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Heteroatom-Guided, Palladium-Catalyzed Regioselective C–H Functionalization in the Synthesis of 3-Arylquinolines

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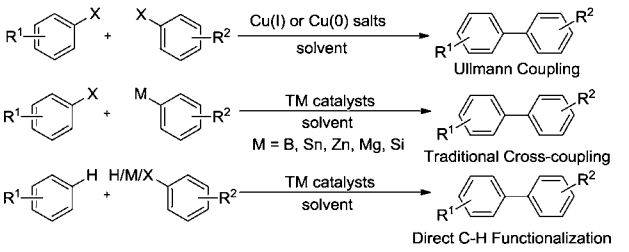
ABSTRACT

A new approach for the regioselective functionalization of the C-3-position of quinolines is described. The method utilizes heteroatom guided regioselective C-3 palladation followed by arylation via transmetalation with aryl boronic acids to yield 3-aryl-*N*-acyl-1,2-dihydroquinolines. In a one-pot sequence, *N*-deacylation followed by aromatization leads to important 3-arylquinolines in good yields.

Heteroatom-guided transition metal catalyzed C–H functionalization is one of the fastest developing tools in organic synthesis.[1−5] Regioselective direct arylation of substrates is an extremely important synthetic tool in organic transformations. Before the advances in C–H functionalization,[2] a few methods were available for direct arylation of arenes or heteroarenes. The usual approaches for (hetero)biaryl formation employed either Ullmann couplings or transition metal catalyzed cross-coupling reactions between aryl halides or pseudohalides (Ar-X) with aryl stannates, boronates, aryl zinc, magnesium, or silicon reagents (Ar-M) (Scheme 1) or via other homocoupling reactions.[6]

Scheme 1. Conventional Biaryl Synthesis



Quinolines are important constituents of several natural products possessing biological properties of high importance.[7] There are several methods for the synthesis of quinolines which have traditionally been used, including recent ones employing transition-metal catalysis. 3-Arylquinolines, in particular, are vital molecules in medicinal chemistry and have also been isolated from natural sources.[8] A recent report[8i] has brought out an extremely important aspect of biological activity of substituted 3-arylquinolines, several of which showed high activity against various human tumor cell lines and low cytotoxicity in the normal human liver cell line.

Of the methods available for the synthesis of 3-arylquinolines, one of the most frequently adopted methodologies

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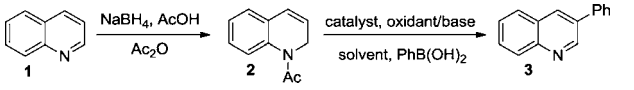
are the Suzuki or Stille cross-couplings of 3-haloquinolines with suitable coupling partners. This approach obviously needs prefunctionalization of the quinoline substrate and at times limits the utility. A recent report by Wang and co-workers utilized an iron-promoted tandem reaction of styrene oxides and anilines to yield 3-arylquinolines in good yields.[9] We report herein a new approach to 3-arylquinolines which utilizes a regioselective C−H functionalization via a heteroatom-guided palladation followed by transmetalation with arylboronic acids and in situ aromatization. The method has broad scope and results in good yields in almost all substrates. This method effectively amounts to a two-step arylation reaction of quinoline itself.

The starting material **2** for the C−H activation step was easily prepared from the parent quinoline via either $NaBH_4$ reduction and in situ acylation or via stepwise LAH reduction and *N*-acylation. A variety of conditions and combinations of catalyst systems and oxidants were screened for optimization of the reaction (Table 1). Under most of the reaction conditions attempted, C-3 arylation was the major isomer, with varying amounts of homocoupling product resulting from of the aryl boronic acid. Interestingly, the reaction under acidic conditions (entry 10, Table 1) resulted in minimum amount of homocoupling but also resulted in C-4 arylation as a minor product (C-3/C-4 arylation 3:2). The C−H functionalization at C-4 most probably resulted from a concerted metalation deprotonation (CMD) process. Of all the conditions screened, the best conditions for regioselective C-3 arylation were found to be $Pd(OAc)_2/Cu(OTf)_2/Ag_2O$ in toluene (entry 12, Table 1).

Table 1. Various Catalyst Systems Screened



entry	reaction conditions	yield (%)
1	$Pd(OAc)_2/Cu(OAc)_2\cdot H_2O$/THF/65 °C/24 h	trace
2	$Pd(OAc)_2$/AgOAc/Tol/110 °C/12 h	trace
3	$Pd(OAc)_2/Cu(OTf)_2/Ag_2O$/ Amyl−OH/80 °C/12 h	20
4	$Ni(acac)_2/Cu(OTf)_2/Ag_2O$/Tol/110 °C/12 h	homocoupling
5	$[Ru(p\text{-cymene})Cl_2]_2$/AgOAc/Xylene/110 °C/12 h	NR
6	$Pd(OAc)_2$/BQ/Ag_2O/Tol/110 °C/12 h	<10
7	$PdCl_2(PhCN)_2/Cu(OTf)_2/Ag_2O$/Tol/110 °C/12 h	
8	$Pd(O_2CCF_3)_2/Cu(OTf)_2/Ag_2O$/Tol/110 °C/12 h	81
9	$PdCl_2$(dppf)/$Cu(OTf)_2/Ag_2O$/Tol/110 °C/12 h	35
10	$Pd(OAc)_2/Cu(OTf)_2/Ag_2O$/TFA/74 °C/16 h	85% total yield (3:2 C3/C4 arylation)
11	$Pd(OAc)_2/K_2CO_3$/TFA/75 °C/30 h	trace
12	$Pd(OAc)_2/Cu(OTf)_2/Ag_2O$/Tol/110 °C/8 h	78

Under these conditions, the homocoupling of the arylboronic acid was the least and the formation of the parent quinoline **1** from *N*-acyl-1,2-dihydroquinoline **2** was minimal. The substrate scope of the reaction is depicted in Scheme 2.

The reaction sequence worked well on unsubstituted as well as substituted quinolines, leading to decent yields of substituted 3-arylquinolines.

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(6) For initial reports and extensive reviews in this area, see: (a) Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174–2185. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469. (d) Anastasia, L.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; pp 311−334. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (f) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205. (g) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (h) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35–41. (i) Campeau, L.-C.; Fagnou, K. *Chem. Soc. Rev.* **2007**, *36*, 1058–1068. (j) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013–3039. (k) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949–957. (l) McGlacken, G. P.; Bateman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447–2454. (m) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (n) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, *24*, 4087–4109. (o) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310. (p) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345.

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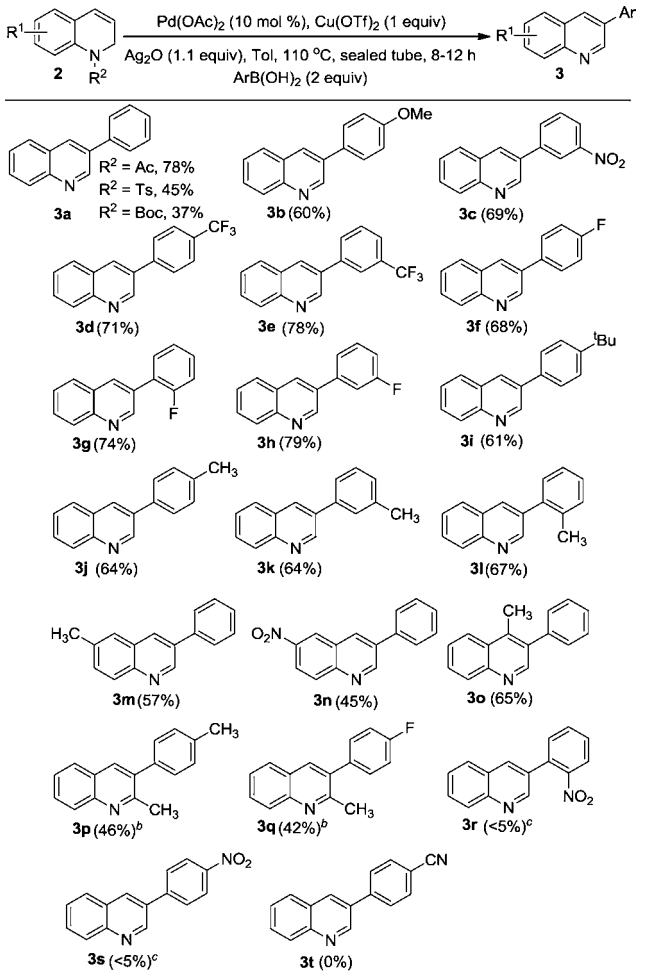
(9) Zhang, Y.; Wang, M.; Li, P.; Wang, L. *Org. Lett.* **2012**, *14*, 2206–2209.

Scheme 2. Substrate Scope[a]



[a] All yields are isolated yields, for R^2 = Ac. [b] An almost equal amount of unaromatized product was also obtained. [c] By GCMS, product not isolated.

In the case of some electron-deficient boronic acids (entries **3r**–**t**, Scheme 2), only protodeboronation products were obtained; the desired 3-arylquinolines were observed only in trace quantities. In all substrates, where the reaction worked well, the regioselectivity was excellent and C-3 arylation was the major product in all cases (Figure 1).[10]

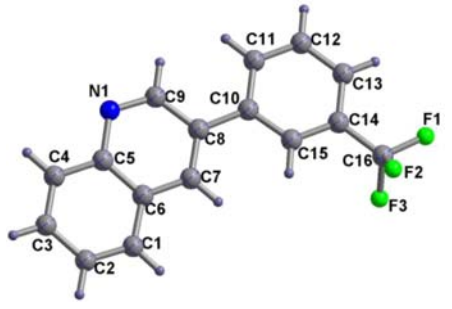
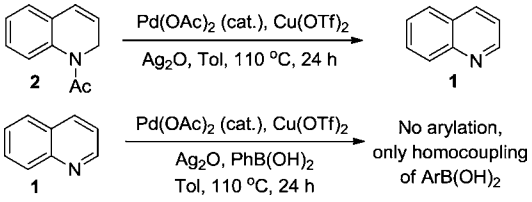


Figure 1. X-ray structure of **3e**.

Electron-rich as well as electron-neutral substituents on both the dihydroquinolines **2** as well as the arylboronic acids were well tolerated. The reaction worked well with fluoro-substituted arylboronic acids. In a few cases, upon prolonged heating, C-3 as well as C-4 arylation products (diarylation) were detected (~5–10%). In the case of 6-substituted dihydroquinolines, regioisomer (~6–13%) was also formed. These, however, could not be isolated in a pure form but were confirmed by NMR and GC-MS. In the case of 2-substituted quinolines, the N-deacylation and concomitant aromatization was very slow and the *N*-acyl-3-aryl-1,2-dihydroquioline was also obtained in considerable quantities (~50%) along with **3p** and **3q**.

Aromatization of **2** to give **1** was also detected in small quantities (~5%). The amount of **1** formed in the reaction was dependent on the reactivity of the arylboronic acid. In a control experiment, the reaction was run under the same conditions in absence of $ArB(OH)_2$ and it resulted in 85% of **1** after 24 h (Scheme 3). This shows that this reaction may be a slow process with the C–H functionalization being the faster one.

Scheme 3. Control Experiments



The arylation reaction also worked with *N*-Boc- or *N*-tosyldihydroquinolines; however, best yields were obtained with *N*-acetyldihydroquinolines.[11] In another experiment, the arylation was attempted on unprotected 1,2-dihydroquinoline, which resulted only in the total decomposition of the starting materials.

The C-3 arylation probably follows the pathway delineated in Scheme 4. The first step is the heteroatom-guided C-3-palladation followed by transmetalation with the arylboronic acid. Subsequent reductive elimination results in the arylation product. The Pd(0) is reoxidized by $Cu(OTf)_2$ with Ag_2O probably acting as the base as well as the oxidant. At this moment, the exact mechanism of deacylation and aromatization is not clear but may occur only after the C–H functionalization step.[12] This mechanism is currently under investigation. In another experiment (Scheme 3), the arylation was attempted on **1** and it resulted in no reaction at all, thereby indirectly proving that the C–H activation at C-3 is heteroatom-guided in **2** and that **1** is not an intermediate toward desired products.

(10) Crystal structure submitted to the Cambridge Cystallographic Data Centre, CCDC deposition no. CCDC 938845.

(11) The addition of arylboronic acid in small portions over a period of 3–5 h is essential for the suppression of the homocoupling reaction. See the Supporting Information for details.

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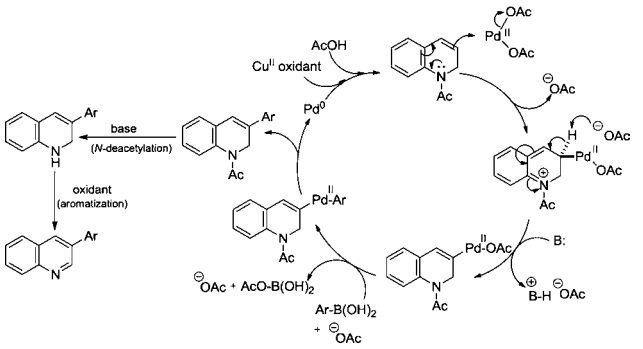
Scheme 4. Plausible Reaction Mechanism



In conclusion, we have developed a new approach to important 3-arylquinolines, utilizing heteroatom-guided regioselective C−H functionalization as the key step in the sequence. The approach is general and results in good yields in almost all substrates. This methodology requires no prefunctionalization of the quinoline for the coupling reaction and is completely different from previously reported approaches for the same class of compounds. The ease of this C−H functionalization reaction holds a promising outlook for its utility in organic synthesis.

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

The authors declare no competing financial interest.