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Facile Palladium-Mediated Substitution of Chlorine in 2-Chloroquinolines

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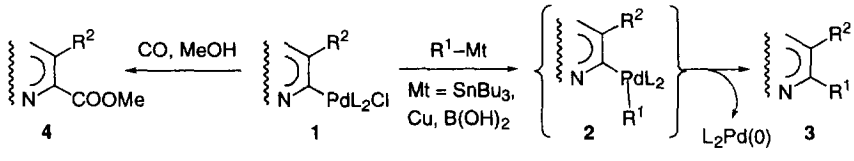
ABSTRACT: Unlike ordinary aryl chlorides, the title hererocycles participate readily in Castro-Stephens, Stille, Suzuki, and carbonylation reactions under the catalytic influence of Pd(0).

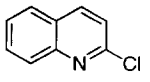
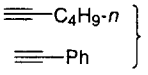
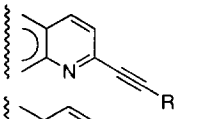
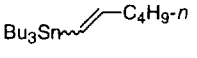
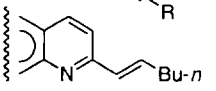
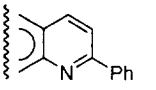
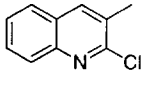
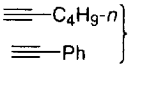
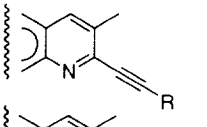
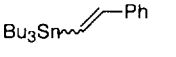
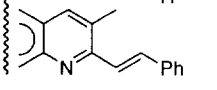
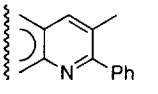
Palladium-mediated coupling reactions have revolutionized the field of aromatic chemistry. Thus, many issues relating to efficiency, regioselectivity, functional group compatibility, etc., have vanished with the advent of, e.g., Heck,[3] Castro-Stephens,[4] Stille,[5] Suzuki[6] and various carbonylative processes. In general, these trasformations succeed only with aryl bromides, iodides or triflates. Aryl chlorides are unreactive, though carbonylations have been achieved with specialized catalysts.[7] In response to a need to prepare 2,3-dialkyl quinolines, we entertained the possibility of inducing Pd-mediated substitution reactions of readily accessible 2-chloro-3-alkyl quinolines, available in quantity through the excellent Meth-Cohn quinoline synthesis.[8] This approach, inspired by the recent disclosure of successful coupling of a 2-chloropyridine with an arylboronic acid,[9] may offer advantages over classical Friedländer syntheses of the end-products,[10] both in terms of overall efficiency and because the need for sensitive / costly 2-aminobenzaldehydes would be fully circumvented.[11] It seemed plausible that the unusual mobility of the 2-halogen in quinolines might permit an otherwise difficult oxidative insertion of Pd(0) into the C–Cl bond, and a consequent entry into the corresponding organometallic manifold (cf. **1**-**2**, Scheme 1). This expectation was realized. Details are discussed below.

Scheme 1



Typical conditions for all the reactions described in this Letter are provided in Tables 1 and 2. Castro-Stephens substitution by Cu(I) acetylide was effected in generally good to excellent yields under the influence of 4 mol % of the especially good catalyst, $(Ph_3P)_4Pd$.[12] No coupling occurred in blank runs wherein the Pd complex had been omitted, signaling that a Cu(I) acetylide is not sufficiently reactive, at least under our conditions, to displace the halogen from the substrates, and that a Pd species is indeed necessary for the reaction to occur. By contrast, Stille coupling favored the catalyst, bis(1,3-diphenylphosphinopropane)palladium [$Pd(dppp)_2$] (4 mol %), generated *in situ* from $Pd(OAc)_2$ and two equivalents of dppp, and occurred generally slower than Castro-Stephens or Suzuki transformations. The latter reaction, explored with commercial phenylbor-

Table 1: Representative Pd-Mediated Alkylation Reactions of 2-Chloroquinolines

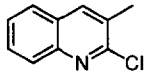
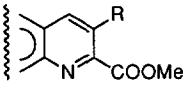
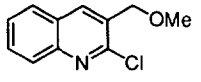
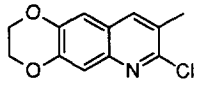
2-Chloroquinoline	Reagent	Conditions[a]	Product type	Entry	Yield[b]
		A		**4** (R = Bu-*n*) **5** (R = Ph)	50 20
		B		**6**[c]	48
	Ph-B(OH)$_2$	C		**7**	67
		A		**8** (R = Bu-*n*) **9** (R = Ph)	98 88
		B		**10**	75
	Ph-B(OH)$_2$	C		**11**	81

[a]**A**. A dry flask containing the 2-chloroquinoline (0.6 mmol), fresh dry CuI (0.2 mmol, 33 mol %)[13] and Pd(PPh$_3$)$_4$ (0.024 mmol, 4 mol %), a small amount of BHT (ca. 5 small crystals) and a stirring bar was sealed under argon. Dry DMF (1.8 mL) and tBuNH$_2$ (1.2 mmol, 200 mol %) were syringed in and the mixture was heated to 80°C in an oil bath. After five minutes, 1-hexyne was syringed in (0.66 mmol, 110 mol %). The mixture darkenend immediately and the color of the solution deepened during the reaction, which typically completed in 4 hrs (TLC). Addition of more alkyne (0.3 mmol, 50 mol %) helped in slow reactions. The mixture was cooled and partitioned between H$_2$O and CH$_2$Cl$_2$ and the crude product was chromatographed (70-230 mesh silica gel, 2-5 % EtOAc / hexanes). **B**. A dry flask containing the 2-chloroquinoline (0.6 mmol), Pd(OAc)$_2$ (0.024 mmol, 4 mol %), DPPP (0.48 mmol, 8 mol %), BHT (ca. 5 small crystals) and a stirring bar was sealed under argon. Dry DMF (1.8 mL) and NEt$_3$ (0.9 mmol, 150 mol %) were syringed in and the mixture was heated to 80°C in an oil bath. After five minutes, a 1-tributylstannyl-alkene (mixture of *E* and *Z* isomers) was syringed in (0.66 mmol, 110 mol %) and heating at 80°C was continued. The mixture darkenend slowly over time. Typically, TLC indicated completion of the reaction after 24-36 hours, depending on the specific system. The mixture was worked up as described in **A**, but chromatography was carried out with 230-400 mesh silica gel with 1 % ether in petroleum ether (38-55°C). **C**. A dry flask containing the 2-chloroquinoline (0.6 mmol), freshly prepared Pd(PPh$_3$)$_4$ (0.012 mmol, 2 mol %), a small amount of BHT (ca. 5 small crystals), phenylboronic acid (0.72 mmol, 120 mol %), Ba(OH)$_2$•8H$_2$O (1.44 mmol, 240 mol %) and a stirring bar was sealed under argon. Dry, freshly distilled THF (1.8 mL) was injected and the mixture was heated to 75°C in an oil bath. The initially orangish suspension turned white after ca. 5 minutes. Typically, TLC indicated completion of the reaction after 1.5 to 2 hours. Workup and purification were carried out as described in **A**. [b]Chromatographed yield of pure (TLC, ^{1}H and ^{13}C NMR) compounds. [c]Complete isomerization to the *trans* isomer occurred during the reaction

onic acid activated by Ba(OH)$_2$,[14] proceeded very well across the board with (Ph$_3$P)$_4$Pd as the catalyst, and no comparative studies with other Pd complexes were undertaken.

The data of Table 1 suggest that the presence of a methyl group at position 3 of the quinoline has a beneficial effect on reaction rates and efficiency. This is in agreement with our previous observations on intramolecular Pd-mediated displacement of aromatic nucleofuges with soft enolates,[15] and it may be attributed to steric acceleration of reductive elimination of Pd(0) from a Pd(II) complex of the type **2**. Steric shielding of this intermediate from

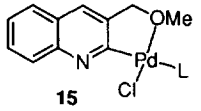
Table 2: Representative Pd-Mediated Carbonylation Reactions of 2-Chloroquinolines

2-Chloroquinoline	Conditions[a]	Product type	Entry	Yield
	A		12	98[b]
	B	"	13	72[c,d]
	A	"	14	61[c,d]

[a]**A**. A Parr bomb containing a stirring bar, a 2-chloroquinoline (23 mmol), $Pd(OAc)_2$ (0.46 mmol, 2 mol %), 1,3-bis-(diphenylphospino)propane (0.92 mmol), NaOAc (23 mmol), MeOH (2.3 mL) and DMF (7.6 mL), was pressurized to 100 atm of CO. The mixture was stirred for 2 days at 140°C, then cooled and partitioned between ether and H_2O. If necesasry, the product was chromatographed over 70-230 mesh silica gel with 20-25% EtOAc/hexanes. **B**. Same as in **A** except that 4 mol % of Pd catalyst was employed, N-methylpyrrolidinone was used as the solvent, and the reaction was conducted at 100°C for 4 days (text). [b]Isolated yield of pure (TLC, ^1H and ^{13}C NMR) product. [c]Chromatographed yield of pure (TLC, ^1H and ^{13}C NMR) compounds. [d]Some unreacted starting material (10-20%) was also recovered.

external agents may also contribute to generally better results.

Like Stille couplings, carbonylative transformations leading to quinaldic esters were best promoted by *in situ* generated $Pd(dppp)_2$ (2 mol %). While many carbonylations occur rapidly at or near 1 atm. of CO, our reactions proceeded at an unusually slow rate and required high pressures of CO (Table 2). The beneficial effect of a C-3 substituent was apparent in this case as well (cf. **12**, Table 2). However, efficiency suffered with those substrates displaying resonant interaction of electron-releasing groups with position 2 of the quinoline (cf. **15**). Reaction rates were noticeably slower with substrates such as 3-methoxymethyl-2-chloroquinoline, carbonylation of which was also complicated by significant dechlorination. Perhaps, ligation of the Pd by the methoxy group in a presumed intermediate of the type **15** retards migratory insertion and renders the complex more vulnerable to reduction, e.g. by the DMF used as the solvent. This problem was brought under control by increasing the amount of catalyst to 4 mol %, by using N-methylpyrrolidinone instead of DMF as the solvent, and by allowing a longer contact time at lower temperatures. Three additional limitations of the new chemistry should be mentioned. Aldehyde **16** was a poor substrate for any of the foregoing of Pd-mediated reactions (complex mixtures). Attempts to induce carbonylative Stille coupling with 1-tributylstannyl-1-hexene (*E* / *Z* mixture) under CO (1–100 atm) were only marginally successful: only modest yields of ketone **17** were obtained at elevated CO pressure, in all cases the major product being the one of plain Stille coupling. Finally, chloroquinolines did not seem inclined to engage in Heck reaction with methyl acrylate. This behavior is consistent with the known reluctance of similar heteroaromatic halides to participate in such transformations.[16,17]



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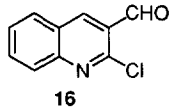
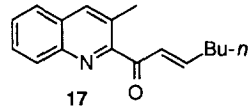


16



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References and Footnotes

1. Fellow of the Alfred P. Sloan Foundation, 1994-1996.
2. Current Address: Department of Chemistry, Scripps Research Institute, La Jolla, CA.
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12. Freshly prepared according to Coulson, D. R. *Inorg. Synth.* **1977**, *13*, 121.
13. CuI was prepared by addition of an aq. solution of NaI (2.5 eq.) to an aq. solution of $CuSO_4 \cdot 5H_2O$ (1 eq.) with good stirring, followed by filtration of the white ppt., washing with ether and vacuum drying.
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16. Frank, W. C.; Kim, Y. C.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2947. See also ref. 3.
17. Physical data for representative compounds (^{1}H [250 MHz] & ^{13}C NMR [75 MHz] in $CDCl_3$; shifts in ppm on the δ scale, coupling constants J in Hz; IR [films] in cm^{-1}; MS [EI, 70 eV] as m/e). **8** ^{1}H: 8.00 (app. d, 1H, J = 8.2); 7.84 (d, 1H, J = 0.7); 7.65-7.54 (m, 2H); 7.42 (app. dt, 1H, J_1 = 7.2, J_2 = 0.5); 2.52 (t, 2H, J = 7.0); 2.51 (s, 3H); 1.68-1.45 (m, 2H); 0.94 (s, 3H, J = 7.2). ^{13}C: 146.4, 139.7, 138.3, 128.1, 125.5, 122.0, 121.9, 120.5, 119.8 (two signals), 88.7, 72.8, 23.6, 15.2, 12.9, 12.5, 6.9, 6.7. IR: 3060, 2950, 2870, 2228. MS: 223 (M^+), 222, 221, 207, 192, 179 (100%), 166, 151. HRMS calc. for $C_{16}H_{17}N$ 223.1360; found 223.1361. **10** ^{1}H: 8.10 (d, 1H, J = 8.5); 8.03 (d, 1H, J = 15.5); 7.87 (s, 1H); 7.71-7.61 (m, 5H); 7.51 (d, 1H, J = 15.5); 7.45-7.30 (m, 3H); 2.60 (s, 3H). ^{13}C: 154.8, 146.9, 136.9, 136.1, 135.4, 129.3, 128.9, 128.6 (two signals), 128.4, 127.7, 127.4, 126.6, 125.9, 124.9, 124.2, 19.4. IR: 3060, 2930, 1596, 1379, 908. MS: 245 (M^+), 244, 230, 168 (100%), 115. HRMS calc. for $C_{18}H_{15}N$ 245.1204; found 245.1204. **11** ^{1}H: 9.18 (d, 1H, J = 8.2); 7.95 (s, 1H); 7.74 (app. dd, 1H, J_1 = 8.0, J_2 = 1.2); 7.69-7.40 (m, 7H); 2.43 (s, 3H). ^{13}C: 153.5, 139,6, 129.7, 127.3, 122.1, 121.9, 121.7, 121.3, 121.2, 120.6, 119.7, 119.4, 12.6. IR: 3056, 1597, 1373. MS: 219 (M^+), 218 (100%), 217, 216. **12** ^{1}H: 8.20-8.16 (d, 1H), 8.03 (s, 1H), 7.79-7.75 (dd, 1H, J_1=8.1, J_2=1.0), 7.73-7.66 (dt, 1H, J_1 = 6.9, J_2=1.5), 7.61-7.55 (dt, 3H, J_1=7.1, J_2 = 1.2), 4.05 (s, 3H), 2.69 (s, 3H). ^{13}C: 166.8, 149.2, 145.8, 138.1, 130.4, 129.9, 129.3, 129.0, 128.3, 126.7, 52.8, 19.8. IR: 1678. MS: 201 (M+), 143 (100%). HRMS calc. $C_{12}H_{11}NO_2$ 201.0789, found 201.0785. **13** m.p. 63-64°C. ^{1}H: 8.43 (d, 1H, J=0.7), 8.25-8.22 (d, 1H, J=8.4), 7.89-7.86 (dd, 1H, J_1=8.1, J_2=0.9), 7.79-7.72 (dt, 1H, J_1=6.9, J_2=1.4), 7.67-7.60 (dt, 3H, J_1=7.0, J_2=1.2), 4.95 (d, 2H, J=1.0) 4.05 (s, 3H), 3.54 (s, 3H). ^{13}C: 166.0, 146.4, 145.7, 135.0, 131.5, 129.5, 128.3, 128.0, 127.1, 70.6, 58.4, 52.5. IR: 1723. MS: 231 (M^+), 216, 184 (100%). HRMS calc. $C_{13}H_{13}NO_3$: 231.0895 (M^+), found: 201.0895.

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