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Bromodecarboxylation of Quinoline Salicylic Acids: Increasing the Diversity of Accessible Substituted Quinolines

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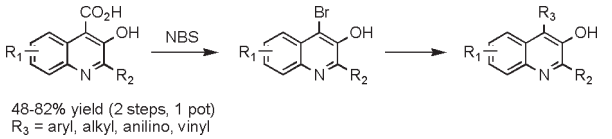


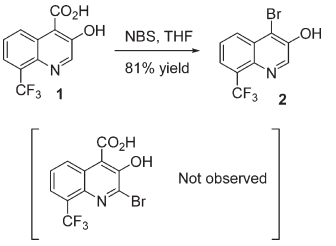
Quinoline salicylic acids underwent bromodecarboxylation at room temperature upon treatment with *N*-bromosuccinimide. A wide variety of functional groups was tolerated. Several one-pot transformations were also carried out, allowing the preparation of diverse 4-substituted quinolines.

The quinoline ring system is a common motif in both natural products and synthetic organic molecules of biological interest.[1] Quinoline derivatives have found medicinal use as antimalarials,[2] antiasthmatic agents[3] and anticancer drugs. We recently reported a series of quinoline salicylic acids with good inhibitory potency against P-selectin, work that culminated in the discovery of clinical candidate PSI-697.[5]

As part of this discovery campaign, we wanted to introduce a bromide at the C-2 position of the quinoline ring. However, when a solution of quinoline salicylic acid **1** was treated with a slight excess of NBS at room temperature, we were surprised to observe exclusive bromination at C-4 with concomitant loss of CO_2 (Scheme 1).

To determine the scope of the reaction, we subjected a diverse array of quinoline salicylic acids to these NBS-mediated bromodecarboxylation conditions (Table 1). Alkyl groups are tolerated (entries 1−3), as are aryl (entry 4),

SCHEME 1. Bromodecarboxylation of Quinoline Salicylic Acid 1



heteroaryl (entries 5 and 6), methoxy (entry 7), and benzyl (entry 8). Carboxylic acid groups are tolerated elsewhere in the molecule (entry 9), but bromodecarboxylation does not occur unless the acid is already activated toward electrophilic substitution (entry 13). The activating hydroxy group can be replaced by an amino group (entry 11), but not by a methoxy group (entry 14). The quinoline nitrogen is not required (entry 12). Side reactions do occur if a second amino or hydroxy group is present elsewhere in the molecule (entry 10).

Halodecarboxylation is well-known for aromatic and heteroaromatic substrates in which a carboxylic acid group is located at a position activated toward electrophilic substitution, such as salicylic and anthranilic acids, pyrrole-2-carboxylic acids, and furan-2-carboxylic acids.[6] To the best of our knowledge, it has not yet been reported for 3-hydroxyquinoline-4-carboxylic acids.[7] The reaction is reminiscent of the Hunsdiecker reaction,[8] the metal (usually silver)-mediated replacement of a carboxylic acid with a halogen. However, rather than the radical mechanism invoked for the Hunsdiecker, halodecarboxylation of these electron-rich aromatic acids is believed to proceed via a typical electrophilic aromatic substitution mechanism. By analogy with the extensive mechanistic studies carried out on the bromodecarboxylation of dibromohydroxybenzoic acids by Grovenstein et al.,[6] we believe that an intermediate of structure **30** is initially formed, as shown in Scheme 2. This undergoes deprotonation and finally rearomatization by loss of CO_2.

The lack of reactivity for the 3-methoxy analogue (entry 14) is surprising. However, methoxy groups are less activating for electrophilic aromatic substitution than hydroxy and amino groups,[9] and in the quinoline salicylic acids, C-4 is deactivated by the quinoline nitrogen. It may be that, for these substrates, the methoxy group is incapable of providing sufficient resonance stabilization of the developing positive charge at C-3.

In retrospect, the lack of bromination at C-2 (Scheme 1; also Table 1, entries 9 and 12) is not surprising. Naphthalenes

(1) Larsen, R. D.; Cai, D. *Science of Synthesis: Hetarenes and Related Ring Systems*; Black, D. StC., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2005; Vol. 15, Chapter 3, pp 389.

(2) Ridley, R. G.; Hudson, A. T. *Expert Opin. Ther. Pat.* **1998**, *8*, 121.

(3) Markham, A.; Faulds, D. *Drugs* **1998**, *56*, 251.

(4) (a) Kingsbury, W. D.; Boehm, J. C.; Jakas, D. R.; Holden, K. G.; Hecht, S. M.; Gallagher, G.; Caranfa, M. J.; McCabe, F. L.; Faucette, L. F.; Johnson, R. K.; Hertzberg, R. P. *J. Med. Chem.* **1991**, *34*, 98. (b) Josien, H.; Ko, S.-B.; Bom, D.; Curran, D. P. *Chem.—Eur. J.* **1998**, *4*, 67.

(5) (a) Kaila, N.; Janz, K.; DeBernardo, S.; Bedard, P. W.; Camphausen, R. T.; Tam, S.; Tsao, D. H. H.; Keith, J. C., Jr.; Nickerson-Nutter, C.; Schilling, A.; Young-Sciame, R.; Wang, Q. *J. Med. Chem.* **2007**, *50*, 21. (b) Kaila, N.; Janz, K.; Huang, A.; Moretto, A.; DeBernardo, S.; Bedard, P. W.; Tam, S.; Clerin, V.; Keith, J. C., Jr.; Tsao, D. H. H.; Sushkova, N.; Shaw, G. D.; Camphausen, R. T.; Schaub, R. G.; Wang, Q. *J. Med. Chem.* **2007**, *50*, 40.

(6) (a) Grovenstein, E. G., Jr.; Henderson, U. V., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 569. (b) Grovenstein, E. G., Jr.; Ropp, G. A. *J. Am. Chem. Soc.* **1956**, *78*, 2560.

(7) However, for bromodecarboxylation of 8-hydroxyquinoline-7-carboxylic acid, see: Schmitt, R.; Engelmann, F. *Chem. Ber.* **1887**, *20*, 2690. Bromination also occurs at the 5-position here, to give 5,7-dibromo-8-hydroxyquinoline.

(8) Johnson, R. G.; Ingham, R. K. *Chem. Rev.* **1956**, *56*, 219.

(9) Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001: Chapter 11, pp 683.

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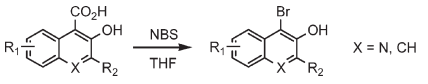
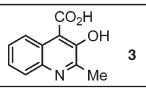
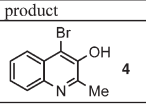
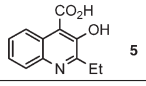
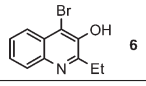
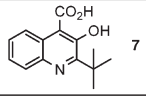
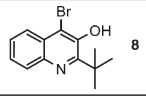
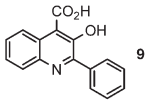
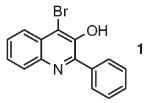
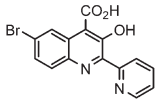
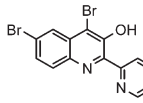
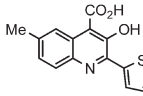
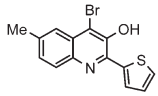
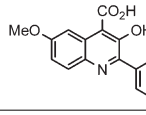
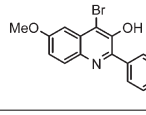
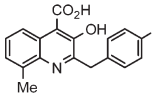
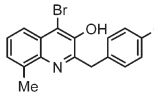
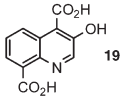
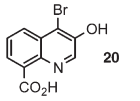
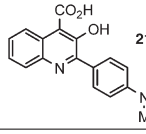
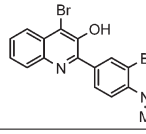
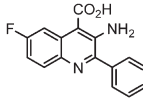
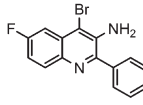
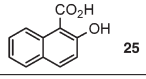
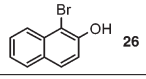
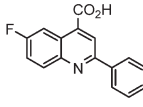
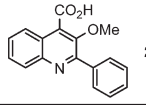
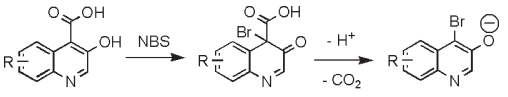
TABLE 1. Scope of Bromodecarboxylation Reaction with Quinoline Salicyclic Acids and Related Substrates



entry[a]	substrate	product	yield[b]
1	 **3**	 **4**	74%
2	 **5**	 **6**	78%
3	 **7**	 **8**	74%
4	 **9**	 **10**	73%
5	 **11**	 **12**	56%
6	 **13**	 **14**	76%
7	 **15**	 **16**	83%
8	 **17**	 **18**	78%
9	 **19**	 **20**	66%
10	 **21**	 **22**	16%[c]
11	 **23**	 **24**	85%
12	 **25**	 **26**	80%
13	 **27**	No reaction	0%[d]
14	 **28**	No reaction	0%[d]

[a]Typical reaction conditions: 0.4 mmol acid, 1.05 equiv NBS, 4 mL THF, rt, overnight. Complete conversion often observed in < 1 h for substrates with good solubility in THF. [b]Isolated yield of pure product, unless otherwise indicated. [c]Starting material was also observed. Similar result observed upon replacement of NMe_2 by OH. [d]Only starting material was observed.

SCHEME 2. Proposed Mechanism for the Bromodecarboxylation of Quinoline Salicylic Acids



29 30 31

and quinolines bearing activating substituents β to the second ring (and specifically at C-3, for quinolines) generally undergo electrophilic substitution adjacent to the second ring, rather than at the other *ortho* position (for quinolines, C-4 rather than C-2),[9−11] and clearly the presence of a carboxylic acid group at this position is no hindrance. Although most of our substrates were substituted at C-2, this is not required in order to direct bromination to C-4.

Brominated heterocycles are useful precursors to more elaborate structures. Although 4-bromo-3-hydroxyquinoline has been prepared,[10] few substituted 3-hydroxyquinolines are commercially available, making it difficult to prepare analogues. The most straightforward synthesis of 3-hydroxyquinolines involves decarboxylation of the quinoline salicylic acid at reflux in a high-boiling solvent such as nitrobenzene.[12a] Thus, we feel that our simple and direct preparation of functionalized 4-bromo-3-hydroxyquinolines from the quinoline salicylic acids in a low-boiling solvent at room temperature offers a significant advantage in terms of both practice and substrate scope. Quinoline salicylic acids are readily available by Pfitzinger reaction[12] of isatins with α-hydroxy or α-acetoxy ketones; isatins that are not commercially available can be prepared from the corresponding anilines via the Sandmeyer isatin synthesis,[13] *o*-lithiation and cyclization,[14] or various other methods.

One common use of aryl and heteroaryl bromides is as substrates for Suzuki−Miyaura cross-coupling reaction with boronic acids and related compounds.[15] 4-Aryl-3-hydroxyquinolines have been prepared by the Friedländer condensation[16] of *o*-aminobenzophenones with α-hydroxyketones, but few examples are known. We were interested in synthesizing these in a one-pot bromodecarboxylation/Suzuki coupling approach from quinoline salicylic acids, which should allow for greater variation of the 4-aryl group, due to the wide range of commercially available boronic acids.[17] As we had hoped, 4-aryl products could be prepared in useful yields (Table 2), carrying out the Suzuki coupling by either conventional or microwave heating, and the reaction

(10) Smirnov, L. D.; Androvna, N. A.; Lezina, V. P.; Zaitsev, B. E.; Dyumaev, K. M. *Bull. Acad. Sci. USSR Div. Chem. Sci.* (*Engl. Transl.*) **1971**, *20*, 400.

(11) We were eventually able to introduce a bromide at C-2 by protecting the carboxylic acid as the methyl ester, preventing decarboxylation. The reaction with NBS in refluxing THF was slow and low-yielding (< 30% conversion), demonstrating the relative lack of activation at C-2. See ref 5b for details.

(12) (a) Cragoe, E. J.; Bealor, M. D.; Robb, C. M.; Ziegler, C.; Sprague, J. M. *J. Org. Chem.* **1953**, *18*, 561. (b) Pfitzinger, W. *J. Prakt. Chem.* **1897**, *56*, 308.

(13) (a) Sandmeyer, T. *Helv. Chim. Acta* **1919**, *2*, 234. (b) Marvel, C. S.; Hiers, G. S. *Org. Synth.* **1925**, *V*, 71.

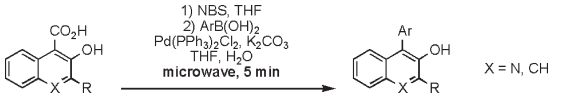
(14) Hewawasam, P.; Meanwell, N. A. *Tetrahedron Lett.* **1994**, *35*, 7303.

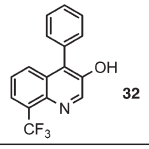
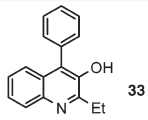
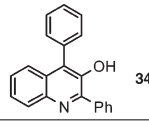
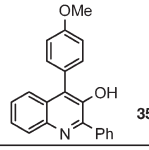
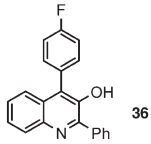
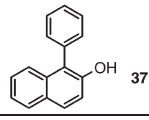
(15) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(16) Fehnel, E. A. *J. Heterocycl. Chem.* **1967**, *4*, 565.

(17) For examples of one-pot halodecarboxylation/cross-coupling applied to cinnamic acids, see: (a) Naskar, D.; Roy, S. *Tetrahedron* **2000**, *56*, 1369. (b) Bazin, M.-A.; El Kihel, L; Lancelot, J.-C.; Rault, S. *Tetrahedron Lett.* **2007**, *48*, 4347.

TABLE 2. One-Pot Bromodecarboxylation/Suzuki Coupling



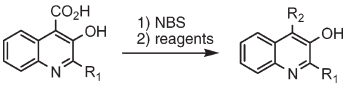
entry[a]	product	yield[b]
1	 **32**	63%
2	 **33**	74%
3[c]	 **34**	82%
4	 **35**	54%
5	 **36**	49%
6	 **37**	74%

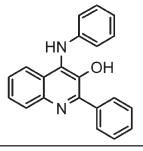
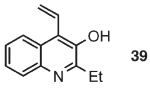
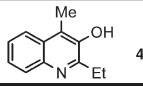
[a]Reaction conditions: (i) 200 mg quinoline salicylic acid and 1.05 equiv NBS in 4 mL THF, overnight; (ii) added 1.1 equiv $ArB(OH)_2$, 2 equiv K_2CO_3, 0.05 equiv $Pd(PPh_3)Cl_2$ and 2 mL water, microwave, 135 °C, 5 min. [b]Isolated yield of pure product. [c]3 g scale, conventional heating. See Supporting Information for details.

was successfully scaled up to 3 g of quinoline salicylic acid (entry 3).[18] Biaryls have been prepared in a single step by palladium-mediated decarboxylative coupling of carboxylic acids and aryl halides.[19] However, the reaction conditions are generally less robust than those reported herein; also, to the best of our knowledge, quinoline carboxylic acids have not been used as substrates.

Other successful one-pot reaction sequences are shown in Table 3. Bromodecarboxylation followed by nucleophilic displacement gave 4-anilino-3-hydroxyquinoline (entry 1). Stille (entry 2) and Negishi (entry 3) couplings could also be carried out to introduce a vinyl or alkyl group at the 4-position.[20] While 4-alkyl-3-hydroxyquinolines are known, most reported syntheses are lengthy and low-yielding.[21] We have not seen any examples of 3-hydroxyquinolines substituted by anilino or vinyl groups at the 4-position.

TABLE 3. Other One-Pot Reaction Sequences



entry	reagent	product	yield[a]
1[b]		 **38**	76%
2[c]	$(vinyl)SnBu_3$	 **39**	48%
3[d]	Me_2Zn	 **40**	49%

[a]Isolated yield of pure product. [b]Reaction conditions: (i) 200 mg acid, 1.05 equiv NBS, 5 mL THF, 1.5 h; (ii) added 2.0 equiv aniline, microwave, 150 °C, 20 min. [c]Reaction conditions: (i) 200 mg acid, 1.05 equiv NBS, 3 mL 1,4-dioxane, overnight; (ii) added 3.5 equiv $(vinyl)SnBu_3$, 0.05 equiv $Pd(PPh_3)_4$, microwave, 150 °C, 5 min. [d]Reaction condtions: (i) 200 mg acid, 1.05 equiv NBS, 3 mL 1,4-dioxane, overnight; (ii) added 3.5 equiv Me_2Zn (1.0 M THF solution), 0.05 equiv $Pd(PPh_3)_4$, microwave, 150 °C, 5 min.

In conclusion, bromodecarboxylation chemistry provides access to a diverse array of 4-substituted 3-hydroxyquinolines. The chemistry is amenable to both small and multigram-scale reactions and insensitive to adventitious air and moisture. Of particular interest to medicinal chemists, the one-pot procedures allow extensive variation of the 4-position from common intermediates, which should be useful for carrying out structure−activity relationship studies on biologically active quinolines.

Experimental Section

Representative Procedure: 4-Bromo-8-(trifluoromethyl)quinolin-3-ol (2). In a 20 mL glass scintillation vial, 3-hydroxy-8-(trifluoromethyl)quinoline-4-carboxylic acid (**1**)[5b] (224 mg, 0.872 mmol) was taken up in 4 mL of THF, and NBS (160 mg, 0.92 mmol) was added. Vigorous gas evolution was observed. The mixture was stirred at rt for 1 h, until LC−MS analysis showed complete consumption of starting material. THF was removed by rotary evaporation, and the residue purified by flash chromatography over silica gel (2−50% ethyl acetate in hexanes) to give a white powder (0.207 g, 81% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (t, J = 7.8 Hz, 1 H), 8.04 (d, J = 7.1 Hz, 1 H), 8.33 (d, J = 8.6 Hz, 1 H), 8.79 (s, 1 H), 11.51 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 114.0 (C), 123.9 (q, CF_3), 125.3 (q, CH-7), 126.3 (q, C-8), 127.2 (CH), 128.9 (C), 130.0 (CH), 138.5 (C), 143.4 (CH), 149.6 (C); HRMS (ESI+) calcd for $C_{10}H_6BrF_3NO$ 291.95794, found 291.95752. Anal. Calcd for $C_{10}H_5BrF_3NO$: C, 41.13; H, 1.73; N, 4.80. Found: C, 41.28; H, 1.71; N 4.70.

(18) Reagents and catalysts were weighed out on a benchtop, and no special precautions were taken to exclude air.

(19) (a) Goossen, L. J.; Rodriguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100 and references therein. (b) For an earlier example of a Pd-mediated decarboxylative Heck-type reaction, see: Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250.

(20) Except for the use of a fresh bottle of anhydrous dioxane, no special precautions were taken to exclude air or moisture.

(21) (a) Jendralla, H.; Granzer, E.; v. Kerekjarto, B.; Krause, R.; Schacht, U.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Kesseler, K.; Wess, G.; Chen, L.-J.; Granata, S.; Herchen, J.; Kleine, H.; Schüssler, H.; Wagner, K. *J. Med. Chem.* **1991**, *34*, 2962. (b) Söderberg, B. C. G.; Shriver, J. A.; Cooper, S. H.; Shrout, T. L.; Helton, E. S.; Austin, L. R.; Odens, H. H.; Hearn, B. R.; Jones, P. C.; Kouadio, T. N.; Ngi, T. H.; Baswell, R.; Caprara, H. J.; Meritt, M. D.; Mai, T. T. *Tetrahedron* **2003**, *59*, 8775. (c) Kato, T.; Hakura, A.; Mizutani, T.; Saeki, K. *Mutat. Res.* **2000**, *465*, 173.

The same procedure was followed for all reactions described in Table 1, except that the reactions were generally run overnight to account for varying solubilities in THF. Entries 5 and 9 were purified by trituration with boiling water.

Representative Procedure: 4-Phenyl-8-(trifluoromethyl)quinolin-3-ol (32, Table 2, entry 1). The procedure described above for the preparation of **2** was followed, using a 10 mL round-bottomed Biotage microwave vial (for 2−5 mL reaction volumes) as the reaction vessel and 4 mL of THF as the solvent. Once complete conversion to **2** had been observed by LC−MS analysis, phenylboronic acid (0.104 g, 0.856 mmol), $Pd(PPh_3)_2Cl_2$ (27 mg, 39 μmol) and K_2CO_3 (0.215 g, 1.56 mmol) were added to the vial, followed by 1 mL of water. The vial was crimp-sealed and heated in a Biotage Initiator microwave reactor for 5 min at 135 °C. The vial contents were then filtered through Celite, washing with ethyl acetate, and the ethyl acetate solution was evaporated and purified by flash chromatography over silica gel (5−40% ethyl acetate in hexanes), giving a white solid (0.143 g, 63% yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (ddd, J = 6.6, 1.6, 1.4 Hz, 2 H), 7.46−7.52 (m, 1 H), 7.53−7.59 (m, 3 H), 7.68 (d, J = 8.6 Hz, 1 H), 7.95 (d, J = 6.8 Hz, 1 H), 8.89 (s, 1 H), 10.46 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 124.3 (CF_3, q, J = 270 Hz), 124.4 (CH-7, q, J = 5.9 Hz), 125.8 (CH), 126.2 (C-8, q, J = 28 Hz), 128.0 (CH), 128.4 (2 CH), 128.5 (C), 128.7 (C), 129.4 (CH), 130.3 (2 CH), 133.0 (C), 138.4 (C), 144.1 (CH), 148.2 (C); HRMS (ESI+) calcd for $C_{16}H_{11}F_3NO$ 290.0787, found 290.0790. Anal. Calcd for $C_{16}H_{10}F_3NO$: C, 66.44; H, 3.48; N, 4.84. Found: C, 66.30; H, 3.34; N 4.64.

The same procedure was followed for all reactions described in Table 2.

2-Phenyl-4-(phenylamino)quinolin-3-ol (38, Table 3, entry 1). In a 10 mL round-bottomed microwave vial, 3-hydroxy-2-phenylquinoline-carboxylic acid (**9**, see Supporting Information; 0.200 g, 0.754 mmol) was taken up in 5 mL THF. NBS (0.141 g, 0.792 mmol) was added, and the vial was loosely covered and allowed to stir at room temperature until LC−MS analysis showed complete consumption of the acid (1.5 h). Aniline (138 μL, 0.140 g, 1.51 mmol) was then added, and the vial was crimp-sealed and heated in a microwave reactor for 20 min at 150 °C, until most of the bromide was gone. A large amount of bright yellow solid precipitated out of solution, and this was collected by filtration and purified by flash chromatography over silica gel (1−10% methanol in dichloromethane) to give an orange powder (0.180 g, 76% yield): HPLC purity, 100%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.68 (d, J = 7.6 Hz, 2 H), 6.73 (t, J = 7.3 Hz, 1 H), 7.14 (dd, J = 8.2, 7.5 Hz, 2 H), 7.41−7.56 (m, 5 H), 7.77 (dd, J = 8.3, 1.3 Hz, 1 H), 7.94−7.98 (m, 1 H), 8.00−8.06 (m, 3 H), 9.33 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 114.8 (2 CH), 118.4 (CH), 122.7 (CH), 125.4 (C), 125.8 (CH), 126.5 (CH), 127.8 (2 CH), 128.5 (CH), 128.8 (2 CH), 129.3 (CH), 129.6 (2 CH), 129.9 (C), 138.3 (C), 143.2 (C), 143.8 (C), 145.6 (C), 151.2 (C); HRMS (ESI+) calcd for $C_{21}H_{17}N_2O$ 313.13354, found 313.13327.

2-Ethyl-4-vinylquinolin-3-ol (39, Table 3, entry 2). In a 20 mL Biotage microwave vial (for 5−10 mL reaction volumes), 2-ethyl-3-hydroxyquinoline-4-carboxylic acid (**5**)[22] (0.200 g, 0.921 mmol) was taken up in 3 mL of anhydrous dioxane. NBS (0.172 g, 0.967 mmol) was added, and the vial was crimp-sealed and allowed to stir overnight at room temperature. The vial was then opened, and $Pd(PPh_3)_4$ (53 mg, 46 μmol) and tributyl(vinyl)tin (0.94 mL, 1.0 g, 3.2 mmol) were added before resealing. The mixture was heated in a microwave reactor for 5 min at 150 °C and then quenched by addition of 2 mL of water under nitrogen. The vial was then opened, and the contents were taken up in ethyl acetate, filtered through Celite, evaporated, and purified by flash chromatography over silica gel (6−50% ethyl acetate in hexanes) to give a pale yellow solid (89 mg, 48% yield): HPLC purity, 97.1%; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.28 (t, 3 H), 2.96 (q, J = 7.6 Hz, 2 H), 5.82 (dd, J = 17.8, 1.9 Hz, 1 H), 5.87 (dd, J = 11.7, 1.9 Hz, 1 H), 7.07 (dd, J = 17.9, 11.6 Hz, 1 H), 7.42−7.53 (m, 2 H), 7.82−7.88 (m, 1 H), 7.97−8.02 (m, 1 H), 9.20 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 12.0 (CH_3), 26.5 (CH_2), 123.5 (CH), 123.5 (=CH_2), 124.6 (C), 125.8 (CH), 125.8 (CH), 126.0 (C), 128.7 (CH), 128.9 (CH), 142.3 (C), 145.2 (C), 156.2 (C); HRMS (ESI+) calcd for $C_{13}H_{14}NO$ 200.10699, found 200.10689.

The same procedure was followed for entry 3, substituting a 1.0 M THF solution of dimethylzinc for the tributyl(vinyl)tin.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(22) Cross, L. B.; Henze, H. R. *J. Am. Chem. Soc.* **1939**, *61*, 2730.