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# Cobalt-catalyzed electrochemical cross-coupling of functionalized phenyl halides with 4-chloroquinoline derivatives

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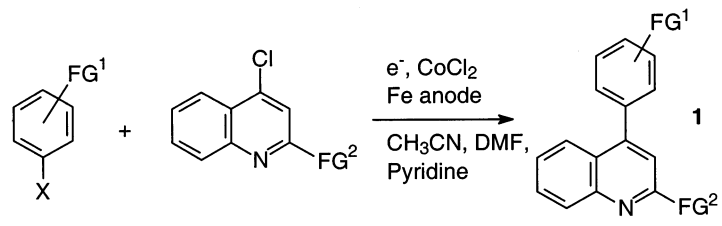
**Abstract**—A novel electrochemical procedure allowing the synthesis of various 4-phenylquinoline derivatives in satisfactory to high yields is described. This method relies on a cobalt-catalyzed cross-coupling reaction of functionalized phenyl halides with 4-chloroquinoline derivatives and is conducted in a one-compartment cell using the sacrificial anode process. 

Formation of C–C bonds has long been recognized as one of the most challenging features in organic chemistry. In the field of biaryl synthesis, numerous works were directed towards cross-coupling reactions between 'activated' aromatic compounds, which could be for instance aryl halides. Among several catalytic processes[1] which have been developed during the last decades, the Suzuki reaction[2] involving arylboronic acids and aryl halides has widely been employed.[3,4]

In a previous paper, we reported the efficient nickel-catalyzed electrochemical cross-coupling of 2-chloropyridines with aryl halides.[5] Only slight modifications of this procedure allowed the efficient synthesis of 2-phenylpyrimidines and pyrazines,[6] e.g. it was shown that the nature of the anode played a major role and that the presence of $FeBr_2$ at the beginning of the electrolysis was necessary for the cross-coupling reaction to occur. However, the scope of these reactions was minimized insofar as these procedures could not be applied to the synthesis of rarely-described 4-phenylquinoline derivatives.

Considering several works devoted to the catalytic activation of aromatic halides by electroreduced cobalt chloride, in progress in this laboratory,[7] we undertook to scan other possibilities provided by this catalyst and decided to focus our attention on the synthesis of these 4-phenylquinoline derivatives. Thus, we wish to describe herein a new powerful tool for this purpose, consisting of the cobalt chloride-catalyzed electrochemical cross-coupling reactions of phenyl halides and 4-chloroquinoline derivatives.

First, we tried to define standard conditions for all electrolyses. A typical electrolysis medium was found to be a mixture of acetonitrile, dimethylformamide and pyridine in the presence of a catalytic amount of cobalt chloride. The presence of pyridine proved to be essential for the coupling reaction to occur providing the




**Scheme 1.**

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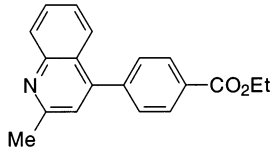
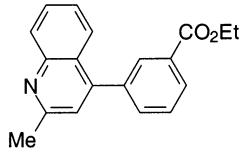
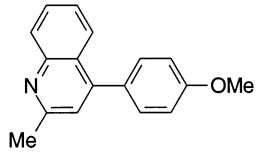
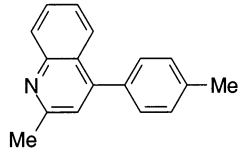
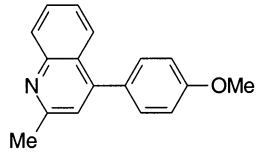
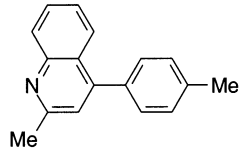
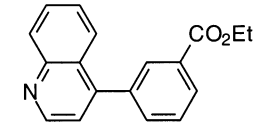
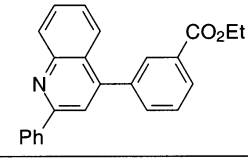
experimental evidence that DMF and MeCN were unable to stabilize electroreduced cobalt. Several attempts towards cross-coupling reactions between phenyl halides and 4-chloroquinoline derivatives were realized according to general conditions given in Scheme 1.

*Typical procedure*: The electrochemical cell,[8] fitted with an iron rod as the anode and a stainless steel grid as the cathode, was flushed with argon. Acetonitrile (40 ml), dimethylformamide (5 ml) and pyridine (5 ml) were added using a syringe. To the solution were added anhydrous cobalt chloride (2.6 mmol, 0.26 equiv.) and tetrabutylammonium tetrafluoroborate (0.2 g) in order to raise the conductivity of the electrolysis medium. The 4-chloroquinoline derivative (10 mmol, 1 equiv.) and the functionalized halogenobenzene (10–20 mmol, 1–2 equiv.) were added and a constant current intensity of 0.2 A was applied until complete disappearance of the

**Table 1.** Cobalt-catalyzed cross-coupling of phenyl halides with 4-chloroquinoline derivatives

| Entry | $FG^1$-Ph-X (mmole) | $FG^1$ = | $FG^2$ = | Coupling product | Compound | Isolated yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | $FG^1$-Ph-Br (15) | p-$CO_2$Et | Me |  | **1a** | 56 |
| 2 | $FG^1$-Ph-Br (15) | m-$CO_2$Et | Me |  | **1b** | 68 |
| 3 | $FG^1$-Ph-Br (12.5) | p-OMe | Me |  | **1c** | 60 |
| 4 | $FG^1$-Ph-Br (12.5) | p-Me | Me |  | **1d** | 50 |
| 5 | $FG^1$-Ph-I (12.5) | p-OMe | Me |  | **1c** | 68 |
| 6 | $FG^1$-Ph-I (20) | p-Me | Me |  | **1d** | 81 |
| 7 | $FG^1$-Ph-Br (10) | m-$CO_2$Et | H |  | **1e** | 48 |
| 8 | $FG^1$-Ph-Br (10) | m-$CO_2$Et | Ph |  | **1f** | 65 |

a : based on starting 4-chloro amine

starting 4-chloroamine had occurred (range 2000–4000 C). The mixture was then poured into 50 ml of a saturated ammonium chloride solution. After evaporation of acetonitrile under reduced pressure, sodium chloride was added to the aqueous layer, which was extracted with 3×100 ml diethyl ether. The organic layer was dried over magnesium sulfate and evaporated to dryness. The resulting oil was purified using silica gel chromatography with diethyl ether and pentane as the eluent to afford the analytically-pure 4-phenylquinoline derivative in 48–81% yield.[9]

It should be pointed out that the choice of an iron rod as the anode was of crucial importance for the efficiency of the electrochemical process. Indeed, the use of metallic rods other than an iron rod as the anode invariably led to failure. This observation clearly indicates that ferrous salts that are released during the electrolysis participate in the catalytic process. Nevertheless, it should be mentioned that in that case and contrary to the coupling of chloropyrimidines with aryl halides,[6] preelectrolyses furnishing $FeBr_2$ at the beginning of the electrolyses were not realized. The results are listed in Table 1.

It is worth noting that both electron donating and withdrawing groups (entries 1–4) allow coupling products to be obtained in satisfactory yields. These results can be slightly improved by using iodinated rather than brominated benzenes when an electron donating group is connected to the phenyl moiety (entries 5 and 6) but, in this case, increased amounts of the starting compound have to be used and lead to the rise of biaryl formation. This method can be extended to other aromatic amines than quinaldine. Indeed, 4-chloroquinoline (entry 7) and 4-chloro-2-phenylquinoline (entry 8) react in the same fashion providing the desired cross-coupling products in 48 and 65% yields, respectively.

In conclusion, we reported in this paper the efficient and versatile synthesis of rarely described 4-phenylquinoline derivatives. These compounds are obtained in satisfactory to high yields starting from commercially available compounds and using a particularly simple electrochemical procedure.

## Acknowledgements

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## References

1. Stanforth, S. P. *Tetrahedron* **1997**, *54*, 263–303.
2. Miayaura, N.; Yamagi, T.; Suzuki, A. *Synth. Commun.* **1981**, *11*, 513–519.
3. Ali, N. M.; McKillop, A.; Mitchell, M. B.; Rebelo, R. A.; Wallbank, P. J. *Tetrahedron* **1992**, *48*, 8117–8126.
4. Lohse, O.; Thevenin, P.; Waldvogel, E. *Synlett* **1999**, 45–48.
5. Gosmini, C.; Lasry, S.; Nédélec, J. Y.; Périchon, J. *Tetrahedron* **1998**, *54*, 1289–1298.
6. Gosmini, C.; Nédélec, J. Y.; Périchon, J. *Tetrahedron Lett.* **2000**, *41*, 201–203.
7. (a) Patent Application 99/08480, France, July 1, 1999. (b) Gosmini, C.; Rollin, Y.; Nédélec, J. Y.; Périchon, J. *J. Org. Chem.* **2000**, *65*, 6024–6026.
8. Troupel, M.; Rollin, Y.; Sock, O.; Meyer, G.; Périchon, J. *Nouv. J. Chim.* **1986**, *11*, 593–599.
9. Physical data for selected compounds. *4-(2-Methylquino-4-yl)benzoic acid ethyl ester* **1a**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 1.37 (t, $J=7$ Hz, 3H), 2.72 (s, 3H), 4.37 (q, $J=7$ Hz, 2H), 7.16 (s, 1H), 7.20–7.70 (m, 5H), 8.03 (d, $J=8.5$ Hz, 1H), 8.13 (d, $J=8$ Hz, 2H). $^{13}$C NMR($CDCl_3$, 50 MHz) $\delta$ (ppm): 14.33, 25.30, 61.11, 121.98, 124.56, 125.15, 125.96, 129.14, 129.48, 129.68, 130.37, 142.57, 147.29, 148.33, 158.40, 166.10. MS, $m/z$ (relative intensity): 291 (M, 100), 263 (M−28, 32), 246 (M−45, 45), 218 (M−73, 31). Analysis calcd for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81; O, 10.99. Found: C, 78.41; H, 5.91; N, 4.89; O, 10.90. *4-(4-Methoxyphenyl)quinaldine* **1c**: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ (ppm): 2.69 (s, 3H), 3.81 (s, 3H), 6.97 (d, $J=9$ Hz, 2H), 7.13 (s, 1H), 7.28–7.40 (m, 3H), 7.60 (t, $J=7.5$ Hz, 1H), 7.82 (d, $J=8$ Hz, 1H), 8.00 (d, $J=8$ Hz, 1H). $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ (ppm): 25.34, 55.29, 114.00, 122.12, 125.24, 125.61, 125.67, 129.06, 129.19, 130.36, 130.73, 148.16, 148.52, 158.44, 159.80. MS, $m/z$ (relative intensity): 249 (M, 100), 234 (M−15, 20), 206 (M−43, 12). Analysis calcd for $C_{17}H_{15}NO$: C, 81.92; H, 6.02; N, 5.62; O, 6.43. Found: C, 81.39; H, 5.98; N, 5.67; O, 6.47.