) and DMF (0.2 mL, 1.2 mol·L^{-1}, 3.0 mmol) afforded compound **23g** (76.0 mg, 67%) as a white solid after chromatographic purification using EtOAc/hexanes (1:19) as an eluent; m.p.: 159−160 °C; IR (ATR, cm^{-1}): 3107, 1680, 1549, 915; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 11.26 (s, 1H), 8.90 (d, J = 4.7 Hz, 1H), 8.35 (d, J = 9.0 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 4.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 191.7, 151.3, 149.2, 143.5, 137.2, 130.8, 129.7, 129.3, 125.3, 122.3; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_{10}H_6{}^{35}Cl_2NO$: 225.9821, found: 225.9825 (Δ = 1.8 ppm). Flow setup: flow rates (FR_A = FR_B = FR_C = 1.2 mL·min^{-1}), injection loops (loops A−C = 2.5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 1 min), and second coil reactor (volume: V_R = 18 mL; residence time: RT = 5 min).

*8-Bromo-4,7-dichloroquinoline (**23h**).* CAS number: 1694567-12-8. Following the general procedure **TP8**, 4,7-dichloroquinoline (**18**) (99.0 mg, 0.2 mol·L^{-1}, 0.5 mmol) and 1,2-dibromotetrachloroethane (976.9 mg, 1.2 mol·L^{-1}, 3.0 mmol) afforded compound **23h** (130.1 mg, 94%) as a white solid after chromatographic purification using EtOAc/hexanes (1:19) as an eluent; m.p.: 136−137 °C; IR (ATR, cm^{-1}): 3081, 1592, 825; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.92 (d, J = 4.7 Hz, 1H), 8.17 (d, J = 9.0 Hz, 1H), 7.69 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 4.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ: 151.4, 147.3, 143.4, 138.1, 129.3, 126.0, 125.3, 124.4, 122.1; HRMS (ESI/Q-TOF) m/z: [M + H]$^+$ calcd for $C_9H_5{}^{79}Br^{35}Cl_2N$: 275.8977, found: 275.8968 (Δ = −3.3 ppm). Flow setup: flow rates (FR_A = FR_B = FR_C = 1.2 mL·min^{-1}), injection loops (loops A−C = 2.5 mL), first coil reactor (volume: V_R = 3 mL; residence time: RT = 1 min), and second coil reactor (volume: V_R = 18 mL; residence time: RT = 5 min).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c01521.

Details of the computational study and biological assay, ^{1}H and ^{13}C NMR spectra, and additional analytical data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Ian R. Baxendale − *Department of Chemistry, Durham University, Durham DH1 3LE, United Kingdom;* orcid.org/0000-0003-1297-1552; Email: i.r.baxendale@durham.ac.uk

Giuliano C. Clososki − *Department of Chemistry, Durham University, Durham DH1 3LE, United Kingdom; Departamento de Química, Faculdade de Filosofia Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-901, Brazil;* orcid.org/0000-0001-7605-4150; Email: gclososki@usp.br

Authors

Valter E. Murie − *Departamento de Ciências BioMoleculares, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-903, Brazil*

Paula V. Nicolino − *Departamento de Ciências BioMoleculares, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-903, Brazil*

Thiago dos Santos − *Departamento de Ciências BioMoleculares, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-903, Brazil*
Guido Gambacorta − *Department of Chemistry, Durham University, Durham DH1 3LE, United Kingdom*
Rodolfo H. V. Nishimura − *Departamento de Ciências BioMoleculares, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-903, Brazil*
Icaro S. Perovani − *Departamento de Química, Faculdade de Filosofia Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-901, Brazil*
Luciana C. Furtado − *Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo 05508-900, Brazil*
Leticia V. Costa-Lotufo − *Departamento de Farmacologia, Instituto de Ciências Biomédicas, Universidade de São Paulo, São Paulo 05508-900, Brazil*
Anderson Moraes de Oliveira − *Departamento de Química, Faculdade de Filosofia Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-901, Brazil*
Ricardo Vessecchi − *Departamento de Química, Faculdade de Filosofia Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto 14040-901, Brazil*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c01521

Author Contributions

[⊥]V.E.M. and P.V.N. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support for this work by the Brazilian foundations Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, grants 2015/21364-6, 2019/05838-9, 2018/14150-8, 2015/17177-6, and 2013/00758-0), Conselho Nacional de Desenvolvimento e Tecnológico (CNPq, grants 140137/2018-1 and 442384/2014-9), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Additionally, the authors acknowledge the assistance of Dr. Rodrigo Moreira da Silva and Mr. José Carlos Tomaz during the HRMS analyses.

■ REFERENCES

(1) Solomon, V. R.; Lee, H. Quinoline as a Privileged Scaffold in Cancer Drug Discovery. *Curr. Med. Chem.* **2011**, *18*, 1488.
(2) Zhang, H.; Wu, W.; Feng, C.; Liu, Z.; Bai, E.; Wang, X.; Lei, M.; Cheng, H.; Feng, H.; Shi, J.; Wang, J.; Zhang, Z.; Jin, T.; Chen, S.; Hu, S.; Zhu, Y. Design, Synthesis, SAR Discussion, in Vitro and in Vivo Evaluation of Novel Selective EGFR Modulator to Inhibit L858R/T790M Double Mutants. *Eur. J. Med. Chem.* **2017**, *135*, 12.
(3) Wissner, A.; Brawner Floyd, M.; Rabindran, S. K.; Nilakantan, R.; Greenberger, L. M.; Shen, R.; Wang, Y.-F.; Tsou, H.-R. Syntheses and EGFR and HER-2 Kinase Inhibitory Activities of 4-Anilinoquinoline-3-Carbonitriles: Analogues of Three Important 4-Anilinoquinazolines Currently Undergoing Clinical Evaluation as Therapeutic Antitumor Agents. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2893.
(4) Wissner, A.; Overbeek, E.; Reich, M. F.; Floyd, M. B.; Johnson, B. D.; Mamuya, N.; Rosfjord, E. C.; Discafani, C.; Davis, R.; Shi, X.; Rabindran, S. K.; Gruber, B. C.; Ye, F.; Hallett, W. A.; Nilakantan, R.; Shen, R.; Wang, Y.-F.; Greenberger, L. M.; Tsou, H.-R. Synthesis and Structure−Activity Relationships of 6,7-Disubstituted 4-Anilinoquinoline-3-Carbonitriles. The Design of an Orally Active, Irreversible Inhibitor of the Tyrosine Kinase Activity of the Epidermal Growth Factor Receptor (EGFR) and the Human Epidermal Growth Factor Receptor-2 (HER-2). *J. Med. Chem.* **2003**, *46*, 49.
(5) Tang, Q.; Zhai, X.; Tu, Y.; Wang, P.; Wang, L.; Wu, C.; Wang, W.; Xie, H.; Gong, P.; Zheng, P. Synthesis and Antiproliferative Activity of 6,7-Disubstituted-4-Phenoxyquinoline Derivatives Bearing the 2-Oxo-4-Chloro-1,2-Dihydroquinoline-3-Carboxamide Moiety. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1794.
(6) Ding, H. X.; Leverett, C. A.; Kyne, R. E., Jr.; Liu, K. K.-C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J. Synthetic Approaches to the 2012 New Drugs. *Bioorg. Med. Chem.* **2014**, *22*, 2005.
(7) Flick, A. C.; Ding, H. X.; Leverett, C. A.; Kyne, R. E., Jr.; Liu, K. K.-C.; Fink, S. J.; O'Donnell, C. J. Synthetic Approaches to the New Drugs Approved During 2015. *J. Med. Chem.* **2017**, *60*, 6480.
(8) Kataoka, Y.; Mukohara, T.; Tomioka, H.; Funakoshi, Y.; Kiyota, N.; Fujiwara, Y.; Yashiro, M.; Hirakawa, K.; Hirai, M.; Minami, H. Foretinib (GSK1363089), a Multi-Kinase Inhibitor of MET and VEGFRs, Inhibits Growth of Gastric Cancer Cell Lines by Blocking Inter-Receptor Tyrosine Kinase Networks. *Invest. New Drugs* **2012**, *30*, 1352.
(9) Romero, J. A.; Acosta, M. E.; Gamboa, N. D.; Mijares, M. R.; De Sanctis, J. B.; Charris, J. E. Optimization of Antimalarial, and Anticancer Activities of (E)-Methyl 2-(7-Chloroquinolin-4-Ylthio)-3-(4-Hydroxyphenyl) Acrylate. *Bioorg. Med. Chem.* **2018**, *26*, 815.
(10) Wiesner, J.; Ortmann, R.; Jomaa, H.; Schlitzer, M. New Antimalarial Drugs. *Angew. Chem., Int. Ed.* **2003**, *42*, 5274.
(11) Pinheiro, L. C. S.; Feitosa, L. M.; Gandi, M. O.; Silveira, F. F.; Boechat, N. The Development of Novel Compounds Against Malaria: Quinolines, Triazolpyridines, Pyrazolopyridines and Pyrazolopyrimidines. *Molecules* **2019**, *24*, 4095.
(12) da Silva Araújo, A.; Moraes, A. M.; Lourenço, M. C. S.; Pessoa, C. O.; da Silva, E. T.; de Souza, M. V. N. Synthesis and Antibacterial Activity of Mefloquine-Based Analogs Against Sensitive and Resistant Mycobacterium Tuberculosis Strains. *Curr. Top. Med. Chem.* **2019**, *19*, 683.
(13) Weyesa, A.; Mulugeta, E. Recent Advances in the Synthesis of Biologically and Pharmaceutically Active Quinoline and Its Analogues: A Review. *RSC Adv.* **2020**, *10*, 20784.
(14) Gambacorta, G.; Apperley, D. C.; Baxendale, I. R. A One-Pot Divergent Sequence to Pyrazole and Quinoline Derivatives. *Molecules* **2020**, *25*, 2160.
(15) Cravotto, G.; Bonrath, W.; Tagliapietra, S.; Speranza, C.; Gaudino, E. C.; Barge, A. Intensification of Organic Reactions with Hybrid Flow Reactors. *Chem. Eng. Process.* **2010**, *49*, 930.
(16) Lengyel, L.; Nagy, T. Z.; Sipos, G.; Jones, R.; Dormán, G.; Ürge, L.; Darvas, F. Highly Efficient Thermal Cyclization Reactions of Alkylidene Esters in Continuous Flow to Give Aromatic/Heteroaromatic Derivatives. *Tetrahedron Lett.* **2012**, *53*, 738.
(17) Yalgin, H.; Luart, D.; Len, C. First Examples of Doebner-Miller Reaction in Flow: Efficient Production of 2-Methylquinoline Derivatives in Water. *J. Flow Chem.* **2016**, *6*, 80.
(18) Baumann, M.; Baxendale, I. R. Batch and Flow Synthesis of Pyrrolo[1,2-a]-Quinolines via an Allene-Based Reaction Cascade. *J. Org. Chem.* **2015**, *80*, 10806.
(19) Goyal, M.; Singh, P.; Alam, A.; Kumar Das, S.; Shameel Iqbal, M.; Dey, S.; Bindu, S.; Pal, C.; Kumar Das, S.; Panda, G.; Bandyopadhyay, U. Aryl Aryl Methyl Thio Arenes Prevent Multidrug-Resistant Malaria in Mouse by Promoting Oxidative Stress in Parasites. *Free Radical Biol. Med.* **2012**, *53*, 129.
(20) Gemma, S.; Campiani, G.; Butini, S.; Kukreja, G.; Coccone, S. S.; Joshi, B. P.; Persico, M.; Nacci, V.; Fiorini, I.; Novellino, E.; Fattorusso, E.; Taglialatela-Scafati, O.; Savini, L.; Taramelli, D.; Basilico, N.; Parapini, S.; Morace, G.; Yardley, V.; Croft, S.; Coletta, M.; Marini, S.; Fattorusso, C. Clotrimazole Scaffold as an Innovative Pharmacophore Towards Potent Antimalarial Agents: Design, Synthesis, and Biological and Structure−Activity Relationship Studies. *J. Med. Chem.* **2008**, *51*, 1278.

(21) Jia, X.; Wang, J.; Ding, X.; Yang, J.; Li, N.; Zhao, N.; Huang, Z. Mg-Prompted Polyfluoroarene C−H Functionalization: Formal Synthesis of Transfluthrin, Fenfluthrin, and Tefluthrin. *J. Org. Chem.* **2015**, *80*, 10874.
(22) Plobeck, N.; Delorme, D.; Wei, Z.-Y.; Yang, H.; Zhou, F.; Schwarz, P.; Gawell, L.; Gagnon, H.; Pelcman, B.; Schmidt, R.; Yue, S. Y.; Walpole, C.; Brown, W.; Zhou, E.; Labarre, M.; Payza, K.; St-Onge, S.; Kamassah, A.; Morin, P.-E.; Projean, D.; Ducharme, J.; Roberts, E. New Diarylmethylpiperazines as Potent and Selective Nonpeptidic δ Opioid Receptor Agonists with Increased In Vitro Metabolic Stability. *J. Med. Chem.* **2000**, *43*, 3878.
(23) Furukawa, N.; Shibutani, T.; Matsumura, K.; Fujihara, H.; Oae, S. Reactions of Pyridyl and Quinolyl Sulfoxides with Grignard Reagent: A Convenient Preparation of Pyridyl and Quinolyl Grignard Reagents. *Tetrahedron Lett.* **1986**, *27*, 3899.
(24) Relitti, N.; Federico, S.; Pozzetti, L.; Butini, S.; Lamponi, S.; Taramelli, D.; D'Alessandro, S.; Martin, R. E.; Shafik, S. H.; Summers, R. L.; Babij, S. K.; Habluetzel, A.; Tapanelli, S.; Caldelari, R.; Gemma, S.; Campiani, G. Synthesis and Biological Evaluation of Benzhydryl-Based Antiplasmodial Agents Possessing Plasmodium Falciparum Chloroquine Resistance Transporter (PfCRT) Inhibitory Activity. *Eur. J. Med. Chem.* **2021**, *215*, 113227.
(25) Comins, D. L.; Nolan, J. M.; Bori, I. D. Regioselective Lithium-Halogen Exchange and Palladium-Catalyzed Cross-Coupling Reactions of 2,4-Dihaloquinolines. *Tetrahedron Lett.* **2005**, *46*, 6697.
(26) Chen, X.-T.; Ghavimi, B.; Corbett, R. L.; Xue, C.-B.; Liu, R.-Q.; Covington, M. B.; Qian, M.; Vaddi, K. G.; Christ, D. D.; Hartman, K. D.; Ribadeneira, M. D.; Trzaskos, J. M.; Newton, R. C.; Decicco, C. P.; Duan, J. J.-W. A New 4-(2-Methylquinolin-4-Ylmethyl)Phenyl P1′ Group for the β-Amino Hydroxamic Acid Derived TACE Inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1865.
(27) Kim, H. S.; Hong, M.; Ann, J.; Yoon, S.; Nguyen, C.-T.; Lee, S.-C.; Lee, H.-Y.; Suh, Y.-G.; Seo, J. H.; Choi, H.; Kim, J. Y.; Kim, K.-W.; Kim, J.; Kim, Y.-M.; Park, S.-J.; Park, H.-J.; Lee, J. Synthesis and Biological Evaluation of C-Ring Truncated Deguelin Derivatives as Heat Shock Protein 90 (HSP90) Inhibitors. *Bioorg. Med. Chem.* **2016**, *24*, 6082.
(28) Bao, R. L.-Y.; Zhao, R.; Shi, L. Progress and Developments in the Turbo Grignard Reagent I-PrMgCl•LiCl: A Ten-Year Journey. *Chem. Commun.* **2015**, *51*, 6884.
(29) Bhanu Prasad, A. S.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. Preparation and Reactions of New Zincated Nitrogen-Containing Heterocycles. *Tetrahedron* **1997**, *53*, 7237.
(30) Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. Tributylmagnesium Ate Complex-Mediated Bromine−Magnesium Exchange of Bromoquinolines: A Convenient Access to Functionalized Quinolines. *Tetrahedron Lett.* **2003**, *44*, 2033.
(31) Dumouchel, S.; Mongin, F.; Trécourt, F.; Quéguiner, G. Synthesis and Reactivity of Lithium Tri(Quinolinyl)Magnesates. *Tetrahedron* **2003**, *59*, 8629.
(32) Krasovskiy, A.; Knochel, P. A LiCl-Mediated Br/Mg Exchange Reaction for the Preparation of Functionalized Aryl- and Heteroarylmagnesium Compounds from Organic Bromides. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.
(33) Ziegler, D. S.; Wei, B.; Knochel, P. Improving the Halogen-Magnesium Exchange by Using New Turbo-Grignard Reagents. *Chem. - Eur. J.* **2019**, *25*, 2695.
(34) Boudet, N.; Lachs, J. R.; Knochel, P. Multiple Regioselective Functionalizations of Quinolines via Magnesiations. *Org. Lett.* **2007**, *9*, 5525.
(35) León, B.; Fong, J. C. N.; Peach, K. C.; Wong, W. R.; Yildiz, F. H.; Linington, R. G. Development of Quinoline-Based Disruptors of Biofilm Formation Against Vibrio Cholerae. *Org. Lett.* **2013**, *15*, 1234.
(36) Singh, P.; Singh, P.; Kumar, M.; Gut, J.; Rosenthal, P. J.; Kumar, K.; Kumar, V.; Mahajan, M. P.; Bisetty, K. Synthesis, Docking and in Vitro Antimalarial Evaluation of Bifunctional Hybrids Derived from β-Lactams and 7-Chloroquinoline Using Click Chemistry. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 57.
(37) Singh, B.; Chetia, D.; Puri, S. K.; Srivastava, K.; Prakash, A. Synthesis and in Vitro and in Vivo Antimalarial Activity of Novel 4-Anilinoquinoline Mannich Base Derivatives. *Med. Chem. Res.* **2011**, *20*, 1523.
(38) Aboelnaga, A.; El-Sayed, T. H. Click Synthesis of New 7-Chloroquinoline Derivatives by Using Ultrasound Irradiation and Evaluation of Their Biological Activity. *Green Chem. Lett. Rev.* **2018**, *11*, 254.
(39) Nishimura, R. H. V.; de Vaz, A. d. L. L.; Bozzini, L. A.; Murie, V. E.; Clososki, G. C. Recent Applications of Magnesium- and Zinc-TMP Amides in the Synthesis of Bioactive Targets. *Tetrahedron* **2019**, *75*, 464.
(40) Bozzini, L. A.; Batista, J. H. C.; de Mello, M. B. M.; Vessecchi, R.; Clososki, G. C. Selective Functionalization of Cyano-Phenyl-2-Oxazolines Using TMPMgCl·LiCl. *Tetrahedron Lett.* **2017**, *58*, 4186.
(41) Nishimura, R. H. V.; Murie, V. E.; Soldi, R. A.; Lopes, J. L. C.; Clososki, G. C. Zinc, Lithium and Magnesium Carbenoids: Chemical Properties and Relevant Applications in Organic Synthesis. *J. Braz. Chem. Soc.* **2015**, *26*, 2175.
(42) Bertallo, C. R. d. S.; Arroio, T. R.; Toledo, M. F. Z. J.; Sadler, S. A.; Vessecchi, R.; Steel, P. G.; Clososki, G. C. C-H Activation/Metalation Approaches for the Synthesis of Indolizine Derivatives. *Eur. J. Org. Chem.* **2019**, *2019*, 5205.
(43) Murie, V. E.; Nishimura, R. H. V.; Rolim, L. A.; Vessecchi, R.; Lopes, N. P.; Clososki, G. C. Base-Controlled Regioselective Functionalization of Chloro-Substituted Quinolines. *J. Org. Chem.* **2018**, *83*, 871.
(44) Kloetzing, R. J.; Krasovskiy, A.; Knochel, P. The Mg-Oppenauer Oxidation as a Mild Method for the Synthesis of Aryl and Metallocenyl Ketones. *Chem. - Eur. J.* **2007**, *13*, 215.
(45) Byrne, B.; Karras, M. Magnesium-Oppenauer Oxidation of Alcohols to Aldehydes and Ketones. *Tetrahedron Lett.* **1987**, *28*, 769.
(46) Fu, Y.; Zhao, X. L.; Hügel, H.; Huang, D.; Du, Z.; Wang, K.; Hu, Y. Magnesium Salt Promoted Tandem Nucleophilic Addition−Oppenauer Oxidation of Aldehydes with Organozinc Reagents. *Org. Biomol. Chem.* **2016**, *14*, 9720.
(47) Su, T.; Zhu, J.; Sun, R.; Zhang, H.; Huang, Q.; Zhang, X.; Du, R.; Qiu, L.; Cao, R. Design, Synthesis and Biological Evaluation of New Quinoline Derivatives as Potential Antitumor Agents. *Eur. J. Med. Chem.* **2019**, *178*, 154.
(48) Meyer, S. D.; Schreiber, S. L. Acceleration of the Dess-Martin Oxidation by Water. *J. Org. Chem.* **1994**, *59*, 7549.
(49) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. One-Pot Negishi Cross-Coupling Reactions of In Situ Generated Zinc Reagents with Aryl Chlorides, Bromides, and Triflates. *J. Org. Chem.* **2008**, *73*, 7380.
(50) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. Recent Developments in Negishi Cross-Coupling Reactions. *ACS Catal.* **2016**, *6*, 1540.
(51) Brittain, W. D. G.; Cobb, S. L. Negishi Cross-Couplings in the Synthesis of Amino Acids. *Org. Biomol. Chem.* **2018**, *16*, 10.
(52) Sain, S.; Jain, S.; Srivastava, M.; Vishwakarma, R.; Dwivedi, J. Application of Palladium-Catalyzed Cross-Coupling Reactions in Organic Synthesis. *Curr. Org. Synth.* **2020**, *16*, 1105.
(53) Yang, D.; Yip, Y.-C.; Wang, X.-C. Oxidative Cleavage of Aryl Oxazolines Using Methyl(Trifluoromethyl)Dioxirane Generated in Situ. *Tetrahedron Lett.* **1997**, *38*, 7083.
(54) Phillion, D. P.; Pratt, J. K. A New Method for Hydrolyzing 2-Aryl-4,4-Dimethyl-2-Oxazolines to Aryl Carboxylic Acids. *Synth. Commun.* **1992**, *22*, 13.
(55) Croisy-Delcey, M.; Carrez, D.; Bisagni, E. Aminoalkylamino Derivatives of Dihydroxy-Benzo[g]Isoquinoline Dione and of Trihydroxy-Naphtho[2,3-g]Isoquinoline Dione: Synthesis and Anti-Tumor Evaluation. *Eur. J. Med. Chem.* **1988**, *23*, 101.
(56) Snieckus, V. Directed Ortho Metalation. Tertiary Amide and O-Carbamate Directors in Synthetic Strategies for Polysubstituted Aromatics. *Chem. Rev.* **1990**, *90*, 879.

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419

(57) Beak, P.; Meyers, A. I. Stereo- and Regiocontrol by Complex Induced Proximity Effects: Reactions of Organolithium Compounds. *Acc. Chem. Res.* **1986**, *19*, 356.
(58) Batista, J. H. C.; dos Santos, F. M.; Bozzini, L. A.; Vessecchi, R.; Oliveira, A. R. M.; Clososki, G. C. Directed Functionalization of Halophenyl-2-Oxazolines with TMPMgCl·LiCl. *Eur. J. Org. Chem.* **2015**, *2015*, 967.
(59) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. Mixed Mg/Li Amides of the Type $R_2NMgCl·LiCl$ as Highly Efficient Bases for the Regioselective Generation of Functionalized Aryl and Heteroaryl Magnesium Compounds. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958.
(60) Bozzini, L. A.; dos Santos, T.; Murie, V. E.; de Mello, M. B. M.; Vessecchi, R.; Clososki, G. C. Regioselective Functionalization of Ester-, Amide-, Carbonate-, and Carbamate-Substituted 2-Phenyl-2-Oxazolines with Mixed Lithium−Magnesium Amides. *J. Org. Chem.* **2021**, *86*, 1204.
(61) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. Beyond Thermodynamic Acidity: A Perspective on the Complex-Induced Proximity Effect (CIPE) in Deprotonation Reactions. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206.
(62) Göbel, D.; Clamor, N.; Lork, E.; Nachtsheim, B. J. Aerobic $C(Sp^2)$−H Hydroxylations of 2-Aryloxazolines: Fast Access to Excited-State Intramolecular Proton Transfer (ESIPT)-Based Luminophores. *Org. Lett.* **2019**, *21*, 5373.
(63) Unsinn, A.; Rohbogner, C. J.; Knochel, P. Directed Magnesiation of Polyhaloaromatics Using the Tetramethylpiperidylmagnesium Reagents $TMP_2Mg·2$ LiCl and TMPMgCl·LiCl. *Adv. Synth. Catal.* **2013**, *355*, 1553.
(64) Becke, A. D. Density-Functional Exchange-Energy Approximation with Correct Asymptotic Behavior. *Phys. Rev. A* **1988**, *38*, 3098.
(65) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B* **1988**, *37*, 785.
(66) Frisch, G. E. S. M. J.; Trucks, G. W.; Schlegel, H. B.; Robb, T. V. M. A.; Cheeseman, J. R.; Montgomery, J. A.; Kudin, J. T. K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, N. R. V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Reg, J. A. *Gaussian 03*; Gaussian, Inc.: Wallingford, CT, 2004.
(67) Hedidi, M.; Bentabed-Ababsa, G.; Derdour, A.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Mongin, F. Deprotometalation of Substituted Pyridines and Regioselectivity-Computed CH Acidity Relationships. *Tetrahedron* **2016**, *72*, 2196.
(68) Casasnovas, R.; Ortega-Castro, J.; Frau, J.; Donoso, J.; Muöoz, F. Theoretical pK_a Calculations with Continuum Model Solvents, Alternative Protocols to Thermodynamic Cycles. *Int. J. Quantum Chem.* **2014**, *114*, 1350.
(69) Nishimura, R. H. V.; Murie, V. E.; Vessecchi, R.; Clososki, G. C. Selective Functionalization of Benzo-Fused N-Heterocycles by Using In Situ Trapping Metalations. *ChemistrySelect* **2020**, *5*, 11106.
(70) Pastre, J. C.; Browne, D. L.; Ley, S. V. Flow Chemistry Syntheses of Natural Products. *Chem. Soc. Rev.* **2013**, *42*, 8849.
(71) Porta, R.; Benaglia, M.; Puglisi, A. Flow Chemistry: Recent Developments in the Synthesis of Pharmaceutical Products. *Org. Process Res. Dev.* **2016**, *20*, 2.
(72) Baumann, M.; Baxendale, I. R. The Synthesis of Active Pharmaceutical Ingredients (APIs) Using Continuous Flow Chemistry. *Beilstein J. Org. Chem.* **2015**, *11*, 1194.
(73) Baumann, M.; Baxendale, I. R. Continuous Photochemistry: The Flow Synthesis of Ibuprofen via a Photo-Favorskii Rearrangement. *React. Chem. Eng.* **2016**, *1*, 147.
(74) Gambacorta, G.; Sharley, J. S.; Baxendale, I. R. A Comprehensive Review of Flow Chemistry Techniques Tailored to the Flavours and Fragrances Industries. *Beilstein J. Org. Chem.* **2021**, *17*, 1181−1312.
(75) Di Filippo, M.; Baumann, M. Continuous Flow Synthesis of Quinolines via a Scalable Tandem Photoisomerization-Cyclization Process. *Eur. J. Org. Chem.* **2020**, *2020*, 6199.
(76) Qi, H.; Li, X.; Liu, Z.; Miao, S.-S.; Fang, Z.; Chen, L.; Fang, Z.; Guo, K. Regioselective Chlorination of Quinoline Derivatives via Fluorine Mediation in a Microfluidic Reactor. *ChemistrySelect* **2018**, *3*, 10689.
(77) Therkelsen, M.; Rasmussen, M. T.; Lindhardt, A. T. Decarboxylative Reissert Type Trifluoro- and Trichloro-Methylation of (Iso)Quinoline Derivatives in Batch and Continuous Flow. *Chem. Commun.* **2015**, *51*, 9651.
(78) Noël, T.; Musacchio, A. J. Suzuki−Miyaura Cross-Coupling of Heteroaryl Halides and Arylboronic Acids in Continuous Flow. *Org. Lett.* **2011**, *13*, 5180.
(79) Nishimura, R. H. V.; Weidmann, N.; Knochel, P. Preparation of Diorganomagnesium Reagents by Halogen−Lithium Exchange of Functionalized Heteroaryl Halides and Subsequent in Situ Trapping with $MgCl_2$·LiCl in Continuous Flow. *Synthesis* **2020**, *52*, 3036.
(80) Ketels, M.; Ganiek, M. A.; Weidmann, N.; Knochel, P. Synthesis of Polyfunctional Diorganomagnesium and Diorganozinc Reagents through In Situ Trapping Halogen-Lithium Exchange of Highly Functionalized (Hetero)Aryl Halides in Continuous Flow. *Angew. Chem., Int. Ed.* **2017**, *56*, 12770.
(81) Heinz, B.; Djukanovic, D.; Ganiek, M. A.; Martin, B.; Schenkel, B.; Knochel, P. Selective Acylation of Aryl- and Heteroarylmagnesium Reagents with Esters in Continuous Flow. *Org. Lett.* **2020**, *22*, 493.
(82) Yoshida, J.-I. Flash Chemistry: Flow Microreactor Synthesis Based on High-Resolution Reaction Time Control. *Chem. Rec.* **2010**, *10*, 332.
(83) Petersen, T. P.; Becker, M. R.; Knochel, P. Continuous Flow Magnesiation of Functionalized Heterocycles and Acrylates with TMPMgCl·LiCl. *Angew. Chem., Int. Ed.* **2014**, *53*, 7933.
(84) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. Quinolines and Structurally Related Heterocycles as Antimalarials. *Eur. J. Med. Chem.* **2010**, *45*, 3245.
(85) Rámirez, H.; Rodrigues, J. R.; Mijares, M. R.; De Sanctis, J. B.; Charris, J. E. Synthesis and Biological Activity of 2-[2-(7-Chloroquinolin-4-Ylthio)-4-Methylthiazol-5-Yl]-N-Phenylacetamide Derivatives as Antimalarial and Cytotoxic Agents. *J. Chem. Res.* **2020**, *44*, 305.
(86) Oliveira, J. P.; Caleffi, G.; Silva, E.; Coelho, M.; Castro, A.; Mendes, R.; Olegário, T.; Lima-Junior, C.; Vasconcellos, M.; Souza, J.; Souza, S.; Militão, G.; Vaz, B.; Ramalho, R. Morita-Baylis-Hillman Reaction with 7-Chloroquinoline Derivatives-New Compounds with Potential Anticancer Activity. *J. Braz. Chem. Soc.* **2021**, *32*, 347.
(87) Maerten, E.; Agbossou-Niedercorn, F.; Castanet, Y.; Mortreux, A. Preparation of Pyridinyl Aryl Methanol Derivatives by Enantioselective Hydrogenation of Ketones Using Chiral Ru-(Diphosphine)(Diamine) Complexes. Attribution of Their Absolute Configuration by 1H NMR Spectroscopy Using Mosher's Reagent. *Tetrahedron* **2008**, *64*, 8700.
(88) Chen, C.; Reamer, R. A.; Chilenski, J. R.; McWilliams, C. J. Highly Enantioselective Hydrogenation of Aromatic-Heteroaromatic Ketones. *Org. Lett.* **2003**, *5*, 5039.
(89) Armarego, W. L. F.; Chai, C. L. *Purification of Laboratory Chemicals*; Elsevier: 2003.
(90) Mosmann, T. Rapid Colorimetric Assay for Cellular Growth and Survival: Application to Proliferation and Cytotoxicity Assays. *J. Immunol. Methods* **1983**, *65*, 55.

https://doi.org/10.1021/acs.joc.1c01521
J. Org. Chem. 2021, 86, 13402−13419