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Synthesis of Isoquinolones by Sequential Suzuki Coupling of 2-Halobenzonitriles with Vinyl Boronate Followed by Cyclization

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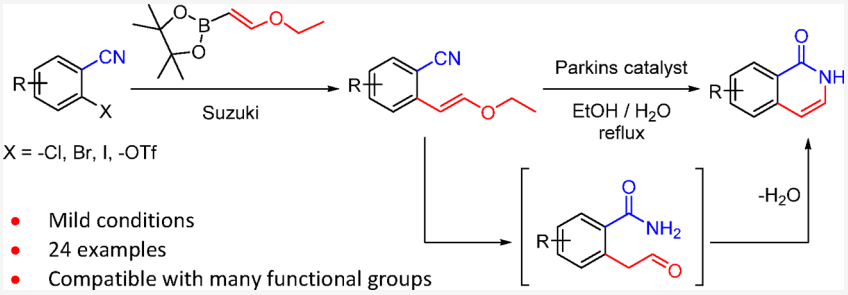

ABSTRACT: A novel, facile, and expeditious two-step synthesis of 3,4-unsubstituted isoquinolin-1(2*H*)-ones from a Suzuki cross-coupling between 2-halobenzonitriles and commercially available vinyl boronates followed by platinum-catalyzed nitrile hydrolysis and cyclization is described.

The isoquinolone scaffold is a privileged structural motif present in many natural products[1,2] and small molecules with pharmacological and biological activities. Compounds of this class are known for their antitumor,[3−5] antihypertensive,[6,7] antithrombotic,[8] anti-inflammatory,[9] and analgesic properties.[10] The isoquinolin-1(2*H*)-one scaffold is present in a wide variety of small-molecule ligands that bind kinases,[7] ion channels,[10] folate-dependent enzymes,[11] tissue factors,[8] glucocorticoid receptors,[9] and several other pharmacologically relevant protein classes (Figure 1).

As a result, several synthetic methodologies have been developed to synthesize this important building block. These approaches include classical methods,[12] typically multistep syntheses that use harsh reaction conditions, and the recently developed elegant syntheses of isoquinolones from benzoic acid derivatives using metal-catalyzed *ortho*-C−H activation,[13−28] which require a directing group on the carboxylic moiety. Unfortunately, the latter are not applicable to the synthesis of 3,4-unsubstituted isoquinolones. Furthermore, they rely on elaborate noncommercial starting materials and lack regioselectivity (Scheme 1).

On the other hand, current synthetic approaches for 3,4-unsubstituted isoquinolones are scarce and consist of mainly multistep processes.[12,14,29,30] Therefore, there is still a need for additional methodologies to access this important chemical scaffold. In this work, we report an improvement of our previously published method,[31] consisting of an expeditious two-step synthesis of 3,4-unsubstituted isoquinolones from 2-halobenzonitriles that use a vinyl boronate as an "acetylene equivalent", which is installed by a Suzuki coupling (Scheme 2).

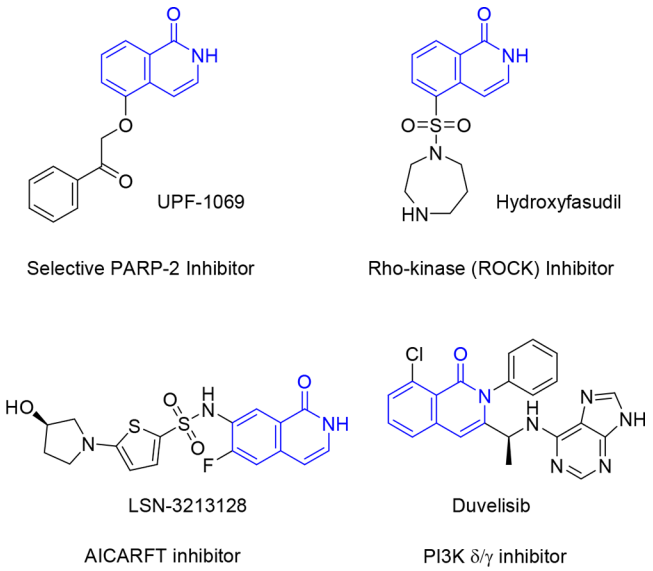

Figure 1. Examples of approved and/or experimental drugs containing the isoquinolone motif.

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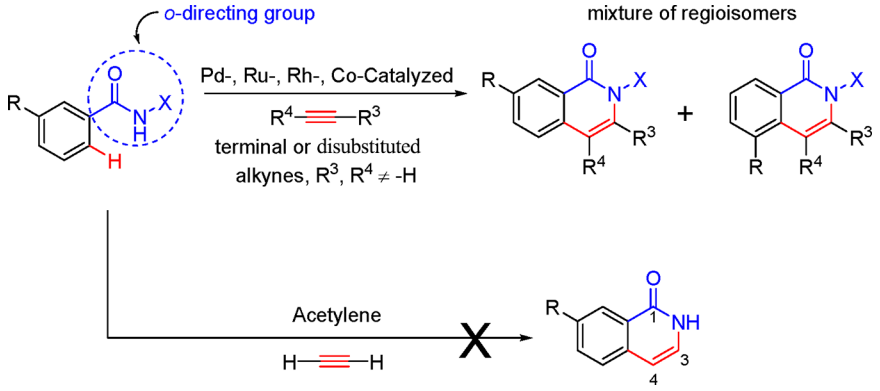
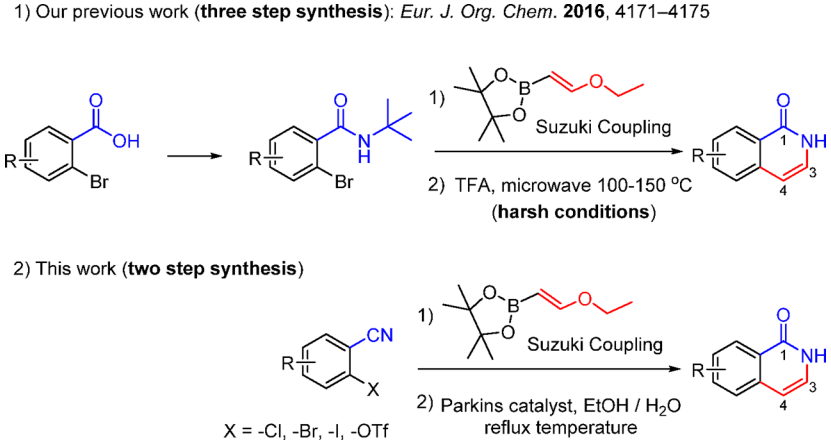
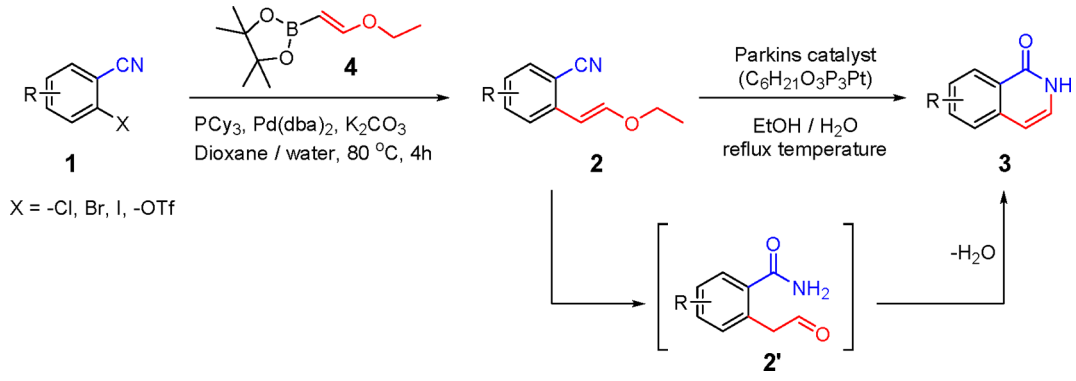
Scheme 1. Current Transition-Metal-Catalyzed C−H Activation Methods to Prepare Isoquinolones



Scheme 2. Synthesis of 3,4-Unsubstituted Isoquinolones by a Suzuki Cross-Coupling Followed by Cyclization



Scheme 3. Synthesis of 3,4-Unsubstituted Isoquinolin-1(2*H*)-ones via a Putative Amide−Aldehyde Intermediate



As part of a current research project, we had to synthesize a library of 3,4-unsubstituted isoquinolones and therefore needed a robust, short, efficient, and versatile synthetic approach. We envisioned that 2-bromobenzonitriles could be an excellent synthon to replace the *N*-*tert*-butylbenzamides that we used in our previous work[31] with the advantage of avoiding an extra step and the harsh conditions needed to deprotect the final cyclic *N*-*tert*-butylisoquinolone as well as being scalable if required. Additionally, there are a wide variety of inexpensive, commercially available 2-bromobenzonitriles to facilitate rapid derivatization.

For the first step in this new approach, the palladium-catalyzed cross-coupling reaction, we used the same optimized reaction conditions described in our previous work,[31] which proved to be a very robust and general protocol. Thus, the Suzuki coupling reaction between a range of 2-bromo or 2-iodobenzonitriles **1**, and the simple, commercially available vinyl boronate ester **4** provides the corresponding vinyl ether intermediates **2** in moderate to high yields (51−88% yield, Tables 1 and 2). For the second step, we hypothesized that the hydrolysis of the nitrile and the vinyl ether could be achieved simultaneously by heating **2** in an aqueous solvent under the appropriate conditions. We envisioned that the amide−aldehyde intermediate **2′** generated would cyclize spontaneously to give isoquinolone **3** under these reaction conditions (Scheme 3). To facilitate this transformation, we chose the Parkins catalyst,[32,33] an air-stable hydride−platinum(II) complex. This platinum-catalyzed process offers mild con-

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Table 1. Substrate Scope of the Synthesis of Isoquinolones from *ortho*-X-benzonitriles

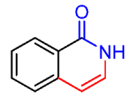
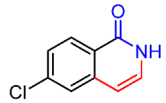
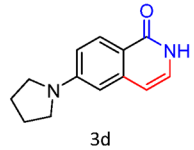
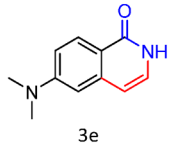
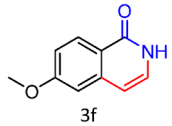
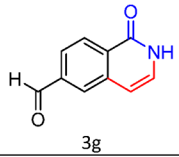
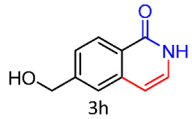
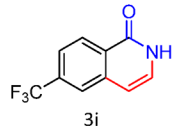
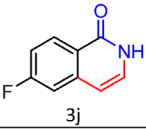
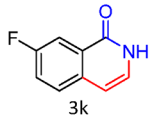
Entry	Reactant **1**	X	R	**2***	Yield	Isoquinolone **3**	Yield
1	1a	-I	-H	2a	81%	 3a	87%
2	1aa	-Br	-H	2a	52%		
3	1ab	-Cl	-H	2a	66%		
4	1ac	-OTf	-H	2a	60%		
5	1b	-Br	3-Me	2b	80%	 3b	81%
6	1c	-Br	4-Cl	2c	82%	 3c	91%
7	1d	-Br	4-(N-pyrrolidinyl)	2d	64%	 3d	88%
8	1e	-Br	4-Dimethylamine	2e	87%	 3e	82%
9	1f	-Br	4-OMe	2f	88%	 3f	47%
10	1g	-Br	4-CHO	2g	66%	 3g	52%
11	1h	-Br	4-Hydroxymethyl	2h	71%	 3h	82%
12	1i	-Br	4-CF_3	2i	73%	 3i	47%
13	1j	-Br	4-F	2j	77%	 3j	79%
14	1ja	-OTf	4-F	2j	63%		
15	1k	-Br	5-F	2k	76%	 3k	83%

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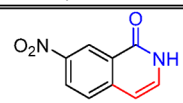
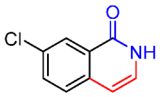
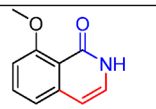
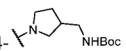
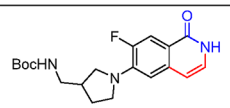
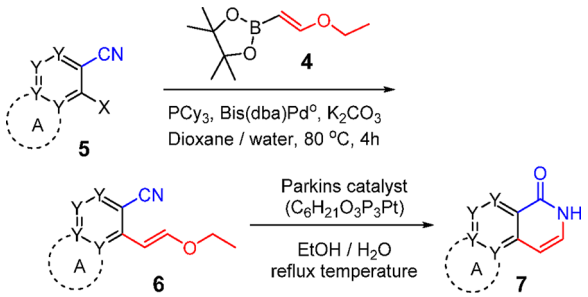
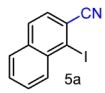
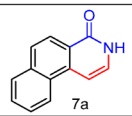
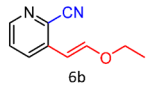
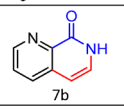
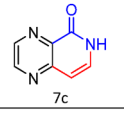
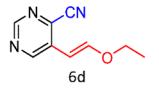
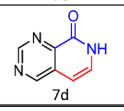
Table 1. continued

Entry	Reactant **1**	X	R	**2***	Yield	Isoquinolone **3**	Yield
16	1l	-Br	5-NO_2	2l	64%	 3l	80%
17	1m	-Cl	5-Cl	2m	51%	 3m	79%
18	1n	-Br	6-OMe	2n	64%	 3n	55%
19	1o	-Br	5-F, 4- 	2o	85%	 3o	78%

*In some cases, small amounts of the *Z*-isomer were formed (detected by NMR).

Table 2. Synthesis of Benzo- and Aza-3,4-unsubstituted Isoquinolin-1(2*H*)-ones



Entry	Reactant **5**	Intermediate **6***	Yield	Product **7**	Yield
1	 5a	 6a	69%	 7a	91%
2	 5b	 6b	68%	 7b	69%
3	 5c	 6c	83%	 7c	80%
4	 5d	 6d	72%	 7d	60%

*In some cases, small amounts of the *Z*-isomer were formed (detected by NMR).

ditions, high reactivity, and compatibility with many chemical functionalities like aldehydes, alcohols, acetals, azides, and most protecting groups.[33] Fortunately, efficient hydrolysis of both the nitrile and the vinyl ether on the parent unsubstituted compound **2a**, followed by cyclization of the carboxamide−aldehyde intermediate **2′**, provided the corresponding 3,4-unsubstituted isoquinolone **3a** in the same reaction step (87% yield, Table 1 and Scheme 3).

Encouraged by this result, we next examined the impact of the electronics of the substituents present on the starting benzonitrile core. Our synthesis proved to be robust, as vinyl ether intermediates bearing both strong electron-donating groups (**2d−f**) and strong electron-withdrawing groups (**2g, 2i**, and **2l**) were prepared and converted into their corresponding isoquinolones in moderate to excellent yield (47−91%). Of note, we were able to greatly improve the yield of 6-dimethylamine isoquinolone **3e** from 16% in previous methodologies[14] to 82% in the present study. The high yields for **3d** and **3e** highlight the ability of our method to efficiently generate isoquinolones substituted with amine functionalities as useful chemical handles for further derivatization. Additionally, we also examined the use of *ortho*-chloro and *ortho*-triflate-benzonitriles to further expand the availability of the starting benzonitriles, especially if the latter can be prepared from the corresponding phenols. We demonstrated that the vinyl ethers **2a** can also be prepared from *ortho*-chloro and *ortho*-triflate-benzonitriles in good yields (entries 3, 4, 14, and 17 on Table 1). Remarkably, when we use 2,5-dichlorobenzonitrile as starting material, we mainly obtained the desired ortho-substituted vinyl ether and just traces of the 5-substitued product (<7% by NMR, entry 17 on Table 1).

In previous reports of 3,4-unsubstituted isoquinolone syntheses, a major challenge was obtaining good product yields from ortho-substituted starting materials.[14,30,31,34] Excitingly, our new strategy was able to efficiently generate 5- and 8-substituted isoquinolones **3b** and **3n** in moderate to good yield (55 and 81%, respectively). Previous attempts at synthesizing 8-methoxyisoquinolones had failed,[14] making the successful synthesis of **3n** noteworthy. Another issue encountered by other synthetic routes has been regioselectivity when generating 5- or 7-substituted isoquinolones.[30] Since our methodology does not rely on an ortho-directing group on the carboxylic moiety, the regioselectivity of the reaction is fully dictated by the position of the halo substituent in the starting benzonitrile. Therefore, we were able to synthesize 5- or 7-substituted isoquinolones (**3b**, **3k**, and **3l**) in a regiospecific manner and in good yields (80−83%).

To further demonstrate the versatility of our novel process, we applied the same approach to the synthesis of other

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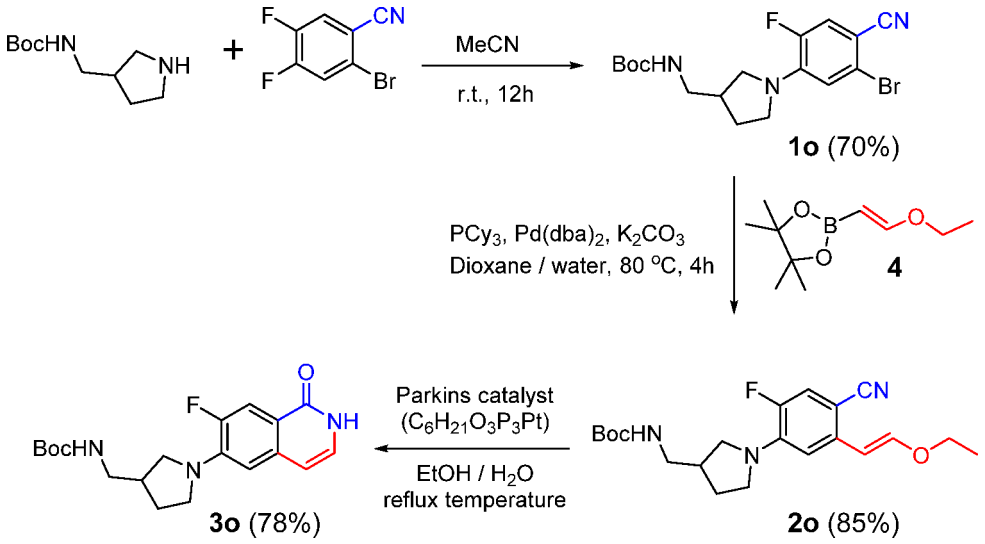
Scheme 4. Synthetic Approach to Give Isoquinolone 3o



heterocycles, by using *ortho*-halo-cyano-arenes other than *ortho*-halobenzonitriles as starting materials (Table 2). In our previous work, we were able to produce diazaheterocycles; however, the isolated products in every case were *N*-*tert*-butylazaisoquinolones that required harsh conditions of neat TFA at 150 °C (microwave) to remove the *tert*-butyl group.[31] Our new approach bypasses the *N*-*tert*-butylisoquinolone intermediates to give a variety of nitrogenous heterocycles (**7a**–**d**) in moderate to good yield (60–91%). Two of these heterocycles, **7c** and **7d**, could not be prepared with our previous method because of the high stability of the corresponding *N*-*tert*-butylisoquinolones.[31] Therefore, this work is a substantial improvement over our previous methodology, since it enables the formation of complex isoquinolones bearing acid-sensitive functional groups.

A major advantage of our new synthetic approach is that the mild reaction conditions are compatible with a wide array of functional groups that can be used to further derivatize the isoquinolone products. We successfully synthesized 3,4-unsubstituted isoquinolones bearing amine (**3d** and **3e**), carbaldehyde (**3g**), hydroxyl (**3h**), and BOC-protecting groups (**3o**). Previous strategies generated only trace amounts of **3h**,[14] further highlighting the power of our two-step synthesis. To underscore the potential utility of our synthetic approach in generating diverse libraries of isoquinolones, we heated 6-fluoro-2*H*-isoquinolin-1-one (**3j**) in neat pyrrolidine for 48 h to form the S_NAr product 6-pyrrolidin-1-yl-2*H*-isoquinolin-1-one in excellent yield (94%, fully characterized as **3d**). Finally, the versatility of this methodology was further demonstrated in an ongoing project in our lab when we prepared large quantities of compound **3o**, which was a critical starting material for the construction of a library of 6-substituted isoquinolones (Scheme 4).

Although we did not perform a comprehensive mechanistic study of our novel synthetic route, we hypothesize that isoquinolones generated through this strategy undergo a sequential hydrolysis of the nitrile followed by hydrolysis of the vinyl ether to the aldehyde, after which cyclization to the isoquinolone is spontaneous. This is inferred from the isolation of the primary amide of **7d′** (for structure see Figure S88 in the SI) that retains the intact vinyl ether moiety during the uncomplete reaction to produce **7d**. We verified this intermediate by LC–MS and ^{1}H NMR, which contained prominent amide and vinyl ether peaks.

In conclusion, we developed an efficient and expeditious synthesis of 3,4-unsubstituted isoquinolin-1(2*H*)-ones using mild conditions with simple, affordable starting materials in two steps. The wide availability of the starting materials, the mild neutral reaction conditions, and experimental simplicity allow the present methodology to have rapid access to these very important isoquinolone scaffolds, some of which were not accessible using previous methodologies.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, common reagents or starting materials were obtained from a commercial source and used without further purification. The Parkins catalyst was purchased from Strem Cheimcals Inc. (Newburyport, MA). Flash column chromatography was performed using silica gel 60 (230–400 mesh). Preparative and analytical thin-layer chromatography (PTLC and TLC) was carried out on Merck silica gel plates with a QF-254 indicator and visualized by UV or $KMnO_4$. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent DD_2 500 (500 MHz ^{1}H; 125 MHz ^{13}C), Agilent DD_2 600 (600 MHz ^{1}H; 150 MHz ^{13}C), or Agilent DD_2 400 (400 MHz ^{1}H; 100 MHz ^{13}C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual $CDCl_3$ (δ 7.26 ppm ^{1}H; δ 77.0 ppm ^{13}C), CD_3OD (δ 3.31 ppm ^{1}H; δ 49.0 ppm ^{13}C), or DMSO-d_6 (δ 2.50 ppm ^{1}H; δ 39.5 ppm ^{13}C). NMR chemical shifts were expressed in ppm relative to internal solvent peaks, and coupling constants were measured in Hz (bs = broad signal). Mass spectrometric measurements were obtained using electrospray ionization (ESI) and performed with a Shimadzu Scientific Instruments QToF 9030 LC–MS system, equipped with a Nexera LC-40D xs UHPLC, consisting of a CBM-40 Lite system controller, a DGU-405 degasser unit, two LC-40D XS UHPLC pumps, a SIL-40C XS autosampler, and a column oven CTO-40S. UV data was collected with a Shimadzu Nexera HPLC/UHPLC photodiode array detector SPD M-40 in the range of 190–800 nm. Mass spectra were subsequently recorded with the quadrupole time-of-flight (QToF) 9030 mass spectrometer.

*Synthesis of tert-Butyl-((1-(5-bromo-4-cyano-2-fluorophenyl)-pyrrolidin-3-yl)methyl)carbamate (**1o**).* *tert*-Butyl-*N*-(pyrrolidin-3-ylmethyl)carbamate (463 mg, 2.31 mmol) was added to a solution of 2-bromo-4,5-difluorobenzonitrile (462 mg, 2.12 mmol) in MeCN (4.00 mL, 0.53 M) at room temperature. The orange solution was stirred for 12 h at room temperature and then concentrated *in vacuo*, and the residue was purified by flash chromatography (SiO_2-100g,

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gradient Hex/EtOAc, 95:5 to 7:3 in 20 min) to afford 585 mg of the desired product (67% yield) as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 13.5, 1.9 Hz, 1H), 6.70 (dd, J = 8.0, 2.1 Hz, 1H), 4.66 (bs, 1H), 3.72−3.40 (m, 3H), 3.32−3.01 (m, 3H), 2.60−2.35 (m, 1H), 2.16−1.99 (m, 1H), 1.82−1.56 (m, 1H), 1.43 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.9, 148.9 (d, J = 243.6 Hz), 140.9 (d, J = 9.9 Hz), 121.3 (d, J = 2.3 Hz), 120.7 (d, J = 25.7 Hz), 117.9 (d, J = 5.9 Hz), 117.7 (d, J = 1.7 Hz), 79.6, 53.0 (d, J = 5.7 Hz), 49.1 (d, J = 5.7 Hz), 42.7, 39.2, 28.7, 28.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −130.08. HRMS (ESI) m/z $[M + H]^+$: Calcd for $C_{17}H_{22}BrFN_3O_2$ 398.0879; Found 398.0896 and 400.0877.

General Procedure for the Synthesis of (*E*)-2-(2-Ethoxyvinyl)-nitriles (2) and (6). To a solution of the ortho-substituted-benzonitrile compound (**1**) or (**5**) (1.15 mmol) and 2-[(*E*)-2-ethoxyvinyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (228 mg, 1.15 mmol) in dioxane (15 mL, 0.08 M) was added K_2CO_3 (476 mg, 3.44 mmol) followed by water (5 mL, 0.02 M). The reaction mixture was degassed under vacuum and purged with argon (5×). Then, PCy_3 (0.11 mmol) and $Pd(dba)_2$ (0.05 mmol) were added. The reaction mixture was heated in an oil bath with vigorous stirring at 80 °C for 2 to 4 h. The reaction mixture was diluted with EtOAc (50 mL) and filtered over a Celite pad. The filtrate was diluted with EtOAc (50 mL), washed with an aqueous saturated solution of NaCl (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude material was purified by flash column chromatography (gradient Hex/EtOAc 1:0 to 8:2) or PTLC to give the product (**2**) or (**6**).

*(E)-2-(2-Ethoxyvinyl)benzonitrile (**2a**).* This compound was prepared following the procedure described above to give 160 mg (81% yield) of pure product as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70 (dd, J = 7.9, 1.4 Hz, 2H), 7.62−7.40 (m, 2H), 7.27 (t, J = 7.6 Hz, 1H), 5.99 (d, J = 12.7 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 152.8, 140.0, 133.1, 132.8, 125.8, 124.0, 118.1, 108.1, 101.4, 66.0, 14.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}NO$ 174.0918; Found 174.0920.

*(E)-2-(2-Ethoxyvinyl)-3-methylbenzonitrile (**2b**).* This compound was prepared following the procedure described above to give 190 mg (80% yield) of pure product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 13.0 Hz, 1H), 5.84 (d, J = 12.9 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 2.32 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.8, 139.0, 137.2, 134.3, 131.3, 126.0, 119.8, 110.6, 101.0, 66.2, 20.9, 14.9. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{13}NO$ 188.1075; Found 188.1082.

*4-Chloro-2-[(E)-2-ethoxyvinyl]benzonitrile (**2c**).* This compound was prepared following the procedure described above to give 98 mg (82% yield) of pure product as a light-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 12.8 Hz, 1H), 7.15 (dd, J = 8.3, 2.0 Hz, 1H), 6.06 (d, J = 12.8 Hz, 1H), 3.99 (q, J = 7.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.7, 142.5, 139.4, 134.2, 126.0, 124.0, 117.8, 108.0, 101.4, 66.3, 14.7. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}ClNO$ 208.0529; Found 208.0534.

*(E)-2-(2-Ethoxyvinyl)-4-(pyrrolidin-1-yl)benzonitrile (**2d**).* This compound was prepared following the procedure described above to give 98 mg (64% yield) of pure product as a yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (d, J = 12.7 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 6.60 (d, J = 2.2 Hz, 1H), 6.39 (dd, J = 8.8, 2.6 Hz, 1H), 5.89 (d, J = 12.7 Hz, 1H), 3.94 (q, J = 7.0 Hz, 2H), 3.42−3.00 (m, 4H), 2.08−1.66 (m, 4H), 1.27 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 152.1, 150.3, 141.0, 134.1, 120.5, 110.3, 106.2, 102.8, 94.1, 66.2, 47.6, 25.3, 15.1. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}N_2O$ 243.1497; Found 243.1504.

*4-(Dimethylamino)-2-[(E)-2-ethoxyvinyl]benzonitrile (**2e**).* This compound was prepared following the procedure described above to give 250 mg (87% yield) of pure product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.8 Hz, 1H), 7.14 (d, J = 12.9 Hz, 1H), 6.55 (d, J = 2.5 Hz, 1H), 6.47 (dd, J = 8.8, 2.5 Hz, 1H), 6.05 (d, J = 12.9 Hz, 1H), 3.95 (q, J = 7.0 Hz, 2H), 3.02 (s, 6H), 1.36 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 152.6, 150.8, 141.5, 134.2, 120.4, 111.5, 109.7, 106.4, 103.2, 65.7, 40.2, 14.8. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{17}N_2O$ 217.1340; Found 217.1355.

*2-[(E)-2-Ethoxyvinyl]-4-methoxybenzonitrile (**2f**).* This compound was prepared following the procedure described above to give 90 mg (88% yield) of pure product as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.68−7.44 (m, 2H), 7.17 (d, J = 2.5 Hz, 1H), 6.80 (dd, J = 8.7, 2.5 Hz, 1H), 5.90 (d, J = 12.7 Hz, 1H), 3.94 (q, J = 7.0 Hz, 2H), 3.80 (s, 3H), 1.25 (t, J = 7.0 Hz, 4H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 163.1, 153.6, 142.6, 135.0, 119.0, 113.3, 108.9, 102.0, 100.8, 66.5, 56.1, 15.1. HRMS (ESI) m/z: $[M + H]^+$Calcd for $C_{12}H_{14}NO_2$ 204.1024; Found 204.1028.

*2-[(E)-2-Ethoxyvinyl]-4-formylbenzonitrile (**2g**).* This compound was prepared following the procedure described above to give 304 mg (66% yield) as a white amorphous solid and was characterized as a mixture of isomers (*E*:*Z* ratio ≈ 3:1). *E*-isomer: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.09 (dd, J = 7.7, 1.4 Hz, 1H), 8.05 (dd, J = 7.8, 1.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.05 (d, J = 12.8 Hz, 1H), 6.36 (d, J = 12.8 Hz, 1H), 4.04 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 190.5, 156.4, 143.0, 137.9, 134.2, 133.3, 126.3, 117.7, 113.0, 98.0, 66.6, 14.6. *Z*-isomer: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.96 (s, 1H), 8.08 (dd, J = 7.7, 1.5 Hz, 1H), 7.99 (dd, J = 7.8, 1.4 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 6.9 Hz, 1H), 5.72 (d, J = 6.8 Hz, 1H), 3.96 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.9, 150.7, 141.4, 137.1, 134.0, 131.5, 127.0, 117.4, 113.4, 97.9, 69.5, 15.0. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{12}NO_2$ 202.0868; Found 202.0878.

*2-[(E)-2-Ethoxyvinyl]-4-(hydroxymethyl)benzonitrile (**2h**).* This compound was prepared following the procedure described above to give 85 mg (71% yield) of pure product as a gray amorphous solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.0 Hz, 1H), 7.45−7.42 (m, 1H), 7.21 (d, J = 12.8 Hz, 1H), 7.15 (dt, J = 8.0, 1.0 Hz, 1H), 6.11 (d, J = 12.8 Hz, 1H), 4.72 (s, 2H), 3.97 (q, J = 7.0 Hz, 2H), 1.91 (s, 1H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 151.8, 146.0, 141.0, 133.3, 123.8, 121.7, 118.6, 108.5, 102.3, 66.1, 64.6, 14.8. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{14}NO_2$204.1024; Found 204.1023.

*2-[(E)-2-Ethoxyvinyl]-4-(trifluoromethyl)benzonitrile (**2i**).* This compound was prepared following the procedure described above to give 393 mg (73% yield) of pure product as a yellow oil. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.79 (d, J = 12.5 Hz, 1H), 7.58 (dd, J = 8.2, 1.7 Hz, 1H), 6.02 (d, J = 12.6 Hz, 1H), 4.03 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 155.5, 141.9, 134.6, 133.4 (q, J = 32.2 Hz), 123.8 (q, J = 273.4 Hz), 122.3 (q, J = 3.8 Hz), 121.0 (q, J = 3.8 Hz), 117.5, 111.97, 101.19, 67.1, 15.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ −62.05. HRMS (ESI) m/z: [M + H]+ Calcd for $C_{12}H_{10}F_3NO$ 242.0793; Found 242.0786.

*4-Fluoro-2-[(E)-2-ethoxyvinyl]benzonitrile (**2j**).* This compound was prepared following the procedure described above to give 90 mg (77% yield) of pure product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.6, 5.7 Hz, 1H), 7.19 (d, J = 12.9 Hz, 1H), 7.10 (dd, J = 10.2, 2.5 Hz, 1H), 6.88 (ddd, J = 8.7, 7.8, 2.5 Hz, 1H), 6.09 (dd, J = 12.8, 1.4 Hz, 1H), 3.99 (q, J = 7.0 Hz, 2H), 1.38 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.3, 163.8, 152.5, 143.8, 143.7, 135.3, 135.2, 117.7, 113.5, 113.2, 110.7, 110.5, 105.7, 105.7, 101.5, 101.5, 66.1, 14.6. ^{19}F NMR (471 MHz, $CDCl_3$) δ −103.75. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}FNO$ 192.0824; Found 192.0825.

*(E)-2-(2-Ethoxyvinyl)-5-fluorobenzonitrile (**2k**).* This compound was prepared following the procedure described above to give 326 mg (76% yield) of pure product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.9, 5.1 Hz, 1H), 7.29−7.22 (m, 1H), 7.18 (ddd, J = 9.0, 7.9, 2.8 Hz, 1H), 7.10 (d, J = 12.9 Hz, 1H), 6.07 (d, J = 12.9 Hz, 1H), 3.97 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 159.9 (d, J = 247.7 Hz), 151.5 (d, J = 1.8 Hz), 137.2 (d, J = 3.6 Hz), 126.0 (d, J = 7.9 Hz), 120.8 (d, J = 21.6 Hz), 119.2 (d, J = 24.3 Hz), 117.3 (d, J = 2.9 Hz), 110.5 (d, J = 9.0 Hz), 101.3, 66.0, 14.7. ^{19}F NMR (471 MHz, DMSO-d_6) δ

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−115.94. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{11}FNO$ 192.0824; Found 192.0829.

*(E)-2-(2-Ethoxyvinyl)-5-nitrobenzonitrile (**2l**).* This compound was prepared following the procedure described above to give 326 mg (64% yield) of pure product as a yellow oil. ^1H NMR (600 MHz, DMSO-d_6) δ 8.60 (d, J = 2.5 Hz, 1H), 8.32 (dd, J = 9.0, 2.5 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.89 (d, J = 12.5 Hz, 1H), 6.06 (d, J = 12.5 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 1.31 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 157.6, 146.9, 144.1, 128.7, 127.5, 124.3, 116.3, 108.3, 100.8, 67.3, 14.7. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{10}N_2O_3Na$ 241.0589; Found 241.0557.

*(E)-5-Chloro-2-(2-ethoxyvinyl)benzonitrile (**2m**).* This compound was prepared following the procedure described above to give 53 mg (51% yield) of pure product as a light-yellow oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 2.3 Hz, 1H), 7.73 (d, J = 8.7 Hz, 1H), 7.62 (dd, J = 8.7, 2.4 Hz, 1H), 7.56 (d, J = 12.7 Hz, 1H), 5.94 (d, J = 12.7 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 154.1, 139.6, 133.7, 132.4, 130.1, 126.0, 117.3, 109.9, 101.0, 66.7, 15.0. HRMS (ESI) m/z: $[M + H]^+$ Calcd for C_9H_7ClNO 180.0216; Found 180.0219.

*2-[(E)-2-Ethoxyvinyl]-6-methoxybenzonitrile (**2n**).* This compound was prepared following the procedure described above to give 291 mg (64% yield) of pure product as a white amorphous solid. ^1H NMR (600 MHz, DMSO-d_6) δ 7.53−7.36 (m, 2H), 7.22 (d, J = 8.0 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H), 5.90 (d, J = 12.7 Hz, 1H), 3.94 (q, J = 7.0 Hz, 2H), 3.84 (s, 3H), 1.25 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 161.4, 153.2, 141.7, 134.1, 115.8, 115.6, 108.0, 101.5, 97.7, 66.1, 56.2, 14.7, 14.7. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{12}H_{13}NO_2$ 204.1024; Found 204.1035.

*tert-Butyl-(E)-((1-(4-cyano-5-(2-ethoxyvinyl)-2-fluorophenyl)-pyrrolidin-3-yl)methyl)carbamate (**2o**).* This compound was prepared following the procedure described above to give 226 mg (85% yield) of pure product as a colorless oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.41−7.24 (m, 2H), 6.97 (t, J = 5.8 Hz, 1H), 6.65 (d, J = 8.8 Hz, 1H), 5.82 (d, J = 12.7 Hz, 1H), 3.91 (q, J = 7.0 Hz, 1H), 3.54−3.35 (m, 3H), 3.22−3.15 (m, 1H), 2.99−2.90 (m, 2H), 2.32 (p, J = 6.9 Hz, 1H), 1.95 (h, J = 6.6 Hz, 1H), 1.69−1.56 (m, 1H), 1.34 (s, 9H), 1.24 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 155.8, 151.8, 147.8 (d, J = 240.1 Hz), 140.2 (d, J = 9.2 Hz), 137.5 (d, J = 1.9 Hz), 119.2 (d, J = 24.5 Hz), 118.6 (d, J = 2.0 Hz), 109.2 (d, J = 5.6 Hz), 101.5, 93.6 (d, J = 8.9 Hz), 77.6, 65.8, 52.8 (d, J = 5.9 Hz), 48.7 (d, J = 5.0 Hz), 42.2, 38.4, 28.2, 14.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ −131.37. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{21}H_{29}FN_3O_3$, 390.2192; Found 390.2218.

*(E)-1-(2-Ethoxyvinyl)-2-naphthonitrile (**6a**).* This compound was prepared following the procedure described above to give 132 mg (69% yield) of pure product as a colorless oil. ^1H NMR (400 MHz, DMSO-d_6) δ 7.70 (dd, J = 7.9, 1.4 Hz, 2H), 7.62−7.40 (m, 2H), 7.27 (t, J = 7.6 Hz, 1H), 5.99 (d, J = 12.7 Hz, 1H), 3.98 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 152.8, 140.0, 133.1, 132.8, 125.8, 124.0, 118.1, 108.1, 101.4, 66.0, 14.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{14}NO$, 224.1075; Found 224.1089.

*3-[(E)-2-Ethoxyvinyl]pyridine-2-carbonitrile (**6b**).* This compound was prepared following the procedure described above to give 271 mg (68% yield) of pure product as an orange amorphous solid. ^1H NMR (600 MHz, DMSO-d_6) δ 8.42 (dd, J = 4.5, 1.5 Hz, 1H), 8.14 (dd, J = 8.3, 1.5 Hz, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.56 (ddd, J = 8.4, 4.5, 0.6 Hz, 1H), 5.91 (d, J = 12.7 Hz, 1H), 3.99 (q, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 154.8, 147.9, 137.4, 131.9, 128.6, 127.4, 116.8, 98.6, 98.3, 66.4, 14.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}N_2O$, 175.0871; Found, 175.0878.

*3-[(E)-2-Ethoxyvinyl]pyrazine-2-carbonitrile (**6c**).* This compound was prepared following the procedure described above to give 331 mg (83% yield) of pure product as an off-white amorphous solid. ^1H NMR (600 MHz, DMSO-d_6) δ 8.69 (d, J = 2.3 Hz, 1H), 8.47 (d, J = 2.3 Hz, 1H), 7.93 (d, J = 12.1 Hz, 1H), 6.03 (d, J = 12.1 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 159.0, 154.6, 147.9, 142.5, 124.7, 116.3, 99.2, 67.8, 15.0. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{10}N_3O$, 176.0823; Found, 176.0835.

*5-[(E)-2-Ethoxyvinyl]pyrimidine-4-carbonitrile (**6d**).* This compound was prepared following the procedure described above to give 240 mg (72%) of pure product as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 8.92 (s, 1H), 7.35 (d, J = 13.0 Hz, 1H), 5.93 (d, J = 13.0 Hz, 1H), 4.05 (q, J = 7.0 Hz, 2H), 1.40 (t, J = 7.0 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.6, 154.2, 154.0, 136.2, 134.1, 115.0, 96.5, 66.9, 14.7. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_9N_3O$, 176.0823; Found 176.0833.

General Procedure for the Synthesis of Isoquinolin-1(2*H*)-ones (3) and (7). To a solution of 2-[(*E*)-3-ethoxyallyl]benzonitrile (**2**) or (**6**) (0.74 mmol) in a mixture of EtOH/water (3:2 mL, 0.49 M/0.74 M) was added Parkins catalyst (0.02 mmol). The solution was heated at reflux temperature in an oil bath with vigorous stirring until the starting material was fully consumed (12 to 48 h). The reaction mixture was concentrated *in vacuo* and crude product was purified by flash column chromatography (gradient DCM/MeOH, 1:0 to 9:1) or PTLC to give the product (**3**) or (**7**).

*Isoquinolin-1(2H)-one (**3a**).* This compound was prepared following the procedure described above to give 95 mg (87% yield) of pure product as a white amorphous solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.22 (bs, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.67 (dt, J = 15.1, 7.6 Hz, 2H), 7.47 (t, J = 8.0 Hz, 1H), 7.16 (t, 1H), 6.54 (d, J = 7.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 161.8, 137.8, 132.2, 128.9, 126.6, 126.2, 126.1, 126.0, 104.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for C_9H_8NO 146.0605; Found 146.0606.

*5-Methyl-2H-isoquinolin-1-one (**3b**).* This compound was prepared following the procedure descried above to give 24 mg (81% yield) of pure product as a white amorphous solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 7.4 Hz, 1H), 6.57 (d, J = 7.4 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 162.5, 137.1, 133.6, 133.3, 129.1, 126.7, 126.3, 125.1, 101.7, 19.1. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{10}NO$ 160.0762; Found 160.0765.

*6-Chloroisoquinolin-1(2H)-one (**3c**).* This compound was prepared following the procedure descried above to give 15 mg (91% yield) of pure product as a white amorphous solid. ^1H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 8.12 (d, J = 8.6 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.44 (dd, J = 8.6, 2.1 Hz, 1H), 7.20 (d, J = 7.1 Hz, 1H), 6.49 (d, J = 7.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 161.3, 139.5, 137.3, 130.7, 129.0, 126.5, 125.3, 124.6, 103.8. HRMS (ESI) m/z: $[M + H]^+$ Calcd for C_9H_7ClNO 180.0216; Found 180.0219.

*6-(Pyrrolidin-1-yl)isoquinolin-1(2H)-one (**3d**).* This compound was prepared following the procedure described above to give 28 mg (88% yield) of pure product as a light-yellow amorphous solid. ^1H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 6.97 (t, J = 6.4 Hz, 1H), 6.73 (d, J = 8.9 Hz, 1H), 6.49 (s, 1H), 6.30 (d, J = 7.1 Hz, 1H), 3.57−2.93 (m, 4H), 2.17−1.67 (m, 4H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 161.8, 149.9, 139.5, 128.7, 128.1, 115.1, 112.5, 104.5, 104.4, 47.2, 24.9. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2O$ 215.1184; Found 215.1173.

*6-(Dimethylamino)-2H-isoquinolin-1-one (**3e**).* This compound was prepared following the procedure described above to give 20 mg (82% yield) of pure product as a white amorphous solid. ^1H NMR (400 MHz, DMSO-d_6) δ 10.68 (s, 1H), 7.94 (d, J = 9.0 Hz, 1H), 6.99 (t, J = 6.3 Hz, 1H), 6.90 (dd, J = 9.0, 2.6 Hz, 1H), 6.66 (d, J = 2.5 Hz, 1H), 6.32 (d, J = 7.2 Hz, 1H), 3.01 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 161.8, 152.6, 139.5, 128.8, 128.0, 115.6, 112.4, 105.0, 104.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{11}H_{12}N_2O$ 189.1028; Found 189.1039.

*6-Methoxy-2H-isoquinolin-1-one (**3f**).* This compound was prepared following the procedure described above to give 9 mg (47% yield) of pure product as a white amorphous solid along with 35% recovered starting material. ^1H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.13−7.06 (m, 2H), 7.00 (dd, J = 8.9, 2.6 Hz, 1H), 6.43 (d, J = 7.1 Hz, 1H), 3.82 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 162.6, 162.0, 140.5, 130.0, 129.1,

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120.2, 116.2, 107.5, 104.9, 55.9. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_9NO_2$ 176.0711; Found 176.0718.

*1-Oxo-2H-isoquinoline-6-carbaldehyde (**3g**).* This compound was prepared following the procedure described above to give 26 mg (52% yield) of pure product as a white amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.60 (s, 1H), 10.33 (s, 1H), 8.51 (d, J = 8.0 Hz, 1H), 8.29 (dd, J = 7.5, 1.6 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.39 (dd, J = 7.5, 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 194.0, 161.7, 139.8, 137.3, 133.4, 132.8, 130.3, 127.5, 126.4, 100.8. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_8NO_2$ 174.0555; Found 174.0557.

*6-(Hydroxymethyl)-2H-isoquinolin-1-one (**3h**).* This compound was prepared following the procedure described above to give 14 mg (82% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.17 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 1.7 Hz, 1H), 7.41 (dd, J = 8.3, 1.6 Hz, 1H), 7.14 (dd, J = 7.1, 5.1 Hz, 1H), 6.52 (d, J = 7.1 Hz, 1H), 5.40 (t, J = 5.7 Hz, 1H), 4.63 (d, J = 5.2 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.8, 147.2, 137.9, 129.0, 126.6, 124.7, 123.0, 104.8, 62.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_9NO_2$ 176.0711; Found 176.0701.

*6-(Trifluoromethyl)-2H-isoquinolin-1-one (**3i**).* This compound was prepared following the procedure described above to give 22 mg (47% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.32 (dd, J = 8.5, 1.2 Hz, 1H), 8.09 (s, 1H), 7.71 (dd, J = 8.4, 1.8 Hz, 1H), 7.28 (dd, J = 7.1, 4.8 Hz, 1H), 6.68 (d, J = 7.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.1, 138.1, 132.1 (q, J = 32.0 Hz), 130.8, 128.4, 128.0, 123.9 (q, J = 273.1 Hz), 123.7 (q, J = 4.0 Hz), 121.9 (q, J = 3.4 Hz), 104.4. ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.57. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_7F_3NO$ 214.0479; Found, 214.0487.

*6-Fluoroisoquinolin-1(2H)-one (**3j**).* This compound was prepared following the procedure descried above to give 16 mg (79% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, 1H), 8.22 (dd, J = 8.9, 6.0 Hz, 1H), 7.47 (dd, J = 10.1, 2.6 Hz, 1H), 7.30 (td, J = 8.9, 2.6 Hz, 1H), 7.22 (d, J = 7.2 Hz, 1H), 6.53 (d, J = 7.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 165.6, 163.1, 161.2, 140.4, 140.3, 130.5, 130.2, 130.1, 123.0, 122.9, 114.9, 114.6, 111.0, 110.8, 104.2, 104.1. ^{19}F NMR (471 MHz, DMSO-d_6) δ −107.46. HRMS (ESI) m/z: $[M + H]^+$ Calcd for C_9H_7FNO 164.0511; Found 164.0510.

*7-Fluoroisoquinolin-1(2H)-one (**3k**).* This compound was prepared following the procedure described above to give 17 mg (83% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.37 (bs, 1H), 7.83 (dd, J = 9.6, 2.8 Hz, 1H), 7.76 (dd, J = 8.8, 5.4 Hz, 1H), 7.60 (td, J = 8.7, 2.8 Hz, 1H), 7.16 (dd, J = 6.2, 2.6 Hz, 2H), 6.59 (d, J = 7.1 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 160.4 (d, J = 244.3 Hz), 161.0 (d, J = 3.5 Hz), 134.7 (d, J = 1.8 Hz), 129.1 (d, J = 8.0 Hz), 128.2 (d, J = 2.3 Hz), 127.4 (d, J = 7.5 Hz), 121.0 (d, J = 23.5 Hz), 111.2 (d, J = 22.2 Hz), 104.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ −113.97. HRMS (ESI) m/z: $[M + H]^+$ Calcd for C_9H_7FNO, 164.0511; Found 164.0496.

*7-Nitroisoquinolin-1(2H)-one (**3l**).* This compound was prepared following the procedure described above to give 26 mg (80% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.88 (d, J = 2.5 Hz, 1H), 8.43 (dd, J = 8.8, 2.5 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 7.2, 4.8 Hz, 1H), 6.72 (d, J = 7.1 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 161.1, 145.0, 142.8, 133.5, 128.1, 126.1, 125.6, 122.6, 104.1. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_7N_2O_3$ 191.0456; Found 191.0452.

*7-Chloroisoquinolin-1(2H)-one (**3m**).* This compound was prepared following the procedure described above to give 29 mg (79% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.43 (s, 1H), 8.11 (s, 1H), 7.87−7.46 (m, 1H), 7.33−7.01 (m, 1H), 6.58 (d, J = 6.9 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.7, 136.6, 132.4, 130.8, 129.5, 128.5, 127.2, 125.6, 104.1. HRMS (ESI) m/z: $[M+1]^+$ Calcd for C_9H_7ClNO180.0216; Found 180.0219.

*8-Methoxy-2H-isoquinolin-1-one (**3n**).* This compound was prepared following the procedure described above to give 24 mg (55% yield) of pure product as an off-white amorphous solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.84 (s, 1H), 7.52 (t, J = 8.1 Hz, 1H), 7.08 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 7.0 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.35 (d, J = 7.0 Hz, 1H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 160.8, 160.8, 141.4, 133.4, 129.9, 118.6, 115.9, 108.6, 104.7, 56.1. HRMS (ESI) m/z[M + H]$^+$ Calcd for $C_{10}H_{10}NO_2$ 176.0711; Found 176.0709.

*tert-Butyl-((1-(7-fluoro-1-oxo-1,2-dihydroisoquinolin-6-yl)-pyrrolidin-3-yl)methyl)carbamate (**3o**).* This compound was prepared following the procedure described above using 216 mg (0.55 mol) of **2o** to give 157 mg (78% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.87 (bs, 1H), 7.63 (dd, J = 14.9, 2.1 Hz, 1H), 7.20−6.87 (m, 2H), 6.70 (d, J = 8.5 Hz, 1H), 6.36 (d, J = 7.0 Hz, 1H), 3.60−3.38 (m, 3H), 3.27−3.15 (m, 1H), 3.13−2.84 (m, 2H), 2.44−2.31 (m, 1H), 2.10−1.91 (m, 1H), 1.75−1.61 (m, 1H), 1.38 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.9 (d, J = 3.3 Hz), 155.8, 150.5 (d, J = 242.8 Hz), 140.7 (d, J = 10.8 Hz), 136.2, 128.3, 115.8 (d, J = 6.8 Hz), 112.2 (d, J = 22.2 Hz), 109.1 (d, J = 5.1 Hz), 103.8, 77.5, 53.0 (d, J = 5.5 Hz), 48.9 (d, J = 5.4 Hz), 42.3, 38.4, 28.3, 28.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ −127.33. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{19}H_{25}FN_3O_3$ 362.1879; Found 362.1869.

*Benzo[f]isoquinolin-4(3H)-one (**7a**).* This compound was prepared following the procedure described above to give 60 mg (91% yield) of pure product as a white amorphous solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.64 (bs, 1H), 8.64 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 8.04 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.79−7.58 (m, 2H), 7.43 (t, J = 6.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 161.7, 136.4, 134.3, 130.5, 128.5, 128.4, 128.1, 126.9, 126.4, 124.4, 123.3, 122.8, 100.3. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{10}NO$ 196.0762; Found 196.0766.

*7H-1,7-Naphthyridin-8-one (**7b**).* This compound was prepared following the procedure described above to give 26 mg (69% yield) of pure product as a yellow amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 8.72 (dd, J = 4.3, 1.7 Hz, 1H), 8.07 (dd, J = 8.1, 1.7 Hz, 1H), 7.63 (dd, J = 8.1, 4.3 Hz, 1H), 7.23 (d, J = 7.1 Hz, 1H), 6.50 (d, J = 7.0 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.2, 149.3, 142.4, 135.2, 134.8, 130.4, 127.2, 103.7. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_8H_7N_2O$ 147.0558; Found 147.0557.

*6H-Pyrido[3,4-b]pyrazin-5-one (**7c**).* This compound was prepared following the procedure described above to give 33 mg (80% yield) of pure product as a orange amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.90 (d, J = 2.1 Hz, 1H), 8.76 (d, J = 2.1 Hz, 1H), 7.50 (d, J = 6.5 Hz, 1H), 6.59 (d, J = 7.3 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.4, 150.6, 149.6, 144.3, 137.8, 134.5, 105.2. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_7H_5N_3O$ 148.0510; Found, 148.0512.

*7H-Pyrido[3,4-d]pyrimidin-8-one (**7d**).* This compound was prepared following the procedure described above to give 10 mg (60% yield) of pure product as a white amorphous solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 9.35 (d, J = 2.0 Hz, 1H), 9.26 (d, J = 2.0 Hz, 1H), 7.39 (t, J = 5.2 Hz, 1H), 6.61 (dd, J = 7.0, 2.2 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 160.0, 158.7, 155.6, 145.7, 132.1, 130.8, 100.6. HRMS (ESI) m/z $[M + H]^+$: Calcd for $C_7H_5N_3O$ 148.0510; Found 148.0514.

*(E)-5-(2-Ethoxyvinyl)pyrimidine-4-carboxamide (**7d′**).* Small amounts of this compound (white amorphous solid) were obtained from the uncomplete reaction to produce **7d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.91 (s, 1H), 7.90 (bs, 1H), 7.08 (d, J = 13.3 Hz, 1H), 7.02 (d, J = 13.3 Hz, 1H), 5.66 (bs, 1H), 4.01 (q, J = 7.0 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H). HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_9H_{12}N_3O_2$ 194.0929; Found 194.0933.

Alternative Synthesis of 6-(Pyrrolidin-1-yl)isoquinolin-1(2*H*)-one (3d). This compound was alternatively prepared by dissolving 4-fluoro-2-[(*E*)-2-ethoxyvinyl]benzonitrile (**3j**) (5.00 mg, 0.03 mmol) in pyrrolidine (1 mL). The reaction was heated at reflux in an oil bath and stirred for 48 h, after which pyrrolidine was removed *in vacuo*. The crude product was purified by PTLC to yield 6.2 mg (94% yield) of the desired product as a light-yellow amorphous solid. The ^{1}H NMR matched that described for (**3d**)

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(fully characterized above). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (s, 1H), 7.94 (d, J = 8.9 Hz, 1H), 6.97 (t, 1H), 6.73 (d, J = 8.9 Hz, 2H), 6.49 (s, 1H), 6.30 (d, J = 7.2 Hz, 1H), 3.50−3.16 (m, 4H), 2.08−1.82 (m, 4H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00472.

NMR spectra for all compounds: ^{1}H, ^{13}C{^{1}H}, and ^{19}F where applicable (PDF)

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Notes

The authors declare the following competing financial interest(s): C.M.C. is founder, shareholder, and consultant to Arvinas, Inc. and Halda, LLC, which support research in his laboratory.

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