JOC Article

Use of Highly Active Palladium-Phosphinous Acid Catalysts in Stille, Heck, Amination, and Thiation Reactions of Chloroquinolines

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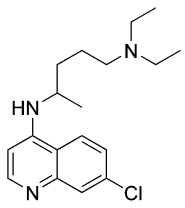
An efficient synthetic route toward a variety of 2,4-disubstituted quinolines has been developed. Alkylation and arylation of 4-chloroquinoline using organolithium reagents proceed with high regioselectivity in position 2 under cryogenic conditions. The intermediate 1,2-dihydro-4-chloroquinoline derivatives are unstable to air and are easily oxidized to the corresponding 2-substituted 4-chloroquinolines in high yields. Highly active palladium-phosphinous acid catalysts POPd, POPd1, and POPd2 have been employed in Stille cross-couplings of quinaldine with arylstannanes and in Heck additions of various 2-substituted 4-chloroquinolines to *tert*-butyl acrylate. In particular, POPd combines high catalytic activity for cross-coupling reactions with simplicity of use due to its stability to air. Utilizing CsF in POPd-catalyzed Stille couplings further increased the reactivity of arylstannanes, which was attributed to the fluorophilicity of organotin compounds. Basic additives were found to exhibit a significant effect on the yields of the POPd-promoted Heck reactions. In general, dicyclohexylmethylamine affords superior results than NaOAc, Cs_2CO_3, or *t*-BuOK. POPd was also found to tolerate amine and thiol substrates and proved to promote carbon−heteroatom bond formation of chloroquinoline derivatives with aliphatic and aromatic amines and thiols, respectively.

Introduction

Quinoline derivatives have been reported to display pronounced biological activities.[1] In particular, chloroquine and structurally similar 4-aminoquinolines have successfully been employed in the treatment and prophylaxis of malaria.[2] The high interest in new synthetic methodologies toward quinolines stems to some extent from an increasing demand for new, highly efficient antimalaria drugs. This is mostly due to the global rise of resistance of the malarial parasite plasmodium falciparum to widely used quinoline-derived agents, such as chloroquine.



Chloroquine

The synthesis of quinoline derivatives thus continues to be an active area of heterocyclic chemistry.[3] To date, the usefulness of haloquinolines as synthetic intermediates has been limited because of the unstable nature of bromo- and iodoquinolines and the low reactivity of chloro hetaryls. Consequently, many synthetic strategies toward quinolines involve ring construction using monocyclic precursors such as aniline derivatives.[4]

From a synthetic standpoint, aryl chlorides are a very interesting class of compounds because of their high availability and low cost. The usefulness of aryl chlorides as synthetic intermediates has somehow been limited because of their low reactivity in coupling reactions,

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(2) (a) O'Neill, P. M.; Bray, P. G.; Hawley, S. R.; Ward, S. A.; Park, B. K. *Pharmacol. Ther.* **1998**, *77*, 29−58. (b) Blauer, G.; Akkawi, M.; Fleischhacker, W.; Hiessboeck, R. *Chirality* **1998**, *10*, 556−563. (c) Egan, T. J.; Hunter, R.; Kaschula, C. H.; Marques, H. M.; Misplon, A.; Walden, J. *J. Med. Chem.* **2000**, *43*, 283−291.

(3) For a recent review, see: Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2491−2515.

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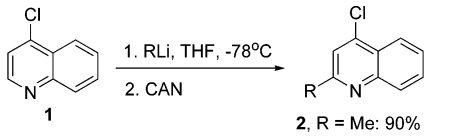
which has been attributed to their reluctance to undergo oxidative addition to transition metals. The recent development of highly active transition metal complexes provides new venues for employing aryl chlorides in Suzuki, Negishi, Hiyama, Kumada, Stille, and Heck reactions.[5] DeShong showed that aryl chlorides also undergo Pd-catalyzed cross-coupling reactions with hypervalent siloxanes.[6] However, only a few studies utilizing chloroquinolines in cross-coupling reactions have been reported to date. Dondoni and co-workers employed 2-chloroquinoline in a Pd-catalyzed Stille coupling with 2-trimethylstannyloxazoles to prepare the corresponding heteroaryl oxazole in 75%.[7] Heck and Stille coupling reactions of chloroquinolines have also been utilized in the synthesis of tricyclic azakynurenic acids and the quinoline-5,8-quinone moiety of streptonigrin.[8] Shiota et al. developed a regioselective Negishi coupling protocol for 2,4-dichloroquinolines that affords 4-substituted 2-chloroquinolines in moderate to high yields.[9] Ciufolini et al. reported that Pd-mediated alkylations and carbonylations of 2-chloroquinolines proceed with good to high yields.[10] Legros and co-workers obtained moderate to good yields employing $Pd(dba)_2$ in Stille couplings of 4-chloroquinolines and 1-ethoxyvinyl-tri-butylstannane.[11] Notably, they reported that 4-chloroquinoline does not undergo a Pd-catalyzed Heck reaction with butyl vinyl ether.

SCHEME 1. Synthesis of 3−5



Herein, we report a new synthetic strategy toward 2,4-disubstituted quinolines that is based on regioselective alkylation or arylation of commercially available 4-chloroquinoline, **1**, followed by transition-metal-catalyzed cross-coupling with organostannanes, *tert*-butyl acrylate, amines, or thiols. Our approach provides access to a variety of quinoline derivatives in just two synthetic steps.

Results and Discussion

We found that **1** undergoes an unprecedented Ziegler reaction[12] with organolithium reagents at −78 °C with high regioselectivity, Scheme 1.[13] Comparison of Et_2O and THF revealed that the latter solvent affords superior results. Thus, quinolines **2**−**5** were obtained in 67−90% yield after reaction of organolithium reagents with quinoline **1** followed by treatment with CAN. We were able to isolate intermediate 2-substituted 4-chloro-1,2-dihydroquinolines that proved to be unstable to air and are readily oxidized to quinolines **3**−**5** in the presence of CAN.[14] Undesirable side reactions such as dehalogenation of the starting material and of the Ziegler reaction product can be avoided through careful reaction control. We observed the formation of significant amounts of quinoline and 2-substituted quinolines at elevated reaction temperatures or increased reaction times. For instance, arylation of **1** using phenyllithium in THF at −78 °C provided 4-chloro-2-phenylquinoline (**5**) in 67% yield. However, **5** was obtained in only 54% yield at −15 °C. It is assumed that the decrease in yield is mainly a result of enhanced halogen−metal exchange under less cryogenic conditions since halogen-directed *ortho*-metalation in position 3 of **1** was not observed.[15]

Recently, Li et al. developed palladium−phosphinous acid complexes $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (POPd), $[[(t\text{-Bu})_2P(OH)(t\text{-Bu})_2PO)]PdCl]_2$ (POPd1), and $[(t\text{-Bu})_2P(OH)PdCl_2]_2$

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(9) Shiota, T.; Yamamori, T. *J. Org. Chem.* **1999**, *64*, 453−457.

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(11) Legros, J.-Y.; Primault, G.; Fiaud, J.-C. *Tetrahedron* **2001**, *57*, 2507−2514.

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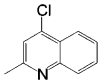
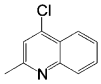
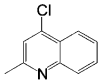
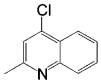
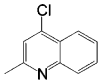
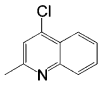
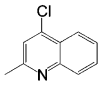
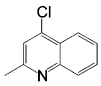
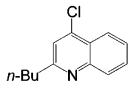
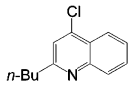
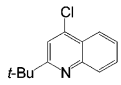
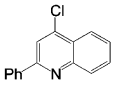
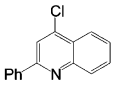
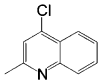
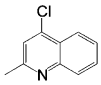
(13) To prove that the Ziegler reaction proceeds in position 2 of 4-chloroquinoline, we synthesized 4-chloro-2-methylquinoline, **2**, using methyllithium in 90% yield. The NMR spectrum was found to be identical to that of commercially available **2**.

(14) We observed that the isolated 2-substituted 4-chloro-1,2-dihydroquinolines oxidize within a few days when exposed to air.

(15) For a review of halogen-directed ortho meatallations, see: Mongin, Florence; Queguiner, G. *Tetrahedron* **2001**, *57*, 4059−4090.

TABLE 1. Pd-Catalyzed Heck Reactions Using *tert*-Butyl Acrylate

entry	4-haloquinoline	catalyst (6 mol%)	base	product	yield (%)
1		POPd	NaOAc	**6**	64
2		POPd	Cy_2NMe	**6**	85
3		POPd	NaOAc	**7**	66
4		POPd	$NaOAc/Bu_4NBr$	**7**	73
5		POPd	Cs_2CO_3	**7**	67
6		POPd	Cs_2CO_3	**7**	73[a]
7		POPd	*t*-BuOK/*t*-BuOH	**7**	60
8		POPd	Cy_2NMe	**7**	75
9		POPd	Cs_2CO_3	**7**	59[b]
10		POPd	Cs_2CO_3	**7**	10[c]
11		POPd	Cy_2NMe	**8**	70
12		POPd	$NaOAc/Bu_4NBr$	**8**	63
13		POPd	Cy_2NMe	**9**	66
14		POPd	Cy_2NMe	**10**	72
15		POPd	NaOAc	**10**	68
16		POPd1	Cs_2CO_3	**7**	20
17		POPd2	Cs_2CO_3	**7**	10

[a] The reaction time was 48 h. [b] The reaction temperature was 100 °C. [c] In refluxing toluene.

(POPd2), which have successfully been used in a variety of cross-coupling reactions, Figure 1.[16] Employing this new class of Pd catalysts in Heck and Stille cross-coupling reactions of 4-chloroquinolines **1**−**5** with arylstannanes and *tert*-butyl acrylate, respectively, we found that these catalysts exhibit high activity and greatly facilitate operation due to their stability to air, Scheme 2.[17]

POPd-promoted Heck reactions were found to proceed with high diastereoselectivity (*E*/*Z* > 25:1), and quino-

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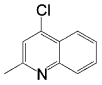
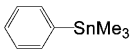
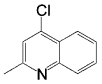
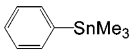
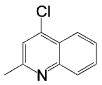
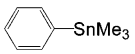
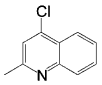
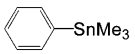
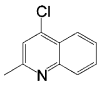
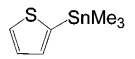
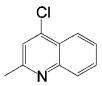
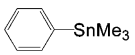
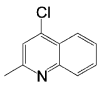
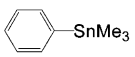
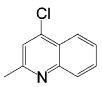
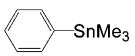
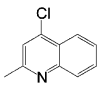
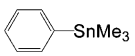
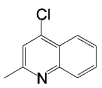
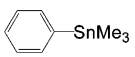
TABLE 2. Pd-Catalyzed Stille Couplings

entry	4-haloquinoline	reagent	catalyst	base	product	yield (%)
1			POPd 6 mol%	Cy_2NMe	**11**	85
2			$Pd(PPh_3)_2Cl_2$ 10mol%	Et_3N	**11**	20
3			$Pd(PPh_3)_2Cl_2$ 10 mol%	Cy_2NMe	**11**	18
4			$Pd(dppf)Cl_2$ 10 mol%	Cy_2NMe	**11**	16
5			POPd 6 mol%	Cy_2NMe	**12**	61
6			POPd1 6 mol%	Cy_2NMe	**11**	43
7			POPd2 6 mol%	Cy_2NMe	**11**	65
8			POPd 6 mol%	Cy_2NMe/CsF	**11**	89
9			POPd1 6 mol%	Cy_2NMe/CsF	**11**	70
10			POPd2 6 mol%	Cy_2NMe/CsF	**11**	73

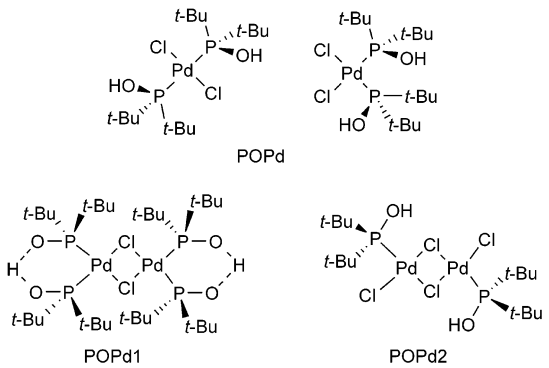
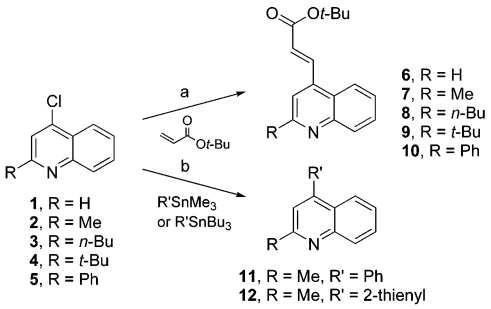


FIGURE 1. Structures of POPd, POPd1, and POPd2.

lines **6**−**10** were obtained in good to high yields using DMF as the solvent, Table 1 (entries 1−9, 11−15). The use of various bases, for example, NaOAc, Cs_2CO_3, *t*-BuOK/*t*-BuOH, and Cy_2NMe, was investigated to optimize the reaction procedure. Using Cy_2NMe as the base, (*E*)-*tert*-butyl 3-(2-methyl-4-quinolyl)acrylate (**7**) was obtained in 75% yield, whereas other bases give lower yields or require longer reaction times (compare entries 3 and 5−8). Noteworthy, we observed that replacing Cy_2NMe with inorganic bases such as NaOAc or Cs_2CO_3 greatly facilitates product purification because the chromatographic separation of the aliphatic amine from quinolyl acrylates proved to be difficult in some cases.

The anionic nature of palladium−phosphinous acids under basic conditions might limit the solubility and therefore accessibility and activity of these catalysts. We anticipated that the employment of ion pair reagents in the Heck reaction would result in homogeneous reaction conditions and further increase the activity of POPd. Addition of 20 mol % tetrabutylammonium bromide indeed improved the yields of the Heck addition of **2** to *tert*-butyl acrylate in the presence of POPd (entries 3 and 4). However, results obtained with 2-*n*-butyl-4-chloro-

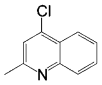
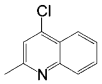
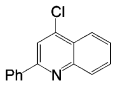
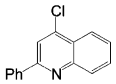
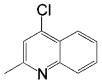
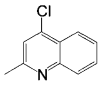
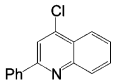
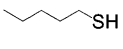
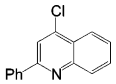
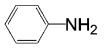
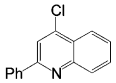
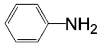
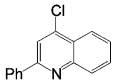
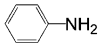
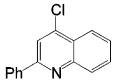
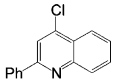
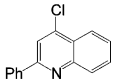
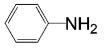
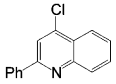
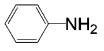
SCHEME 2. POPd-Catalyzed Cross-Coupling Reactions[a]



[a] Reagents and conditions: (a) 6 mol % POPd, 5 equiv of *tert*-butyl acrylate, 1.2 equiv of base, DMF, 135 °C, 24 h. (b) 6 mol % POPd, 1.3 equiv of Rm′$SnMe_3$ (R′$SnBu_3$), 1.1 equiv of Cy_2NMe, DMF, 135 °C, 24 h.

(17) POPd, POPd1, and POPd2 can be purchased from Combiphos Catalysts, Inc., New Jersey. Website: www.combiphos.com.

TABLE 3. Pd-Catalyzed Carbon−Heteroatom Bond Formation

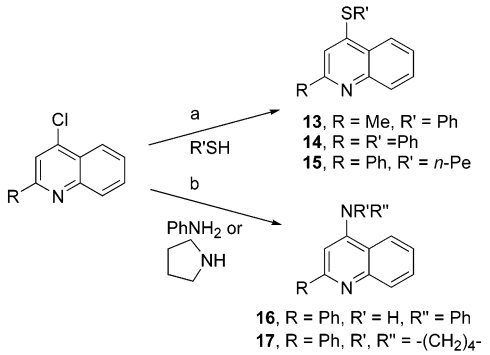
entry	4-haloquinoline	reagent	catalyst	base	product	yield (%)
1			/	Cy_2NMe	**13**	78
2			POPd 6 mol%	Cy_2NMe	**13**	85
3			/	*t*-BuOK/*t*-BuOH	**14**	76
4			POPd 6 mol%	*t*-BuOK/*t*-BuOH	**14**	78
5			POPd1 6 mol%	*t*-BuOK/*t*-BuOH	**13**	78
6			POPd2 6 mol%	*t*-BuOK/*t*-BuOH	**13**	78
7			/	*t*-BuOK/*t*-BuOH	**15**	73
8			/	*t*-BuOK/*t*-BuOH	**16**	68
9			POPd 6 mol%	*t*-BuOK/*t*-BuOH	**16**	72
10			POPd 6 mol%	*t*-BuOK/*t*-BuOH	**16**	48[a]
11			/	*t*-BuOK/*t*-BuOH	**17**	60
12			POPd 6 mol%	*t*-BuOK/*t*-BuOH	**17**	86
13			POPd1 6 mol%	*t*-BuOK/*t*-BuOH	**16**	59
14			POPd2 6 mol%	*t*-BuOK/*t*-BuOH	**16**	60

[a] Reaction temperature was 100 °C.

quinoline (**3**) show that Bu_4NBr/NaOAc does not provide similar yields as Cy_2NMe (entries 11 and 12). Replacement of DMF by toluene or a decrease of the reaction temperature were found to be detrimental, which might be a consequence of decreased solubility and thus reduced availability of POPd and the inorganic base used (entries 9 and 10). In contrast to POPd, POPd1 and POPd2 do not significantly promote the Heck reaction of chloroquinolines. Only low yields were obtained employing POPd1 and POPd2 as catalysts in the Heck reaction of chloroquinoline **2**, and most of the starting material was recovered after workup (entries 16 and 17).

We were pleased to find that POPd, POPd1, and POPd2 catalyze the Stille cross-coupling of 4-chloroquinolines with 2-(tributylstannyl)thiophene and phenyltrimethyltin, respectively, Scheme 2. Thus, 4-phenyl-2-methylquinolines (**11**) and 4-(2-thienyl)-2-methylquinolines (**12**) were obtained in good to high yields, Table 2 (entries 1 and 5−7). Similar to our observations with Heck reactions, POPd was found to be superior over POPd1 and POPd2. Using 6 mol % POPd, we obtained quinoline **11** in 85% yield, whereas POPd1 and POPd2 were found to afford **11** in only 43% and 65% yields, respectively. The reduced yields are likely to be a consequence of the lower activity of these catalysts, since we were able to recover the remaining starting materials in both cases. Noteworthy, all phosphinous acid−Pd catalysts investigated herein afford significantly better results than $Pd(PPh_3)_2Cl_2$ and $Pd(dppf)Cl_2$, which provide **11** in low yields, Table 2 (entries 2−4).[18] Following a recent finding of Fu et al., we utilized 2 equiv of CsF to further activate fluorophilic phenyltrimethyltin for Stille

SCHEME 3. Synthesis of Quinoline-Derived Amines and Sulfides[a]

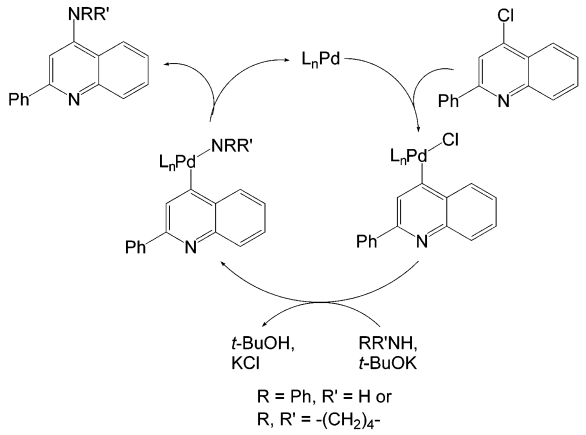


[a] Reagents and Conditions: (a) 1.6 equiv of R′SH, 1.1 equiv of base, DMF, 135 °C, 24 h. (b) 1.1 equiv of $R''NH_2/R''_2NH$, 1.1 equiv of. *t*-BuOK/*t*-BuOH, DMF, 135 °C, 24 h.

coupling.[19] For all three phosphinous acid−Pd catalysts, we observed that the yields of the Stille coupling of **2** and phenyltrimethyltin are indeed enhanced by the addition of CsF (entries 8−10). In particular, a significant increase of the yield of **11** using CsF as an additive in the POPd1-catalyzed coupling of quinaldine **2** and phenyltrimethyltin was observed (compare entries 6 and 9).

Some aryl chlorides have been reported to undergo transition metal-mediated carbon−heteroatom bond formation. Thus, aromatic amines and sulfides have been prepared utilizing palladium(II) complexes.[13a,b,20] Amination and thiation reactions of 4-chloroquinolines are also known to proceed via nucleophilic aromatic substitution in absence of a transition metal catalyst.[21] Accordingly, treatment of **2** and **5**, respectively, with various thiols or amines in the absence of a palladium catalyst in DMF at 135 °C provided quinolines **13**−**17** in good yields, Scheme 3 and Table 3 (entries 1, 3, 7, 8, and 11). Interestingly, employing 6 mol % POPd in the presence of Cy_2NMe or *t*-BuOK under the same reaction conditions improved results in most cases; that is, sulfides **13** and **14** as well as amines **16** and **17** were obtained in superior yields by Pd-mediated catalysis (entries 2, 4, 9, and 12). Accordingly, a Pd-catalyzed amination reaction of 4-chloroquinoline has recently been utilized by Jonckers et al. for the synthesis of isocryptolepine.[22] The POPd-catalyzed amination and thiation of 4-chloroquinoline are expected to proceed via oxidative addition followed by base-promoted nucleophilic displacement of chloride and subsequent reductive elimination, Scheme 4. Employing POPd1 and POPd2, respectively, in the amination or thiation of chloroquinolines **2** and **5** did not reveal any catalytic effects. The same yields of 2-methyl-4-phenylthioquinoline (**13**) were obtained in the absence and presence of these catalysts (compare entries 1, 5, and 6). Moreover, POPd1 and POPd2 proved to be detrimental to the amination of **5** using aniline (compare entries 8, 13, and 14).

SCHEME 4. Catalytic Cycle for the POPd-Catalyzed Amination Reaction



Conclusion

We have developed an efficient route toward 2,4-disubstituted quinolines. Ziegler reaction using organolithium reagents at −78 °C followed by treatment with CAN allows regioselective alkylation or arylation in position 2 of 4-chloroquinoline. Palladium−phosphinous acids, POPd, POPd1, and POPd2, were found to be highly useful catalysts for a variety of cross-coupling reactions. Stille reactions of chloroquinoline derivatives and arylstannanes as well as Heck additions of aryl chlorides to *tert*-butyl acrylate proceed with high yield and diastereoselectivity. In general, POPd exhibits higher catalytic activity toward cross-coupling reactions of 4-chloroquinolines than POPd1 and POPd2. Using tetrabutylammonium bromide and CsF slightly enhances the yields of POPd-catalyzed Heck and Stille reactions, respectively. Electron-deficient 2-substituted-4-chloroquinolines undergo nucleophilic aromatic substitution by amines or thiols at elevated temperature. However, employing POPd under the same reaction conditions affords superior yields. By contrast, POPd1 and POPd2 do not promote carbon−heteroatom bond formation under the reaction conditions employed in this study. The usefulness of palladium−phosphinous acid complexes POPd, POPd1, and POPd2 for the synthesis of a broad variety of biaryls using aryl stannanes or aryl siloxanes is currently under investigation in our laboratories.

Experimental Section

Methods. Chemicals were of reagent grade and used without further purification. All reactions were carried out under a nitrogen atmosphere and anhydrous conditions. Flash chromatography was carried out on SiO_2 (particle size 0.032−0.063 mm). Triethylamine (1%) was always used as a mobile

(18) It should be noted that tri-*n*-butylethynylstannane and tri-*n*-butylvinylstannane did not undergo POPd-catalyzed Stille coupling with quinolines **2** and **5**, respectively.

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phase additive to reduce tailing of the quinolines during chromatography. NMR spectra were obtained at 300 MHz (^{1}H NMR) and 75 MHz (^{13}C NMR) using $CDCl_3$ as the solvent. Chemical shifts are reported in ppm relative to TMS. GC−MS was performed using a 15 m DB-1 GC column.

General Procedure for the Synthesis of 2-Substituted 4-Chloroquinolines 2−5. To a stirred solution of 4-chloroquinoline (300 mg, 1.8 mmol) in 10 mL of anhydrous THF was added the organolithium reagent (1.5 mL, 1.5 M in hexanes) dropwise at −78 °C. The reaction mixure was allowed to proceed for 4 h at −78 °C, quenched with 10% NH_4OH, and extracted with CH_2Cl_2. The combined organic layers were washed with water and concentrated in vacuo. The residue was dissolved in 2 mL of acetone and treated with an aqueous solution of ammonium cerium(IV) nitrate (2.0 g in 10 mL) for 30 min. The orange solution was extracted with CH_2Cl_2 and dried over $MgSO_4$, and the filtrate was concentrated under reduced pressure. The crude products were purified by flash chromatography on silica gel as indicated for each example.

General Procedure for Heck Reactions. A mixture of POPd (16.0 mg, 6 mol %) quinoline derivative (0.56 mmol), *tert*-butyl acrylate (356 mg, 2.8 mmol), and base (0.61 mmol) was stirred in 5 mL of anhydrous DMF at 135 °C for 24 h. The reaction mixture was allowed to cool to room temperature, quenched with water, and extracted with Et_2O. The combined organic layers were washed with water and dried over $MgSO_4$, and the solvents were removed under vacuum. The crude products were purified by flash chromatography on silica gel as indicated for each example.

General Procedure for Stille Couplings. A mixture of POPd (16.0 mg, 6 mol %) quinoline derivative (0.56 mmol), organostannane (0.7 mmol), and Cy_2NMe (120 mg, 0.61 mmol) was stirred in 5 mL of anhydrous DMF at 135 °C for 24 h. The reaction mixture was allowed to cool to room temperature, quenched with water, and extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were removed under vacuum. The residue was purified by flash chromatography on silica gel as indicated for each example.

General Procedure for Amination of 4-Chloroquinolines. A mixture of POPd (16.0 mg, 6 mol %) quinoline derivative (0.56 mmol), amine (0.72 mmol), and base (0.61 mmol) was stirred in 5 mL of anhydrous DMF at 135 °C for 24 h. The reaction mixture was allowed to cool to room temperature, quenched with water, and extracted with Et_2O. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were removed under vacuum. The crude products were purified by flash chromatography on silica gel as indicated for each example.

General Procedure for Thiation of 4-Chloroquinolines. A mixture of POPd (16.0 mg, 6 mol %) quinoline derivative (0.56 mmol), thiol (0.73 mmol), and base (0.61 mmol) was stirred in 5 mL of anhydrous DMF at 135 °C for 24 h. The reaction mixture was allowed to cool to room temperature, quenched with water, and extracted with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$, and the solvents were removed under vacuum. The crude products were purified by flash chromatography on silica gel as indicated for each example.

(*E*)-*tert*-Butyl 3-(4-Quinolyl)acrylate (6). Flash chromatography (hexane/Et_2O 1:1) gave a colorless oil (85% using Cy_2-NMe). ^{1}H NMR: δ 1.59 (s, 9H), 6.59 (d, J = 15.9 Hz, 1H), 7.54 (d, J = 4.6 Hz, 1H), 7.70 (dd, J = 6.6 Hz, 8.8 Hz, 1H), 7.81 (dd, J = 6.6 Hz, 7.4 Hz), 8.14−8.16 (m, 2H), 8.33 (d, J = 15.9 Hz, 1H), 8.9 (d, J = 4.6 Hz, 1H). ^{13}C NMR: δ 28.2, 81.3, 118.0, 123.3, 126.0, 126.5, 127.1, 129.6, 130.1, 135.7, 135.8, 137.8, 140.1, 165.1. EIMS (70 eV) *m*/*z* (%): 255 (15, M^+), 182 (35, $M^+-OC_4H_9$), 154 (100, $M^+-CO_2C_4H_9$), 127 (25, $M^+-CO_2C_4H_9$, −HCN). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 74.92; H, 6.42; N, 5.32.

(*E*)-*tert*-Butyl 3-(2-Methyl-4-quinolyl)acrylate (7). Flash chromatography (hexane/Et_2O 5:1) gave white crystals (75% using Cy_2NMe), mp 40−42 °C. ^{1}H NMR: δ 1.56 (s, 9H), 2.76 (s, 3H), 6.56 (d, J = 16.0 Hz, 1H), 7.43 (s, 1H), 7.54 (ddd, J = 1.4 Hz, 7.0 Hz, 8.0 Hz, 1H), 7.71 (ddd, J = 1.4 Hz, 7.0 Hz, 8.5 Hz, 1H), 8.05 (dd, J = 1.4 Hz, 8.0 Hz, 1H), 8.09 (dd, J = 1.4 Hz, 8.5 Hz, 1H), 8.30 (d, J = 16.0 Hz, 1H). ^{13}C NMR: δ 25.4, 28.2, 81.2, 118.9, 123.1, 124.5, 126.2, 126.2, 129.2, 129.6, 138.1, 140.2, 148.2, 158.5, 165.2. EIMS (70 eV) *m*/*z* (%): 269 (30, M^+), 254 (50, M^+-Me), 181 (10, M^+-Me, $-OC_4H_9$), 153 (100, M^+-Me, $-CO_2C_4H_9$). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.46; H, 7.48; N, 5.06.

(*E*)-*tert*-Butyl 3-(2-*n*-Butyl-4-quinolyl)acrylate (8). Purification by flash chromatography (hexane/Et_2O 5:1) gave a yellow oil (70% using Cy_2NMe). ^{1}H NMR: δ 0.97 (t, J = 7.0 Hz, 3H), 1.44 (m, 2H), 1.57 (s, 9H), 1.79 (m, 2H), 2.96 (t, J = 7.9 Hz, 2H) 6.56 (d, J = 16.0 Hz, 1H), 7.43 (s, 1H), 7.54 (ddd, J = 1.3 Hz, 7.3 Hz, 7.8 Hz, 1H), 7.71 (ddd, J = 1.3 Hz, 6.5 Hz, 7.8 Hz, 1H), 8.03 (dd, J = 1.3 Hz, 6.5 Hz, 1H), 8.10 (dd, J = 1.3 Hz, 7.3 Hz, 1H), 8.30 (d, J = 16.0 Hz, 1H). ^{13}C NMR: δ 14.4, 23.1, 28.5, 32.6, 39.4, 81.5, 118.6, 123.4, 124.8, 125.8, 126.4, 129.0, 129.8, 138.6, 140.5, 148.5, 162.9. EIMS (70 eV): *m*/*z* (%): 311 (50, M^+), 296 (70, M^+-Me), 254 (60, $M^+-C_4H_9$), 181 (21, $M^+-OC_4H_9$, $-C_4H_9$), 153 (100, $M^+-CO_2C_4H_9$, $-C_4H_9$). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 77.46; H, 8.18; N, 4.51.

(*E*)-*tert*-Butyl 3-(2-*tert*-Butyl-4-quinolyl)acrylate (9). Flash chromatography (hexane/Et_2O 25:1) gave a yellow oil (66% using Cy_2NMe). ^{1}H NMR: δ 1.47 (s, 9H), 1.58 (s, 9H), 6.56 (d, J = 16.0 Hz, 1H), 7.53 (ddd, J = 1.3 Hz, 7.6 Hz, 7.7 Hz, 1H), 7.63 (s, 1H), 7.71 (ddd, J = 1.3 Hz, 7.6 Hz, 7.7 Hz, 1H), 8.03−8.11 (m, 2H), 8.30 (d, J = 16.0 Hz, 1H). ^{13}C NMR: δ 28.3, 30.2, 44.1, 81.2, 104.3, 115.2, 122.2, 122.9, 124.2, 125.8, 126.1, 129.2, 130.0, 139.0, 139.8, 165.3. EIMS (70 eV) *m*/*z* (%): 311 (32, M^+), 296 (80, M^+-Me), 281 (49, M^+-2Me), 254 (40, $M^+-C_4H_9$), 181 (40, $M^+-C_4H_9$, $-OC_4H_9$), 153 (100, $M^+-CO_2C_4H_9$, $-C_4H_9$). Anal. Calcd for $C_{20}H_{25}NO_2$: C, 77.14; H, 8.09; N, 4.50. Found: C, 76.81; H, 8.25; N, 4.61.

(*E*)-*tert*-Butyl 3-(2-Phenyl-4-quinolyl)acrylate (10). Purification by flash chromatography (hexane/Et_2O 100:1) gave a clear oil (72% using Cy_2NMe). ^{1}H NMR: δ 1.59 (s, 9H), 6.65 (d, J = 15.7 Hz, 1H), 7.45−7.55 (m, 3H), 7.59 (ddd, J = 1.3 Hz, 7.6 Hz, 7.7 Hz, 1H), 7.76 (ddd, J = 1.3 Hz, 7.5 Hz, 7.7 Hz, 1H), 8.00 (s, 1H), 8.12−8.24 (m, 4H), 8.40 (d, J = 15.7 Hz, 1H). ^{13}C NMR: δ 28.3, 81.3, 116.1, 123.1, 125.0, 126.4, 126.8, 127.4, 128.8, 129.4, 129.8, 130.3, 138.4, 139.2, 140.8, 148.6, 164.5. EIMS (70 eV): *m*/*z* (%): 331 (59, M^+), 254 (23, M^+-Ph), 197 (33, $M^+-C_4H_9$, $-Ph$), 181 (50, M^+-Ph, $-OC_4H_9$), 153 (100, M^+-Ph, $-CO_2C_4H_9$). Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.45; H, 6.03; N, 4.38.

2-Methyl-4-phenylquinoline (11). Purification by flash chromatography (hexane/EtOAc 25:1) gave a colorless oil (85%). ^{1}H NMR: δ 2.78 (s, 3H), 7.23 (s, 1H), 7.43 (ddd, J = 1.4 Hz, 7.6 Hz, 8.5 Hz, 1H), 7.47−7.51 (m, 5H), 7.69 (ddd, J = 1.4 Hz, 7.6 Hz, 8.4 Hz, 1H), 7.86 (dd, J = 1.4 Hz, 8.4 Hz, 1H), 8.08 (dd, J = 1.4 Hz, 8.5 Hz, 1H). ^{13}C NMR: δ 25.4, 122.1, 125.0, 125.5, 125.6, 128.2, 128.4, 128.9, 129.2, 129.4, 138.0, 148.2, 148.3, 158.3. EIMS (70 eV) *m*/*z* (%): 219 (100, M^+), 204 (22, M^+-Me), 142 (10, M^+-Ph), (11, 127 (15, M^+-Me, $-Ph$). Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.98; N, 6.39. Found: C, 87.52; H, 5.82; N, 6.35.

2-Methyl-4-(2-thienyl)quinoline (12). Purification by flash chromatography (hexane/EtOAc 10:1) gave a colorless oil (61%). ^{1}H NMR: δ 2.77 (s, 3H), 7.22 (dd, J = 3.6 Hz, 5.0 Hz, 1H), 7.35 (s, 1H), 7.38 (dd, J = 1.1 Hz, 3.6 Hz, 1H), 7.47−7.53 (m, 2H), 7.70 (ddd, J = 1.4 Hz, 7.6 Hz, 8.3 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 8.22 (dd, J = 1.4 Hz, 8.3 Hz, 1H). ^{13}C NMR: δ 25.4, 121.0, 122.5, 126.0, 126.9, 127.6, 128.3, 129.4, 138.9, 142.1, 146.1, 165.5. EIMS (70 eV) *m*/*z* (%): 225 (100, M^+), 210 (10, M^+-Me), 127 (5, M^+-Me, $-C_4H_3S$). Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22. Found: C, 75.01; H, 5.02; N, 6.35.

2-Methyl-4-phenylthioquinoline (13). Purification by flash chromatography (hexane/EtOAc 5:1) gave white crystals

(85%), mp 76−78 °C. ^{1}H NMR: δ 2.53 (s, 3H), 6.68 (s, 1H), 7.40−7.60 (m, 6H), 7.71 (ddd, J = 1.4 Hz, 7.7 Hz, 8.4 Hz, 1H), 7.98 (dd, J = 1.1 Hz, 8.4 Hz, 1H), 8.17 (dd, J = 1.4 Hz, 8.2 Hz, 1H). ^{13}C NMR: δ 25.4, 118.8, 123.2, 124.3, 125.5, 128.9, 129.2, 129.6, 129.7, 129.8, 134.7, 147.2, 147.7, 157.9. EIMS (70 eV): m/z (%): 251 (70, M^+), 250 (100, M^+-H), 236 (31, M^+-Me), 142 (20, M^+-PhS), 127 (5, M^+-Me, $-PhS$). Anal. Calcd for $C_{16}H_{13}NS$: C, 76.46; H, 5.21; N, 5.57. Found: C, 76.28; H, 4.85; N, 5.44.

2-Phenyl-4-phenylthioquinoline (14). Purification by flash chromatography (hexane/EtOAc 5:1) gave white crystals (85% using Cy_2NMe), mp 110−112 °C. ^{1}H NMR: δ 7.30 (s, 1H), 7.39−7.64 (m, 9H), 7.75 (dd, J = 7.7 Hz, 8.4 Hz, 1H), 7.88−7.91 (m, 2H), 8.16 (d, J = 8.4 Hz, 1H), 8.22, (d, J = 8.7 Hz, 1H). ^{13}C NMR: δ 116.4, 123.4, 125.1, 126.3, 127.4, 128.7, 129.2, 129.4, 129.9, 130.8, 134.7, 137.1, 139.4, 157.2. EIMS (70 eV) m/z (%): 313 (72, M^+), 312 (100, M^+-H), 236 (31, M^+-Ph), 204 (12, M^+-PhS). Anal. Calcd for $C_{21}H_{15}NS$: C, 80.48; H, 4.82; N, 4.47. Found: C, 79.89; H, 4.70; N, 4.37.

4-*n*-Pentylthio-2-phenylquinoline (15). Flash chromatography (hexane/Et_2O 6:1) gave white crystals (73%, using *t*-BuOK and no catalyst), mp 61−63 °C. ^{1}H NMR: δ 0.94 (t, J = 7.3 Hz, 3H), 1.44 (m, 2H), 1.58 (m, 2H), 1.90 (m, 2H), 3.17 (t, J = 7.3 Hz, 2H), 7.42−7.55 (m, 3H), 7.62 (s, 1H), 7.71−7.78 (m, 2H), 7.85 (m, 1H), 8.08−8.21 (m, 3H). ^{13}C NMR: δ 14.1, 22.4, 28.0, 31.3, 31.4, 114.0, 123.3, 125.5, 125.9, 126.2, 127.5, 128.7, 129.2, 129.5, 130.2, 136.6, 148.1, 164.5. EIMS (70 eV) m/z (%): 307 (80, M^+), 306 (100, M^+-H), 230 (20, M^+-Ph), 215 (5, M^+-Ph, $-Me$), 159 (31, M^+-Ph, $-C_5H_{11}$), 127 (10, M^+-Ph, $-SC_5H_{11}$). Anal. Calcd for $C_{20}H_{21}NS$: C, 78.13; H, 6.88; N, 4.56. Found: C, 77.69; H, 6.98; N, 4.44.

***N*-(2-Phenyl-4-quinolyl)pyrrolidine (17).** Flash chromatography (hexane/Et_2O 6:1) gave white crystals (86%, using *t*-BuOK), mp 131−133 °C. ^{1}H NMR: δ 2.07 (m, 4H), 3.76 (m, 4H), 6.91 (s, 1H), 7.31 (ddd, J = 1.4 Hz, 7.6 Hz, 8.6 Hz, 1H), 7.38−7.56 (m, 4H), 7.61 (ddd, J = 1.4 Hz, 7.6 Hz, 8.4 Hz, 1H), 8.02−8.08 (m, 2H), 8.11 (dd, J = 1.4 Hz, 8.6 Hz, 1H). ^{13}C NMR: δ 26.1, 52.3, 100.8, 122.9, 124.8, 125.1, 125.2, 127.6, 128.5, 128.7, 133.1, 144.7, 161.8, 163.8. EIMS (70 eV) m/z (%): 274 (100, M^+), 204 (35, $M^+-C_4H_8N$), 197 (5, M^+-Ph), 127 (10, M^+-Ph, $-C_4H_8N$). Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 82.81; H, 6.40; N, 9.85.

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Supporting Information Available: Procedures for the chromatographic purification of quinolines **3**, **4**, **5**, and **16** and NMR spectroscopy and mass spectrometry data. This material is available free of charge via the Internet at http://pubs.acs.org.

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