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7-Chloroquinoline: a versatile intermediate for the synthesis of 7-substituted quinolines

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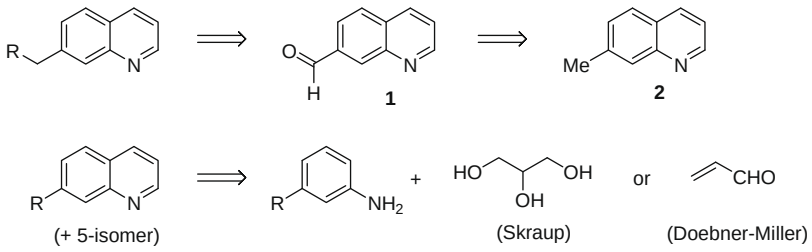
ABSTRACT

A practical synthesis of 7-mono-substituted quinolines has been achieved. Selective reduction of the inexpensive commercial reagent 4,7-dichloroquinoline affords 7-chloroquinoline, which has been converted into more complex 7-mono-substituted quinolines through a series of Pd-catalyzed cross coupling reactions. These studies include the first examples of Suzuki reactions for the preparation of 7-mono-substituted quinolines as well as the first application of the Sonagashira reaction for the synthesis of 7-substituted quinolines. This strategy has been extended to the preparation of 2,7-di-substituted quinolines.

Quinolines with mono-substitution at the 7-position are important structural moieties for numerous medicinal applications, including but not limited to cancer treatment[1] and antibiotics.[2] Therefore a synthesis of these compounds that is practical, concise and selective would be valuable. Broadly defined, the strategies that have been reported to date are categorized as methods that either (a) manipulate functionality appended to a commercially available quinoline core, or (b) construct the quinoline ring system from aniline precursors. With regards to 7-mono-substituted quinolines, the most common tactic employs the former procedure; a multi-step process that utilizes quinoline-7-carboxaldehyde (**1**) or derivatives thereof.[3] In this scenario **1** is usually derived from the SeO_2-mediated oxidation of 7-methylquinoline (**2**)[4] (Scheme 1). One limitation to this approach is the high expense and low availability (on scale) of **1** and **2**. Examples of the latter strategy include the classical Skraup[5] and Doebner–Miller[6] reactions. Unfortunately, these reactions suffer from poor regioselectivity,[7] leading to a mixture of the desired 7-substituted quinoline and the 5-substituted regioisomer. A number of regioselective transition metal-mediated annulation reactions with anilines have been disclosed,[8] but none have lent themselves to the preparation of 7-mono-substituted quinolines.

Recently, the use of Pd-catalyzed cross coupling reactions with 7-haloquinolines has advanced the potential of the 'quinoline functionalization' approach.[9] With no commercial availability of these substrates, however, this methodology ultimately relies on unselective Skraup annulation chemistry in order to obtain the haloquinoline. Nonetheless, this strategy holds much promise. Most work in this area has focused on the use of 7-iodo and 7-trifluoromethane sulfonyl derivatives of highly substituted quinolines, while relatively little attention has been paid to the reactivity of 7-chloroquinolines. The reported examples using aryl chlorides



Scheme 1.

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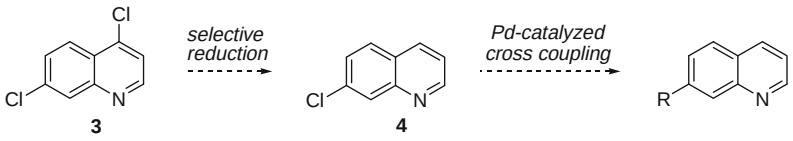


Scheme 2.

concern a single substrate–commercially available 7-chloroquinaldine[10]–and focus heavily on the borylation of this reagent with bis(pinacolato)diboron. Consequently, the use of 7-chloroquinolines as direct coupling partners is largely unexplored, and the application of this strategy to the synthesis of 7-mono-substituted quinolines has not been reported to date. In this Letter, we describe a practical and selective preparation of 7-chloroquinoline and demonstrate its broad utility in cross coupling reactions as part of a concise synthesis of more complex 7-mono-substituted quinolines.

We envisioned the use of 7-chloroquinoline as a direct coupling partner (i.e., the electrophile) in Pd-catalyzed cross coupling reactions. The practicality of this approach relied upon the commercial availability of 4,7-dichloroquinoline (**3**) as an inexpensive reagent that could allow easy access to 7-chloroquinoline (**4**), provided that a selective reduction could be performed (Scheme 2). While the selective functionalization of the 4-chloro moiety of **3** has been reported in the course of Pd-catalyzed cross couplings,[11] the chemoselective reduction of **3** to **4** is, to the best of our knowledge, unknown.

Our efforts focused on transfer hydrogenation conditions as a means to control the stoichiometry of reducing agent (Table 1). The use of Pd/C and NH_4CO_2H in MeOH invariably led to over-reduction, as evidenced by the detection of quinoline (**5**) by HPLC analysis (entries 1–3).[12] Homogeneous catalysis using $Pd(PPh_3)_4$ and Et_3SiH afforded high selectivity but only moderate conversion (entry 4). The use of Pd(II) sources, whereby the active Pd(0) species would be generated in situ, was then investigated. We focused on $Pd(PPh_3)_2Cl_2$ due to its low cost and ease of handling. Initial experiments revealed high selectivity for the desired compound **4**[13] without any detection of over-reduction (entries 5–7). After further optimization, we discovered that the use of 1.4 equivalents of Et_3SiH in MeCN at 70 °C resulted in an optimal balance of conversion and chemoselectivity (entry 8), affording 7-chloroquinoline (**4**) in 85% isolated yield. Although other catalyst complexes[14] derived from Pd(II) pre-catalysts were screened, none offered an improvement over $Pd(PPh_3)_2Cl_2$ in terms of conversion and selectivity. Importantly, 4-chloroquinoline (**6**) is not detected in the crude reaction mixture by HPLC analysis. Aside from the over-reduction byproduct quinoline (5%), the only significant impurity was 7-chloro-4-hydroxy-quinoline (**7**) (8%), which appears to result from a reaction between **3** and water in the reaction solution or in the quench (Fig. 1).[15] Fortunately, these impurities could be removed by column chromatography.

Having achieved an effective method to prepare **4**, we turned our attention towards the proposed Pd-catalyzed cross coupling reactions for the synthesis of more complex 7-substituted quinolines. Our investigations into Suzuki couplings (Table 2)[16] revealed that **4** exhibited reactivity patterns typical of aromatic chlorides. The use of PPh_3 as a ligand for the coupling with phenylboronic acid provided the desired quinoline in modest yield (entry 1). The use of ligands known to activate aromatic chlorides towards oxidative addition afforded improved reactivity.[17] The catalyst combination of $Pd(OAc)_2$ and a water-soluble version of the SPhos ligand[18] promoted an efficient reaction between **4** and an electron-rich boronic acid (entry 2), but only a modest yield in combination with an electron-deficient cross coupling partner (entry 3). The catalyst combination of $Pd(OAc)_2$ and XPhos, in combination with K_3PO_4 as the base, enabled the successful Suzuki reaction between **4** and both *ortho*-substituted (entry 5) and electron-deficient (entry 6) boronic acids. These conditions also resulted in a marked increase in yield in the reaction with phenylboronic acid (entry 4), highlighting the potential for the Suzuki reaction between **4** and a wide variety of boronic acids.

In addition to the Suzuki reaction, we also investigated other Pd-catalyzed cross coupling reactions as a means to diversify substitution at the 7-position of the quinoline ring. The Sonagashira

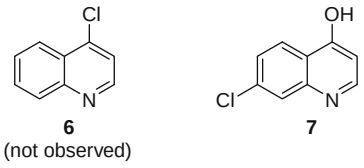
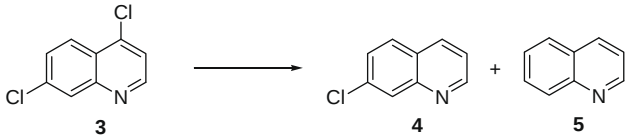


Figure 1.

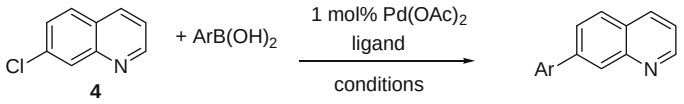
Table 1

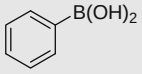
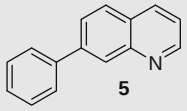
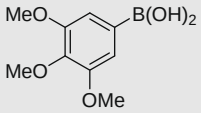
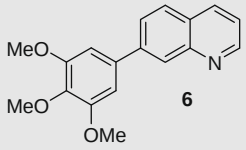
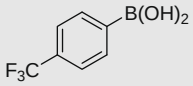
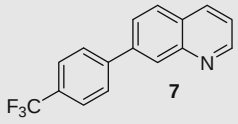
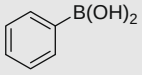
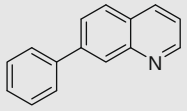
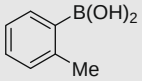
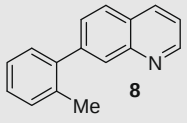
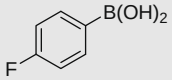
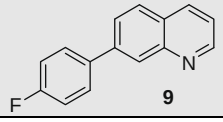


Entry	Catalyst (mol %)	Reducing agent (equiv)	Solvent	Time (h), temp.	Ratio[a] (**4**:**5**)	Conversion[a] (%)
1	Pd/C (5)	NH_4CO_2H (1.3)	MeOH	1 h, reflux	2:1	90
2	Pd/C (5)	NH_4CO_2H (1.1)	MeOH	21 h, 25 °C	6:1	58
3	Pd/C (5)	NH_4CO_2H (2.2)	MeOH	20 h, 25 °C	1:7	99
4	$Pd(PPh_3)_4$ (1)	Et_3SiH (1.4)	MeCN	24 h, 70 °C	1:0	75
5	$Pd(PPh_3)_2Cl_2$ (2)	NH_4CO_2H (1.3)	MeOH	20 h, 25 °C	3:5:1	99
6	$Pd(PPh_3)_2Cl_2$ (2)	Et_3SiH (1.6)	DMF	16 h, 25 °C	1:0	62
7	$Pd(PPh_3)_2Cl_2$ (2)	Et_3SiH (1.6)	MeCN	18 h, 25 °C	1:0	50
8	$Pd(PPh_3)_2Cl_2$ (1)	Et_3SiH (1.4)	MeCN	18 h, 70 °C	21:1	92

[a] Determined by HPLC analysis (see Ref. 12).

Table 2

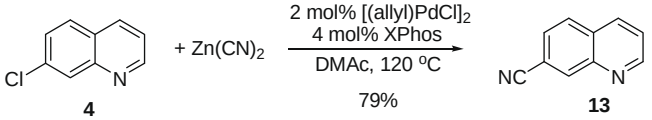


Entry	Ligand (mol %)	$ArB(OH)_2$	Conditions[a]	Product	Yield (%)
1	PPh_3 (4)		A	 **5**	44
2	SPhos[b] (2)		A	 **6**	87
3	SPhos[b] (2)		A	 **7**	48
4	XPhos (2)		B		83
5	XPhos (2)		B	 **8**	77
6	XPhos (2)		B	 **9**	94

[a] Conditions A: 3 N aq Na_2CO_3, PhMe/IPA, 80 °C B: 2 N aq K_3PO_4, PhMe, 70 °C.
[b] Water-soluble SPhos.

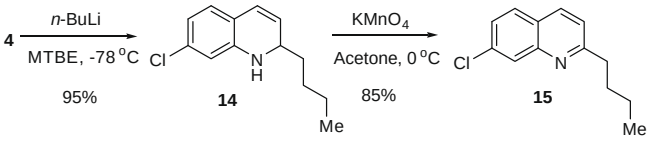
reaction with 7-chloroquinolines is unprecedented, and the reactivity of **4** towards alkynes proved more challenging than in the Suzuki coupling. The initial use of $Pd(OAc)_2$/XPhos and Na_2CO_3 in toluene did furnish the desired product, albeit in low yield (Table 3, entry 1). After screening various pre-catalyst/XPhos combinations with different solvents and bases, we discovered that the use of $Pd(MeCN)_2Cl_2$ and Cs_2CO_3 in acetonitrile afforded the alkyne coupling products in good yield (entries 2 and 3).[19]

As an entry into carbonyl-related quinoline derivatives, we investigated the cyanation of **4**. The use of 0.6 equiv of $Zn(CN)_2$ and the catalyst system composed of 2 mol % $[(allyl)PdCl]_2$ and 4 mol % XPhos afforded 7-cyanoquinoline (**13**) in 79% yield (Eq. 1):[20]



(1)

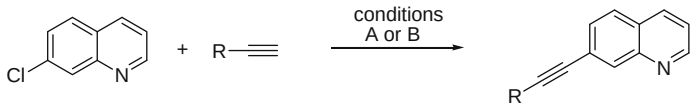
7-Chloroquinoline also proved useful for the synthesis of quinolines with substitution at both the 2- and the 7-positions. As a demonstration of this aptitude, *n*-BuLi was added to **4** to form the dihydroquinoline **14** in 90% yield. No evidence of metal–halogen exchange was observed by HPLC or NMR.[21] This intermediate was readily oxidized to quinoline **15** in 85% yield (Eq. 2):[22]

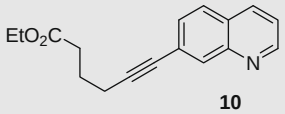
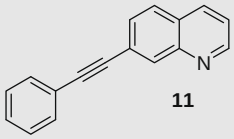
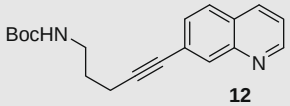


(2)

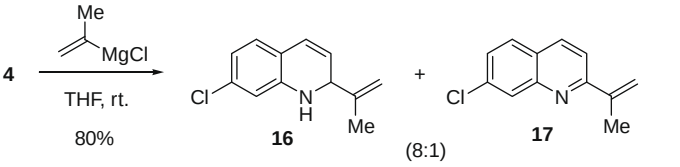
In a similar manner, isopropenylMgCl underwent 1,2-addition to **3** to smoothly afford an 8:1 mixture of dihydroquinoline **16** and quinoline **17** (believed to be derived from the air oxidation of **16**) in 80% combined yield (Eq. 3).[23] When the mixture of **16** and **17** was not isolated but was instead subjected to DDQ-mediated oxidation, **17** was isolated in 55% yield over the two steps. As a proof of concept for the synthesis of 2,7-di-substituted quinolines, **17** was elaborated to quinoline **18** via a Suzuki reaction (Eq. 4).[24]

Table 3

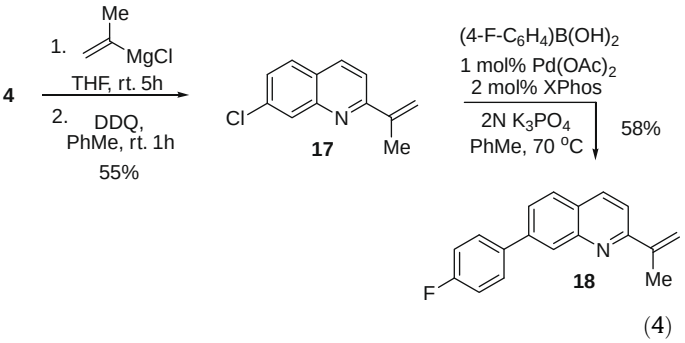


Entry	R—	Conditions[a]	Product	Yield (%)
1	Ethyl-5-hexynoate (1.1 equiv)	A	 **10**	39
2	Phenylacetylene (1.3 equiv)	B	 **11**	57
3	*N*-(Boc)-5-pentyneamine (1.3 equiv)	B	 **12**	68

[a] Conditions A: 2 mol % $Pd(OAc)_2$, 4 mol % XPhos, 2.5 equiv, Na_2CO_3, 1 M in PhMe 90 °C 22 h. Conditions B: 3 mol % $Pd(MeCN)_2Cl_2$, 6 mol% XPhos, 1.5 equiv, Cs_2CO_3, 0.2 M in MeCN 75 °C, 16–22 h.



(3)



(4)

In summary, we have developed a practical synthesis of 7-chloroquinoline via a chemoselective reduction of 4,7-dichloroquinoline. The utility of 7-chloroquinoline for the synthesis of more complex 7-mono-substituted quinolines has been demonstrated through a series of Suzuki and Sonagashira couplings, as well as a cyanation reaction. The versatility of 7-chloroquinoline as a synthetic intermediate has been further expanded to the preparation of 2,7-di-substituted quinolines.

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10. Limited to Suzuki reactions: see: (a) Kulkarni, S. S.; Hauck Newman, A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2987; (b) Milbank, J. B. J.; Knauer, C. S.; Augelli-Szafran, C. E.; Sakkab-Tan, A. T.; Lin, K. K.; Yamagata, K.; Hoffman, J. K.; Zhuang, N.; Thomas, J.; Galatsis, P.; Wendt, J. A.; Mickelson, J. W.; Schwarz, R. D.; Kin ora, J. J.; Lotarski, S. M.; Stakich, K.; Gillespie, K. K.; Lam, W. W.; Mutlib, A. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4415.
11. (a) Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentier, J.-F.; Castanet, Y. *Synlett* **2003**, 1874; (b) Najiba, D.; Carpentier, J.-F.; Castanet, Y.; Biot, C.; Brocard, J.; Mortreux, A. *Tetrahedron Lett.* **1999**, *40*, 3719.
12. The ratio of 4:5 was determined using HPLC by comparison of the area under the curve for each compound in the reaction mixture. This ratio was then corrected with the extinction coefficient of each component as determined from independently prepared samples of known concentration. Conversion values were calculated as the ratio of (**4**+**5**):**3**, with correction by the extinction coefficient as above.
13. *NMR data for* **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (dd, J_1 = 1.6 Hz, J_2 = 4.3 Hz, 1H), 8.20–8.16 (m, 1H), 8.15 (d, J = 2.0 Hz, 1H), 7.54 (dd, J_1 = 2.0 Hz, J_2 = 8.8 Hz, 1H), 7.44 (dd, J_1 = 4.4 Hz, J_2 = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 148.9, 136.1, 135.5, 129.3, 128.7, 127.9, 126.9, 122.5; HRMS for C_9H_7ClN calc'd [M+H] = 164.0267, found 164.0300.

14. $PdCl_2$ + ligands, including numerous triarylphosphines, SPhos and XPhos. Although Pd(0) complexes were active catalysts (entries 1–4), we focused on P(II) species due to their relative ease of handling in air.
15. This assertion is based on the observation that heating a mixture of **3** and HCl (1 equiv) in 9:1 MeCN:H_2O at 70 °C for 18 h resulted in the formation of **7** (15% yield at 15% conversion of 3). This experiment models the reaction conditions whereupon the Et_3SiCl byproduct of the reduction creates acidic conditions for any adventitious water. For relevant observations see: (a) Illuminati, G.; Gilman, H. *J. Am. Chem. Soc.* **1950**, *72*, 4288 and (b) Cutler, R.A..; Surrey, A.. *J. Am. Chem. Soc.* **1950**, *72*, 3394.
16. ^{1}H NMR data (400 MHz, $CDCl_3$) for **5**: δ 8.96 (dd, J_1 = 1.6 Hz, J_2 = 4.3 Hz, 1H), 8.38–8.33 (m, 1H), 8.20 (d, J = 7.9 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.84 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 7.78 (dd, J_1 = 1.4 Hz, J_2 = 7.4 Hz, 2H), 7.52 (dd, J_1 = J_2 = 7.4 Hz, 2H), 7.45–7.39 (m, 2H); for **6**: δ 8.96 (dd, J_1 = 1.6 Hz, J_2 = 4.3 Hz, 1H), 8.33–8.30 (m, 1H), 8.20 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 8.3 Hz, 1H), 7.824 (dd, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 7.42 (dd, J_1 = 4.3 Hz, J_2 = 8.3 Hz, 2H), 6.98 (s, 2H), 3.98 (s, 6H), 3.94 (s, 3H); for **7**: δ 9.00 (dd, J_1 = 1.7 Hz, J_2 = 4.3 Hz, 1H), 8.38–8.34 (m, 1H), 8.24–8.21 (m, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.90–7.85 (m, 2H), 7.83 (dd, J_1 = 1.7 Hz, J_2 = 8.3 Hz, 1H), 7.80–7.75 (m, 2H), 7.46 (dd, J_1 = 4.3 Hz, J_2 = 8.6 Hz, 1H); for **8**: δ 9.00–8.97 (m, 1H), 8.24 (d, J = 8.3 Hz, 1H), 8.10 (s, 1H), 7.90 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.59 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.48–7.43 (m, 1H), 7.40–7.30 (m, 4H), 2.37 (s, 3H); for **9**: δ 8.96 (dd, J_1 = 1.7 Hz, J_2 = 4.3 Hz, 1H), 8.31–8.28 (m, 1H), 8.20 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.79 (dd, J_1 = 1.8 Hz, J_2 = 8.4 Hz, 1H), 7.76–7.70 (m, 2H), 7.42 (dd, J_1 = 4.3 Hz, J_2 = 8.4 Hz, 1H), 7.24–7.17 (m, 2H).
17. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.
18. Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.
19. ^{1}H NMR data for **10**: (400 MHz, $CDCl_3$) δ 8.97–8.91 (m, 1H), 8.30 (s, 1H), 8.10 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.77 (dd, J_1 = 2.3 Hz, J_2 = 8.2 Hz, 1H), 7.70–7.55 (m, 3H), 7.46–7.32 (m, 4H); for **11**: (400 MHz, $CDCl_3$) δ 8.97–8.91 (m, 1H), 8.30 (s, 1H), 8.10 (s, 1H), 8.12 (d, J = 8.2 Hz, 1H), 7.77 (dd, J_1 = 2.3 Hz, J_2 = 8.2 Hz, 1H), 7.70–7.55 (m, 3H), 7.46–7.32 (m, 4H); for **12**: (400 MHz, CD_3CN) δ 8.86 (dd, J_1 = 1.7 Hz, J_2 = 4.3 Hz, 1H), 8.23–8.18 (m, 1H), 8.03 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.50 (dd, J_1 = 1.7 Hz, J_2 = 8.4 Hz, 1H), 7.41 (dd, J_1 = 4.3 Hz, J_2 = 8.4 Hz, 1H), 5.36 (br s, 1H), 3.17 (dt, J_1 = J_2 = 7.0 Hz,, 2H), 2.46 (dd, J_1 = J_2 = 7.0 Hz, 2H), 1.74 (tt, J_1 = J_2 = 7.4 Hz, 2H), 1.37 (s, 9H).
20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (dd, J_1 = 1.7 Hz, J_2 = 4.3 Hz, 1H), 8.50 (s, 1H), 8.23 (dd, J_1 = 1.7 Hz, J_2 = 8.6 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.72 (dd, J_1 = 1.7 Hz, J_2 = 8.4 Hz, 1H), 7.56 (dd, J_1 = 4.3 Hz, J_2 = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 147.1, 136.0, 135.5, 130.3, 129.3, 127.3, 123.6, 118.4, 113.0.
21. A small amount of **15** was observed as an impurity in the crude reaction mixture, presumably arising from air oxidation of **14**. ^{1}H NMR data for **14**: (400 MHz, $CDCl_3$) δ 6.72 (d, J = 7.9 Hz, 1H), 6.50 (dd, J_1 = 2.0 Hz, J_2 = 7.9 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 6.26 (dd, J_1 = 1.3 Hz, J_2 = 10.0 Hz, 1H), 5.55 (dd, J_1 = 3.9 Hz, J_2 = 10.0 Hz, 1H), 4.29–4.20 (m, 1H), 3.81 (br s, 1H), 1.65–1.51 (m, 2H), 1.42–1.30 (m, 2H), 0.92 (t, J = 7.0 Hz, 3H).
22. ^{1}H NMR data for **15**: (400 MHz, $CDCl_3$) δ 8.07–8.02 (m, 2H), 7.71 (d, J = 8.6 Hz, 1H), 7.44 (dd, J_1 = 2.0 Hz, J_2 = 8.6 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 2.79 (t, J = 8.1 Hz, 2H), 1.84–1.77 (m, 2H), 1.49–1.41 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H).
23. Interestingly, *i*PrMgCl was unreactive under these conditions. PhMgCl underwent a similar 1,2-addition as described in Eq. 3.
24. ^{1}H NMR for **17**: (400 MHz, $CDCl_3$) δ 8.08 (d, J = 2.1 Hz, 1H), 7.99 (d, J = 8.7 Hz, 1H), 7.64 (d, J = 8.7 Hz, 1H), 7.63 (d, J = 8.7 Hz, 1H), 7.40 (dd, J_1 = 2.1 Hz, J_2 = 8.7 Hz, 1H), 5.95–5.91 (m, 1H), 5.52–5.49 (m, 1H), 2.35–2.32 (m, 3H); for **18**: (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.78–7.67 (m, 4H), 7.23–7.16 (m, 2H), 5.97–5.94 (m, 1H), 5.54–5.50 (m, 1H), 2.41–2.38 (m, 3H).