Comparison of the Suzuki cross-coupling reactions of 4,7-dichloroquinoline and 7-chloro-4-iodoquinoline with arylboronic acids using phosphine-free palladium catalysis in water[1]

Richard W. Friesen and Laird A. Trimble

Abstract: 4,7-Dichloroquinoline (**1a**) and 7-chloro-4-iodoquinoline (**1b**) undergo Suzuki cross-coupling reactions with arylboronic acids catalyzed by phosphine-free palladium acetate in boiling water. Using phenylboronic acid (**2**), the reaction of **1a** provides 7-chloro-4-phenylquinoline (**3**) (78%) together with diphenylquinoline (**4**) (12%), while **1b** reacts in a much more regioselective fashion and provides **3** in 98% isolated yield. Although **1b** undergoes a more regioselective Suzuki reaction than **1a**, additional important observations are that the overall reaction of **1b** with **2** is three times slower than **1a** and that the reaction occurs in the absence of tetrabutylammonium bromide. Using optimized reaction conditions, a variety of aryl and vinylboronic acids undergo regioselective Suzuki cross-coupling with **1b** to provide the products **7**, **10**, and **11** in good to excellent yield.

Key words: palladium, cross-coupling, regioselectivity, quinolines, boronic acids.

Résumé : La 4,7-dichloroquinoléine (**1a**) et la 7-chloro-4-iodoquinoléine (**1b**) subissent des réactions de couplage de Suzuki avec les acides arylboroniques qui sont catalysées par de l'acétate de palladium sans phosphine dans de l'eau bouillante. Avec l'acide phénylboronique (**2**), la réaction du composé **1a** fournit la 7-chloro-4-phénylquinoléine (**3**) (78%) aux côtés de diphénylquinoléine (**4**) (12%) alors que le composé **1b** réagit d'une façon beaucoup plus régiosélective et fournit le composé **3** avec un rendement de 98% en produit isolé. Même si le composé **1b** donne lieu à une réaction de Suzuki plus régiosélective que celle du composé **1a**, des observations importantes additionnelles sont que la vitesse globale du composé **1b** avec **2** est trois fois plus lente que celle du composé **1a** et que la réaction se produit en l'absence de bromure de tétrabutylammonium. Utilisant des conditions réactionnelles optimisées, une variété d'acides aryl- et vinylboroniques donnent lieu à des réactions régiosélectives de couplage croisé de Suzuki avec le composé **1b** et elles fournissent les produits **7**, **10** et **11** avec des rendements allant de bons à excellents.

Mots clés : palladium, couplage croisé, régiosélectivité, quinoléines, acides boroniques.

[Traduit par la Rédaction]

Introduction

The palladium-catalyzed cross-coupling of aryl halides with boronic acids, commonly referred to as the Suzuki reaction (1–5), is an exceptionally versatile and highly utilized reaction for the construction of carbon-carbon bonds and, in particular, for the preparation of heterobiaryls. The use of heteroaryl chlorides as one of the coupling partners has seen increasing utility (6–11) and is attractive since the starting materials are often more readily available than the corresponding bromides or iodides. We have recently described (12) the synthesis of 2,4,7-trisubstituted quinoline 5-lipoxygenase inhibitors using, as one of the key steps, the regioselective Suzuki cross-coupling reaction of 4,7-dichloroquinoline (**1a**) with arylboronic acids. As originally described by Mitchell and co-workers (6), the reaction of **1a** with 1.1 equiv. of phenylboronic acid (**2**) catalyzed by $Pd(Ph_3P)_4$ (3%) in refluxing aqueous ethanol – benzene and in the presence of Na_2CO_3 provided, after 48 h, 7-chloro-4-phenylquinoline (**3**) in 82% isolated yield (Scheme 1). It was not mentioned whether the bis-addition product 4,7-diphenylquinoline (**4**) or the regioisomeric mono-addition product 4-chloro-7-phenylquinoline (**5**) were observed in this reaction.

We have repeated this Suzuki cross-coupling reaction between **1a** and **2** in connection with our medicinal chemistry program. Dichloride **1a** was consumed in 6 h, and in addition to **3** (81%), a significant amount of bis-addition product **4** (10%) was obtained. Previous reports have demonstrated that 4,7-dichloroquinoline (**1a**) undergoes regioselective palladium-catalyzed Stille (13) and alkoxycarbonylation (14)

Received 7 July 2003. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 20 January 2004.

This paper is dedicated to Professor Ed Piers for his many contributions to synthetic organic chemistry and to the chemistry community in Canada.

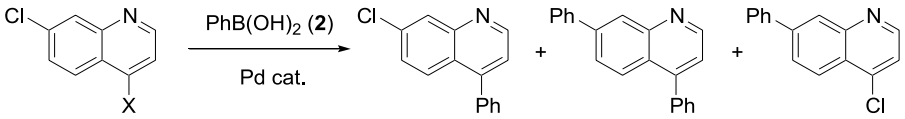
R.W. Friesen[2] and L.A. Trimble. Department of Medicinal Chemistry, Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Hwy., Kirkland, QC H9H 3L1, Canada.

[1]This article is part of a Special Issue dedicated to Professor Ed Piers.

[2]Corresponding author (e-mail: rick_friesen@merck.com).

 doi: 10.1139/V03-187

Scheme 1.



1a X = Cl
1b X = I

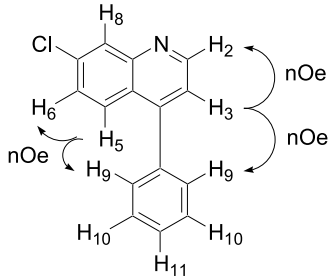
3 **4** **5**

reactions at the C4 position. However, in the latter reaction, alkoxycarbonylation at both C4 and C7 produces varying amounts of diester, depending on the reaction conditions used. Therefore, the observation of **4** in the reaction of **1a** and **2** was not completely unexpected. Since we required an efficient cross-coupling procedure that would bring about regioselective monofunctionalization of a quinoline (6, 7, 13–17), such as **1a**, without consuming more elaborate boronic acids by the production of bis-addition products, we undertook a more detailed study of the reactions of **1a** and the corresponding iodide **1b** to optimize the formation of **3**. The results of this study are presented here.

Results and discussion

Structural assignment

In their initial publication (6), Mitchell and co-workers assigned regioisomer **3** as the product of the Suzuki cross-coupling reaction between **1a** and **2**. This assignment was made without any structural verification, although one might reasonably expect **3** to be produced as the major regioisomer based on precedence with other reactions of **1a** (13, 14, 18). However, we felt that a rigorous structural assignment was warranted since the production of the bis-addition adduct **4** reveals that reactivity at both C4 and C7 is possible. ^{1}H NMR experiments ($CDCl_3$, 600 MHz) indicated that **3** is indeed the predominant mono-substituted regioisomer formed. Thus, proton resonance assignments (see Table 1) were made using a 2D-COSY experiment.[3] In a subsequent series of nuclear Overhauser enhancement (nOe) experiments, clear enhancements in resonance intensity were observed for H9 upon irradiation of H3 and H5, while irradiation of H8 did not result in nOe of any other resonance.



3

Reaction optimization studies

To optimize the reaction of **1a** for mono-substitution at C4, we rapidly surveyed many of the reaction conditions that are typically modified in the Suzuki cross-coupling reaction (1–5), including, for example, the palladium catalyst ($PdCl_2(Ph_3P)_2$, $Pd_2(dba)_3$ (with and without P(*t*-Bu)$_3$), Pd(dppf)Cl_2), solvents (DMF, THF, EtOH), aqueous base (Na_2CO_3, Cs_2CO_3), temperature, and the use of additives (KF). None of these changes substantially altered the yields of **3** and **4** that were observed upon reaction of **1a** with **2**. Several reports over the last decade have described the successful cross-coupling of arylboronic acids and aryl bromides, iodides, or triflates using phosphine-free palladium, such as $Pd(OAc)_2$, in aqueous–organic co-solvents (19, 20) or in water alone (21, 22). Employing reaction conditions optimized by Leadbeater and Marco (22), the reaction of **1a** with 1.1 equiv. of **2** in the presence of 1% $Pd(OAc)_2$ and 0.25 equiv. of nBu$_4$NBr in refluxing water (oil bath at 150 °C) under nitrogen atmosphere provided **3** (78%) and **4** (12%) upon consumption of **1a**. Although this reaction differed little from all the others we had surveyed in terms of the yields of the two products, it was complete within 30 min (Table 2, entry 1), while the majority of the others, including the original reaction described by Mitchell, required extended reaction times (6 h to 2 days). Since the rapidity of the reaction under these conditions was perceived as an advantage, we chose to further characterize the cross-coupling reaction of **1a** using phosphine-free palladium in water.

The results of the two experiments are informative. First, when the reaction between **1a** and **2** was stopped prior to consumption of **1a** (at 15 min), we observed the presence

Table 1. 7-Chloro-4-phenylquinoline (**3**): ^{1}H NMR spectrum and nOe experiments.

Proton[a]	Assignment[b]	nOe observed[c]
H_2	8.94 (d, J = 4.4 Hz)	H_3
H_3	7.34 (d, J = 4.4 Hz)	H_2, H_9
H_5	7.86 (d, J = 9.2 Hz)	H_6, H_9
H_6	7.45 (dd, J = 2.1 9.2 Hz)	
H_8	8.17 (d, J = 2.1 Hz)	None
H_9	7.48 (m)	
H_{10}, H_{11}	7.50–7.56 (m)	

Note: Spectra obtained in $CDCl_3$ at 600 MHz.
[a]See structure **3** for proton labeling.
[b]Resonances reported in ppm (δ) with multiplicity and coupling constants in parentheses.
[c]In an nOe experiment, irradiation of the resonance assigned to the proton in column 1 results in an enhancement in intensity of the listed proton resonances.

[3]This spectrum is available as supplementary material. Supplementary data may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0S2, Canada (http://www.nrc.ca/cisti/irm/unpub_e.shtml for information on ordering electronically).

Table 2. $Pd(OAc)_2$-catalyzed coupling reactions of **1a** and **1b** with phenylboronic acid **2**.

Entry	Substrate	equiv. $PhB(OH)_2$ (**2**)	Additive	Time (min)	Yield **3** (%)	Yield **4** (%)
1	**1a**	1.1	nBu$_4$NBr	30	78	12
2	**1a**	2.2	nBu$_4$NBr	60	72	24
3	**1b**	1.1	nBu$_4$NBr	90	98	0.2
4	**1b**	1.1	nBu$_4$NBr	180	85	12
5	**1a**	1.1	nBu$_4$NI	90	73	13
6	**1b**	1.1	None	30	97	Trace[a]
7	**1a**	1.1	None	10	83	10
8	**1b**	1.02	None	45	96	0.7
9[b]	**1b**	1.02	None	150	96	0.3
10[c]	**1b**	1.02	None	420	95	Trace[a]

Note: Reaction conditions: 1.0 equiv. **1**, 1.02–2.2 equiv. **2**, 1% $Pd(OAc)_2$, 0.25 equiv. additive, 1.0 equiv. Na_2CO_3, H_2O (1 mL/mmol **1**), bath temperature 150 °C.

[a]Observed by TLC but not isolated.

[b]0.1% $Pd(OAc)_2$.

[c]0.01% $Pd(OAc)_2$.

of minor amounts of the regioisomeric mono-addition product 4-chloro-7-phenylquinoline **5** (isolated as an inseparable mixture with **3** and identified by ^{1}H NMR spectroscopy). Second, using excess phenylboronic acid (2.2 equiv.), the yield of **4** could be increased to 24% (Table 2, entry 2). These observations suggest that although the aryl chloride at C4 is more reactive than the C7 aryl chloride, the latter is sufficiently reactive that the bis-addition product **4** can be derived from the initial reaction at either C4 or C7, followed by a second coupling, which is competitive with the first. Owing to the inherent reactivity of the two chlorides, it was expected that it would be difficult to identify reaction conditions for **1a** that would eliminate cross-coupling at C7 and provide **3** exclusively.

Thus, we turned our attention to the reactions of 7-chloro-4-iodoquinoline (**1b**) (15, 18). Since the order of reactivity of aryl halides in the Suzuki cross-coupling reaction is generally accepted to be I > Br >> Cl (1–5), it was thought that introduction of a C4-iodide might enhance the inherent C4 regioselectivity by virtue of the additional chemoselectivity that would be imparted by the more reactive iodide.

The difference in the reactivity of the two dihaloquinolines **1a** and **1b** was clearly seen upon monitoring the time course of their reactions with **2** (1.1 equiv. **2**, 0.25 equiv. nBu$_4$NBr, 1% $Pd(OAc)_2$, 1 equiv. Na_2CO_3, H_2O, reflux) by ^{1}H NMR spectroscopy. At suitable time points, aliquots of each reaction mixture were removed and analyzed for **1a** or **1b**, **3**, **4**, and **5** by the integration of characteristic and well-separated proton resonances (see Experimental section). The data are plotted in Figs. 1 and 2 for the reactions of **1a** and **1b**, respectively. In Fig. 1, it is clearly seen that **3**, **4**, and **5** were formed throughout the time-course of the reaction. When the starting material **1a** was consumed at 30 min, the reaction mixture was composed of **3** and **4** in a ratio of approximately 9:1. In contrast, the reaction of **1b** with **2** (Fig. 2) revealed that **3** was the only product formed until starting material was consumed (at 1.5 h), after which time the bis-addition product **4** was produced at the expense of **3**. The regioisomeric mono-adduct **5** was not observed in this latter reaction. Of note, and somewhat surprising, is the fact that the dramatic improvement in regioselectivity observed with **1b** (compared with **1a**) occurs at an overall reaction rate that is three times slower than that of **1a** (1.5 h vs. 30 min).

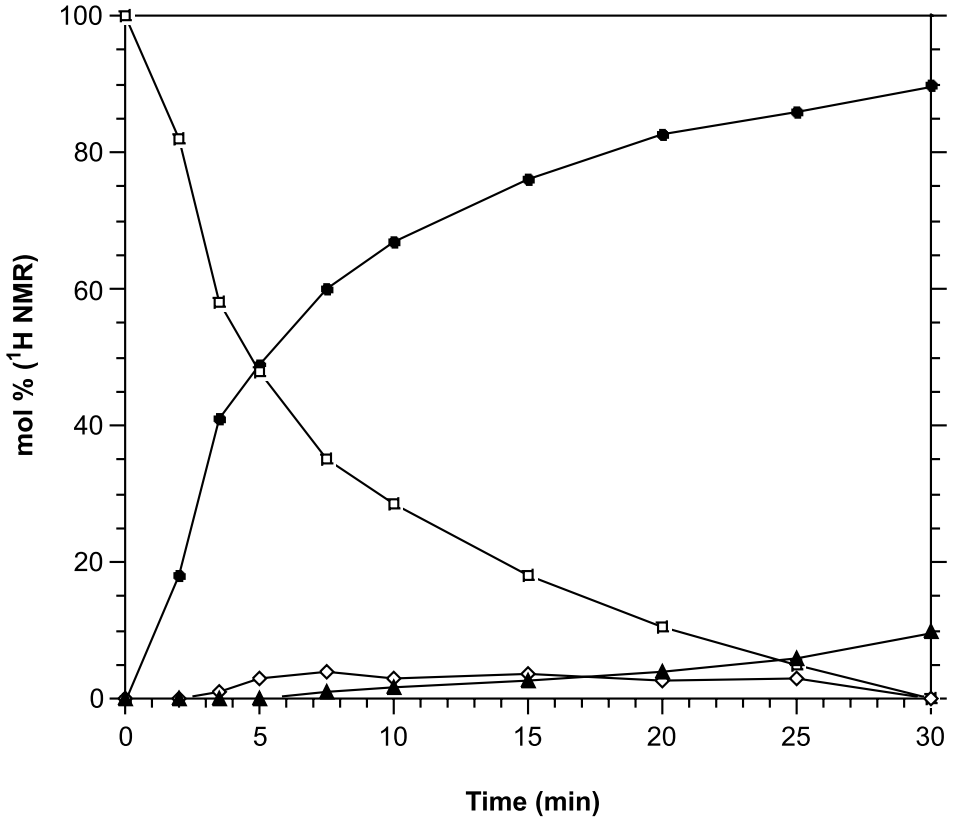
A subsequent reaction of **1b** with 1.1 equiv. of **2** under the conditions described above provided **3** (98%) and **4** (0.2%) upon consumption of **1b** at 1.5 h (Table 2, entry 3). However, if the reaction was allowed to progress for 3 h, the yield of **4** increased to 12% at the expense of **3** (85%) (Table 2, entry 4). These observations are consistent with the results shown in Fig. 2.

Subjection of **1b** and **2** to the reaction conditions originally described by Mitchell also provided **3** (93%) as the sole product upon consumption of **1b** (24 h), suggesting that the regioselectivity observed in the Suzuki reactions of **1b** is not limited to reactions catalyzed by phosphine-free palladium in water but is inherent to the reactivity of **1b**. Similarly, the overall rate of reaction of **1b** is approximately three times slower than that of **1a** under the Mitchell conditions (see introduction), suggesting that the solely aqueous conditions do not significantly impact the relative overall rates of reaction of **1a** and **1b**.

Thus, the cross-coupling reaction of the chloro-iodide **1b** catalyzed by phosphine-free $Pd(OAc)_2$ in water is slower but more regioselective than the dichloride **1a**. The difference in reactivity was further exemplified by the results obtained from conducting a competition experiment between **1a** and **1b** for phenylboronic acid (**2**) (1.0 equiv. of each of the quinolines and 1.02 equiv. of phenylboronic acid) using 1% $Pd(OAc)_2$ (Scheme 2). After 2 h, only the chloro-iodide **1b** was consumed to afford **3** (97%), and the dichloride **1a** was recovered in good yield (93%).

The differences that are observed in the reaction regioselectivity and overall reaction rate of **1a** and **1b** are readily rationalized. First, the regioselectivity of each reaction is reflective of the rate of irreversible oxidative addition of Pd(0) (generated from Pd(2+) and phenylboronic acid (19, 23)) to the C4 and C7 aryl halide bonds. In the case of dichloride **1a**, although the reactivity of the two chlorides is in the order C4—Cl > C7—Cl, the C7—Cl is of sufficient reactivity that the bis-addition product **4** derives from the initial reaction at either site, followed by a second coupling

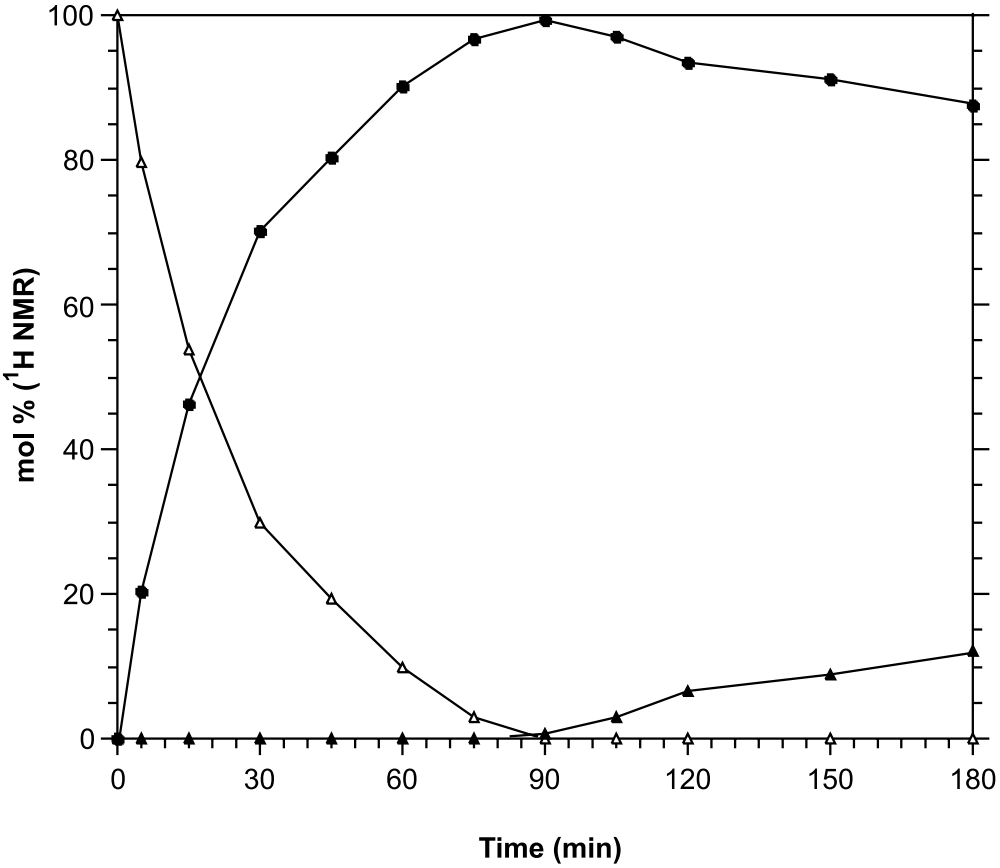
Fig. 1. Time course of the $Pd(OAc)_2$-catalyzed coupling reaction of **1a** and **2**. The mol% of **1a** (□), **3** (●), **4** (▲), and **5** (◇), as measured by ^1H NMR spectroscopy (see Experimental section), are represented as a function of time.



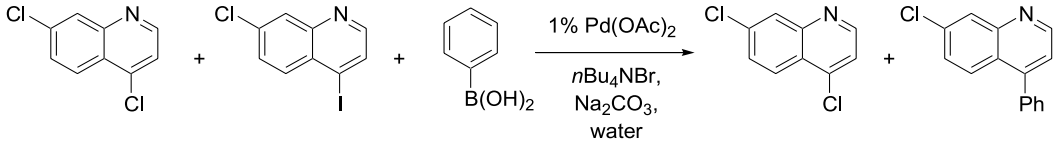
that is competitive with the first. For chloro-iodide **1b**, the difference in reactivity between C4—I and C7—Cl is > 100:1 (Table 2, entry 3). This chemoselectivity dictates that the bis-addition product **4** is produced only when the starting material is essentially completely consumed (see Fig. 2). Second, the more rapid overall reaction of **1a** compared with **1b** suggests that the oxidative addition step is not rate limiting in the overall catalytic cycle of **1b**. In contrast to those Suzuki reactions, in which the oxidative addition step is rate determining (leading to the typical ordering of overall reactivity I > Br >> Cl (1–5)), here transmetalation of the aryl-Pd-I species that is derived from **1b** appears to be rate determining. There are previous reports suggesting that transmetalation, rather than oxidative addition, can be rate determining in Suzuki cross-coupling reactions using both phosphine-free (21) and phosphine-ligated palladium catalysts (24, 25). Subtle differences in reaction conditions also have a dramatic impact on the mechanism since both oxidative addition (19) and transmetalation (21) steps have been found to be rate determining when using ligandless palladium catalysts. Thus, even though **1b** undergoes a rapid, irreversible, and chemoselective oxidative addition of Pd(0) to the aryl iodide bond at C4 (which results in very high regioselectivity compared with **1a**), the decreased rate of transmetalation results in the overall rate of reaction of chloro-iodide **1b** becoming slower than that of dichloride **1a** (note that the rate-determining step in the overall catalytic cycle of **1a** may be the oxidative addition or transmetalation steps). In addition, in spite of the fact that the overall rate of cross-coupling of **1a** is more rapid than **1b**, the highly chemoselective, rapid, and irreversible oxidative addition of Pd(0) to **1b** rationalizes the selective consumption of **1b** over that of **1a** in the competition experiment outlined in Scheme 2. Similar observations were made by Fu and co-workers (25) in their study of the Suzuki cross-coupling reactions catalyzed by $Pd_2(dba)_3$–$P(t\text{-}Bu)_3$. In these examples, the cross-couplings of aryl bromides with phenylboronic acid proceeded more rapidly than the corresponding aryl iodides, and in competition experiments analogous to those outlined in Scheme 2, only the aryl iodides underwent cross-coupling.

Another interesting observation was made when the cross-coupling reaction of **1a** and **2** was conducted in the presence of 0.25 equiv. $n\text{Bu}_4\text{NI}$ rather than $n\text{Bu}_4\text{NBr}$ (compare Table 2, entries 1 and 5). This modification had little effect on the isolated yield of **3** (73%) and **4** (13%), but the reaction now required 1.5 h to reach completion, similar to the rate that was observed using **1b** and $n\text{Bu}_4\text{NBr}$ (Table 2, entry 3). The presence of ammonium salts (21, 26) and the variation of halides (27–29) have been shown to have profound effects on the rate and mechanism of palladium-catalyzed processes in general. Although the reason behind this rate change is not completely understood, one can simplistically speculate that the aryl-Pd-Cl intermediate (formed upon reaction of **1a** with Pd(0)) is converted to aryl-Pd-I in the presence of $n\text{Bu}_4\text{NI}$ (the bond strength for palladium halides is Pd—Cl < Pd—Br < Pd—I (30, 31)). The reaction regioselectivity would still be governed by the relative rate of oxidative addi-

Fig. 2. Time course of the $Pd(OAc)_2$-catalyzed coupling reaction of **1b** and **2**. The mol% of **1b** (△), **3** (●), and **4** (▲), as measured by ^1H NMR spectroscopy (see Experimental section), are represented as a function of time.



Scheme 2.



1a (1.0 equiv.) **1b** (1.0 equiv.) **2** (1.02 equiv.) **1a** (93%) **3** (97%)

tion of Pd(0) to the aryl chlorides at C4 and (or) C7, but the overall rate would depend on the transmetalation of phenylboronic acid (**2**) to the aryl-Pd-I intermediate.

Since **1b** displays superb C4-regioselectivity and provides **3** in excellent yield upon reaction with **2**, we set out to further characterize the cross-coupling reactions of **1b** using **2** as substrate (Table 2, entries 6–10). Surprisingly, when the nBu$_4$NBr additive was removed (Table 2, entry 6), **1b** was consumed within 30 min, a threefold increase in overall rate. The yield of **3** (97%) was not affected. A similar observation of threefold rate enhancement in the absence of nBu$_4$NBr was made, using **1a** as substrate (Table 2, entry 7). These observations are surprising since they are in contrast to literature data (21), which suggest that nBu$_4$NBr is required for successful Suzuki cross-couplings using phosphine-free $Pd(OAc)_2$ in water. It may further imply a possible change in mechanism between the two reaction conditions (27, 28). The yield of **3** (96%) was not affected by decreasing the amount of phenylboronic acid (**2**) from 1.1 to 1.02 equiv. (Table 2, entry 8). This seemingly minor modification is important, since the reaction of **1b** still proceeds to completion, but monitoring for the disappearance of starting material **1b** becomes unnecessary. Recall that monitoring for the disappearance of starting material **1b** is necessary when using 1.1 equiv. of **2** since prolongation of the reaction after consumption of starting material (from 1.5 to 3 h) results in a significant increase in the formation of **4** (Table 2, entries 3 and 4). Finally, although the amount of $Pd(OAc)_2$ used can be decreased from 1% to 0.01%, this reduction in catalyst loading occurs with a corresponding increase in the time required for the reaction to reach completion (Table 2, entries 9 and 10).

Reaction scope

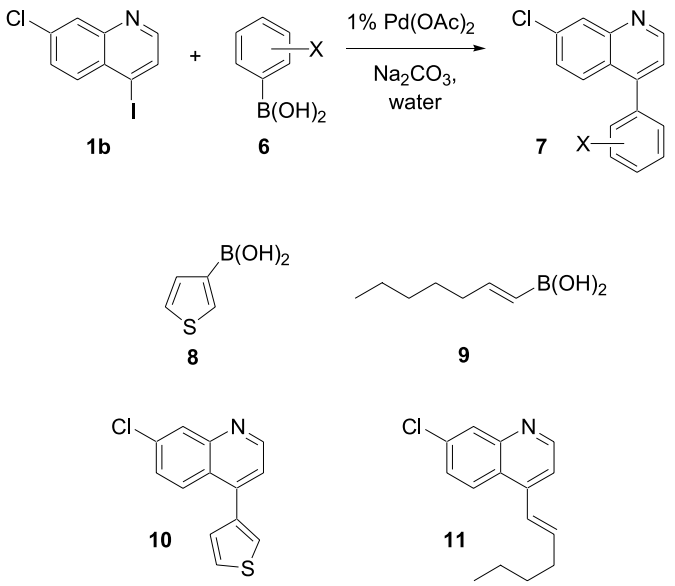
As illustrated in Scheme 3 and Table 3 (entries 1–14), reaction of **1b** using the optimized reaction conditions (A: 1.0 equiv. **1b**, 1.02 equiv. **6** or **8** or **9**, 1% $Pd(OAc)_2$, 1.0 equiv. Na_2CO_3, H_2O (1 mL/mmol **1b**), bath temperature 150 °C) with a variety of boronic acids afforded the expected products **7**, **10**, and **11** in good to excellent yields (84%–97%) without observation of the corresponding bis-addition prod-

Table 3. Palladium-catalyzed coupling reactions of **1b** with arylboronic acids **6**, **8**, and **9**.

Entry	Boronic acid	X	Reaction conditions[a]	Time (min)	Product	Yield (%)[b]
1	**2**	—	A	45	**3**	96
2	**6a**	2-Me	A	15	**7a**	93
3	**6b**	2-OMe-5-Me	A	150	**7b**	91[c]
4	**6c**	2-Cl	A	150	**7c**	58 (85)
5	**6d**	3-F	A	35	**7d**	97
6	**6e**	3-NHAc	A	120	**7e**	76 (84)
7	**6f**	3-CN	A	150	**7f**	88[c]
8	**6g**	4-F	A	30	**7g**	96
9	**6h**	4-OMe	A	60	**7h**	97
10	**6i**	4-Ac	A	90	**7i**	89[c]
11	**6j**	3-F-4-OBn	A	60	**7j**	93
12	**6k**	2,6-diMe	A	120	**7k**	0
13	**8**		A	90	**10**	89[c]
14	**9**		A	15	**11**	95
15	**6c**	2-Cl	B	2880	**7c**	43 (79)
16	**6g**	4-F	B	1440	**7g**	94

[a]Reaction conditions. A: 1.0 equiv. **1b**, 1.02 equiv. **6** or **8** or **9**, 1% $Pd(OAc)_2$, 1.0 equiv. Na_2CO_3, H_2O (1 mL/mmol **1b**), bath temperature 150 °C. B: 1.0 equiv. **1b**, 1.1 equiv. **6**, 3% $Pd(Ph_3P)_4$, 1.5 equiv. aq Na_2CO_3 (2 mol/L), benzene (3 mL/mmol **1b**), ethanol (0.3 mL/mmol **1b**), reflux.
[b]Isolated yield of purified compound. Yield in parentheses based on unrecovered starting material **1b**.
[c]A trace of starting material observed by TLC.

Scheme 3.



ucts analogous to **4**. Degassing of the water (19, 21) is not required for a successful cross-coupling reaction.

The range of arylboronic acids **6** that serve as suitable coupling partners include those bearing electron donating and withdrawing substituents at the *ortho*-, *meta*-, and *para*-positions. 3-Thienylboronic acid **8** (Table 3, entry 13) and (*E*)-1-hexenylboronic acid **9** (Table 3, entry 14) are also suitable substrates. Typically, these reactions are complete within 1 h, but there are some exceptions. No reaction is observed after 2 h when using the sterically encumbered 2,6-dimethylphenylboronic acid (**6k**) (Table 3, entry 12). In several other examples, the reactions do not proceed to completion even after 2.5 h, as evidenced by the observation (TLC) or isolation of starting material **1b**. In each of these examples, the black precipitate that signals the completion of the reaction (and which is typically seen with those substrates that do consume all of **1b**) is not produced even if additional arylboronic acid or palladium catalyst is added. For several cases, the quantity of residual **1b** is minor (not isolated), and products **7** are obtained in yields over 88% (Table 3, entries 3, 7, 10, 13). In two cases (Table 3, entries 4 and 6), significant amounts of **1b** remain, although yields of **7** based on recovered starting material are still good. There does not appear to be any correlation between the steric or electronic nature of the substituent on the arylboronic acid and the extent of consumption of **1b**. Since these reactions are heterogeneous and take place in the absence of organic co-solvent, it is possible that the aqueous solubility or some other physical property of the boronic acid substrates may be responsible for these observed differences. However, this cannot be the sole explanation. Reactions of two representative arylboronic acids (**6c** and **6g**) with **1b** were conducted under the biphasic Mitchell reaction conditions ($Pd(Ph_3P)_4$, aqueous ethanol – toluene) for comparison purposes, and the reactivity patterns observed are similar to those observed under the phosphine-free palladium conditions in water (compare Table 3, entries 4 and 15, and 8 and 16, respectively). In the case of **6g**, **7g** was obtained in good yield (94%), but the reaction was complete after only 24 h. In the case of **6c**, a significant amount of starting material remained after an extended reaction time (2 days).

We have demonstrated that 7-chloro-4-iodoquinoline (**1b**) undergoes highly regioselective Suzuki cross-coupling reactions at C4 with a variety of boronic acids (aryl and vinyl), catalyzed by phosphine-free palladium in water solvent in the absence of nBu$_4$NBr. The regioselectivity that is observed is superior to that observed with the dichloride **1a**, but the overall reaction rate of **1b** is three times slower than **1a** (using phenylboronic acid). These results can be inter-

preted by considering that transmetalation of the intermediate aryl-Pd-I species, rather than the formation of this species by the rapid and chemoselective oxidative addition of Pd(0) to **1b**, is the rate-determining step in the overall catalytic cycle of **1b**.

Experimental section

All reagents were obtained from commercial suppliers except **1b**, which was prepared from **1a** and aqueous HI (57%) as described (15, 18). Melting points are uncorrected. FT-IR spectra were recorded as solutions in chloroform unless stated otherwise, and wavenumbers (ν) are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded as solutions in acetone-d_6, unless stated otherwise, at field strengths of 400 MHz (^1H) or 100 MHz (^{13}C). Chemical shifts are reported in parts per million (ppm) relative to the signals of residual protonated solvent as internal standard. ^{13}C NMR spectra were acquired with proton decoupling, and peak multiplicities refer to J_{CF}. Elemental analyses were performed at the Laboratoire d'Analyse Élémentaire in the Department of Chemistry, Université de Montréal, Montréal.

Reactions for Figs. 1 and 2

A mixture of **1a** (1.00 g, 5.04 mmol) (Fig. 1) or **1b** (1.46 g, 5.04 mmol) (Fig. 2), phenylboronic acid (**2**) (97%, 647 mg, 1.02 equiv.), nBu$_4$NBr (406 mg, 0.25 equiv.), $Pd(OAc)_2$ (11 mg, 0.01 equiv.), Na_2CO_3 (2.5 mL of a 2 mol/L solution, 1.0 equiv.), and water (2.5 mL) was placed in a 50 mL round-bottom flask under a nitrogen atmosphere and immersed in an oil bath at 150 °C. After the time intervals indicated in the figures, a small aliquot of the reaction mixture was removed and dissolved in ethyl acetate. The mixture was dried ($MgSO_4$), filtered, and concentrated. The crude residue was analyzed by ^1H NMR spectroscopy. One or more of the following characteristic resonances were integrated, and for each compound present, the mol% composition of the sample was calculated. **1a**: 7.74 (d, 1H), 7.78 (dd, 1H), 8.30 (d, 1H), 8.89 (d, 1H); **1b**: 7.75 (dd, 1H), 8.20 (d, 1H), 8.53 (d, 1H); **3**: 7.37 (d, 1H), 7.86 (d, 1H), 8.11 (d, 1H), 8.92 (d, 1H); **4**: 8.02 (d, 1H, J = 8.8 Hz), 8.39 (d, 1H), 8.99 (d, 1H); **5**: 8.34 (d, 1H), 8.36 (d, 1H), 8.87 (d, 1H). The resulting data were used to generate Figs. 1 and 2.

Competition experiment (Scheme 2)

A mixture of **1a** (1.00 g, 5.04 mmol), **1b** (1.46 g, 5.04 mmol), phenylboronic acid (**2**) (97%, 647 mg, 1.02 equiv.), nBu$_4$NBr (406 mg, 0.25 equiv.), $Pd(OAc)_2$ (11 mg, 0.01 equiv.), Na_2CO_3 (2.5 mL of a 2 mol/L solution, 1.0 equiv.), and water (2.5 mL) was placed in a 50 mL round-bottom flask under a nitrogen atmosphere and immersed in an oil bath at 150 °C. After stirring for 2 h, the mixture was cooled to room temperature; water (50 mL) was added, and the mixture was extracted twice with ethyl acetate (50 mL). The combined organics were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash column chromatography (SiO_2, eluting with hexane–ether 4:1 volume fraction) to provide **1a** (927 mg, 93%) as a white solid and **3** (1.17 g, 97%) as a white solid.

Typical procedure (Table 3)

A mixture of **1b** (1.46 g, 5.04 mmol), phenylboronic acid **2** (97%, 647 mg, 1.02 equiv.), $Pd(OAc)_2$ (11 mg, 0.01 equiv.), Na_2CO_3 (2.5 mL of a 2 mol/L solution, 1.0 equiv.), and water (2.5 mL) was placed in a 50 mL round-bottom flask under a nitrogen atmosphere and immersed in an oil bath at 150 °C. After stirring for 45 min, the mixture was cooled to room temperature; water (50 mL) was added, and the mixture was extracted twice with ethyl acetate (50 mL). The combined organics were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was subjected to flash column chromatography (SiO_2, eluting with hexane–ether 3:1 volume fraction) to provide **3** (1.16 g, 96%) as a white solid and **4** (9 mg, 0.7%) as a white solid (Table 2, entry 8 and Table 3, entry 1).

7-Chloro-4-phenylquinoline (3)

mp 73 to 74 °C (lit. (6) value mp 73.5–74.5 °C). ^1H NMR δ: 7.37 (d, 1H, J = 4.4 Hz), 7.47–7.58 (m, 6H), 7.86 (d, 1H, J = 9.0 Hz), 8.11 (d, 1H, J = 2.1 Hz), 8.92 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 122.1, 125.4, 127.7, 127.9, 129.0, 129.1, 129.2, 129.9, 134.9, 137.8, 148.5, 149.6, 151.7.

4,7-Diphenylquinoline (4)

mp 128 to 129 °C. IR: 3023. ^1H NMR δ: 7.44 (d, 1H, J = 4.3 Hz), 7.48 (m, 1H), 7.54–7.63 (m, 7H), 7.88 (m, 2H), 7.93 (dd, 1H, J = 1.9, 8.8 Hz), 8.02 (d, 1H, J = 8.8 Hz), 8.39 (d, 1H, J = 1.8 Hz), 8.99 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 122.1, 126.4, 126.8, 127.1, 128.1, 128.8, 129.3, 129.5, 129.9, 130.3, 138.8, 140.7, 142.4, 148.8, 150.1, 151.5. Anal. calcd. for $C_{21}H_{15}N$: C 89.65, H 5.37, N 4.98; found: C 89.47, H 5.38, N 4.99.

The remainder of the examples cited in Table 3 were prepared on the same scale in a manner similar to **3**, with reaction times as listed in the table. The eluting solvents used for column chromatography are indicated below.

7-Chloro-4-(2-methylphenyl)quinoline (7a)

Chromatography (hexane–ether 4:1 volume fraction) provided **7a** as a white solid (1.19 g, 93%), mp 86 to 87 °C. IR: 3017. ^1H NMR δ: 2.07 (s, 3H), 7.26 (d, 1H, J = 7.5 Hz), 7.36–7.49 (m, 5H), 7.55 (dd, 1H, J = 2.1, 9.0 Hz), 8.15 (d, 1H, J = 2.1 Hz), 9.00 (d, 1H, J = 4.3 Hz). ^{13}C NMR δ: 19.6, 122.4, 126.1, 126.4, 127.8, 128.1, 129.0, 129.1, 129.8, 130.7, 135.0, 136.1, 137.3, 148.5, 149.4, 151.9. Anal. calcd. for $C_{16}H_{12}ClN$: C 75.74, H 4.77, N 5.52; found: C 75.67, H 4.78, N 5.55.

7-Chloro-4-(2-methoxy-5-methylphenyl)quinoline (7b)

Chromatography (hexane – ethyl acetate 6:1 volume fraction) provided **7b** as a white solid (1.30 g, 91%), mp 133 to 134 °C. IR: 2961, 1502, 1250. ^1H NMR δ: 2.35 (s, 3H), 3.69 (s, 3H), 7.12 (m, 2H), 7.34 (dd, 1H, J = 1.8, 8.4 Hz), 7.39 (d, 1H, J = 4.4 Hz), 7.50 (dd, 1H, J = 2.2, 9.0 Hz), 7.62 (d, 1H, J = 9.0 Hz), 8.10 (d, 1H, J = 2.2 Hz), 8.95 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 20.4, 55.8, 112.2, 123.3, 126.7, 127.6, 129.1, 129.3, 130.8, 131.5, 132.2, 135.0, 146.9, 149.7, 152.2, 155.6. Anal. calcd. for $C_{17}H_{14}ClNO$: C 71.96, H 4.97, N 4.94; found: C 71.96, H 5.04, N 4.86.

7-Chloro-4-(2-chlorophenyl)quinoline (7c)

Chromatography (hexane – ethyl acetate 6:1 volume fraction) provided **1b** (466 mg, 32%) and **7c** as a white solid (803 mg, 58%), mp 89 to 90 °C. IR: 2976. ^{1}H NMR δ: 7.43 (d, 1H, J = 4.4 Hz), 7.44 (dd, 1H, J = 1.8, 7.3 Hz), 7.49–7.59 (m, 4H), 7.64 (dd, 1H, J = 1.4, 7.8 Hz), 8.16 (d, 1H, J = 1.8 Hz), 9.02 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 122.7, 125.6, 127.8, 128.0, 129.0, 130.2, 130.8, 131.9, 133.1, 135.1, 136.5, 146.0, 149.3, 151.8. Anal. calcd. for $C_{15}H_9Cl_2N$: C 65.72, H 3.31, N 5.11; found: C 65.67, H 3.24, N 5.08.

7-Chloro-4-(3-fluorophenyl)quinoline (7d)

Chromatography (hexane–ether 4:1 volume fraction) provided **7d** as a white solid (1.26 g, 97%), mp 88 to 89 °C. IR: 2979. ^{1}H NMR δ: 7.32–7.41 (m, 3H), 7.49 (d, 1H, J = 4.4 Hz), 7.59 (dd, 1H, J = 2.2, 9.0 Hz), 7.65 (br q, 1H, J = 7.8 Hz), 7.92 (d, 1H, J = 9.0 Hz), 8.13 (d, 1H, J = 2.1 Hz), 8.98 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 115.9 (d, J_{CF} = 21.1 Hz), 116.8 (d, J_{CF} = 22.5 Hz), 122.2, 125.2, 126.0 (d, J_{CF} = 2.7 Hz), 127.8, 128.0, 129.0, 131.2 (d, J_{CF} = 8.5 Hz), 135.1, 140.1 (d, J_{CF} = 7.9 Hz), 147.1, 149.6, 151.8, 163.2 (d, J_{CF} = 245.6 Hz). Anal. calcd. for $C_{15}H_9ClFN$: C 69.91, H 3.52, N 5.44; found: C 69.70, H 3.50, N 5.45.

4-(3-Acetamidophenyl)-7-chloroquinoline (7e)

Chromatography (hexane – ethyl acetate 1:2 volume fraction) provided **1b** (142 mg, 10%) and **7e** as a white solid (1.14 g, 76%), mp 184 to 185 °C. IR: 3435, 3015, 1692. ^{1}H NMR ($CDCl_3$) δ: 2.23 (s, 3H), 7.22 (br d, 1H, J = 7.6 Hz), 7.33 (d, 1H, J = 4.4 Hz), 7.44–7.50 (m, 2H), 7.63–7.69 (m, 3H), 7.89 (d, 1H, J = 9.0 Hz), 8.17 (d, 1H, J = 2.0 Hz), 8.94 (d, 1H, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 24.6, 120.1, 120.8, 121.4, 125.1, 125.2, 127.3, 127.9, 128.1, 129.4, 135.7, 138.0, 138.5, 148.4, 148.7, 150.4, 168.7. Anal. calcd. for $C_{17}H_{13}ClN_2O$: C 68.81, H 4.42, N 9.44; found: C 68.86, H 4.49, N 9.12.

7-Chloro-4-(3-cyanophenyl)quinoline (7f)

Chromatography (hexane – ethyl acetate 3:1 volume fraction) provided **7f** as a white solid (1.18 g, 88%), mp 160 to 161 °C. IR: 2982, 2234. ^{1}H NMR ($CDCl_3$) δ: 7.26 (d, 1H, J = 4.4 Hz), 7.43 (dd, 1H, J = 2.1, 9.0 Hz), 7.62–7.78 (m, 5H), 8.11 (d, 1H, J = 2.1 Hz), 8.91 (d, 1H, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 113.1, 118.1, 121.3, 124.4, 126.3, 128.1, 128.8, 129.6, 132.1, 132.6, 133.6, 135.6, 138.6, 145.8, 148.9, 150.8. Anal. calcd. for $C_{16}H_9ClN_2$: C 72.60, H 3.43, N 10.58; found: C 72.50, H 3.39, N 10.55.

7-Chloro-4-(4-fluorophenyl)quinoline (7g)

Chromatography (hexane – ethyl acetate 4:1 volume fraction) provided **7g** as a white solid (1.25 g, 96%), mp 105 to 106 °C. IR: 2978. ^{1}H NMR δ: 7.39 (br t, 2H, J = 8.8 Hz), 7.47 (d, 1H, J = 4.4 Hz), 7.59 (dd, 1H, J = 2.2, 9.0 Hz), 7.61–7.66 (m, 2H), 7.92 (d, 1H, J = 9.0 Hz), 8.14 (d, 1H, J = 2.2 Hz), 8.98 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 116.1 (d, $J_{C\text{-}F}$ = 21.8 Hz), 122.3, 125.4, 127.81, 127.85, 129.0, 132.0 (d, $J_{C\text{-}F}$ = 8.5 Hz), 134.0, 135.0, 147.5, 149.6, 151.8, 163.4 (d, $J_{C\text{-}F}$ = 246.5 Hz). Anal. calcd. for $C_{15}H_9ClFN$: C 69.91, H 3.52, N 5.44; found: C 69.73, H 3.40, N 5.44.

7-Chloro-4-(4-methoxyphenyl)quinoline (7h)

Chromatography (hexane – ethyl acetate 3:1 volume fraction) provided **7h** as a white solid (1.32 g, 97%), mp 90 to 91 °C. IR: 2963. ^{1}H NMR δ: 3.92 (s, 3H), 7.15 (br d, 2H, J = 8.7 Hz), 7.42 (d, 1H, J = 4.4 Hz), 7.50 (br d, 2H, J = 8.7 Hz), 7.56 (dd, 1H, J = 2.2, 9.0 Hz), 7.98 (d, 1H, J = 9.0 Hz), 8.11 (d, 1H, J = 2.2 Hz), 8.93 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 55.3, 114.6, 122.0, 125.6, 127.5, 128.1, 128.9, 129.9, 131.2, 134.8, 148.3, 149.8, 151.8, 160.7. Anal. calcd. for $C_{16}H_{12}ClNO$: C 71.25, H 4.48, N 5.19; found: C 71.16, H 4.47, N 5.13.

4-(4-Acetylphenyl)-7-chloroquinoline (7i)

Chromatography (hexane – ethyl acetate 3:2 volume fraction) provided **7i** as a white solid (1.27 g, 89%), mp 143 to 144 °C. IR: 3015, 1688. ^{1}H NMR δ: 2.70 (s, 3H), 7.52 (d, 1H, J = 4.4 Hz), 7.61 (dd, 1H, J = 2.2, 9.0 Hz), 7.73 (d, 2H, J = 8.4 Hz), 7.91 (d, 1H, J = 9.0 Hz), 8.16 (d, 1H, J = 2.2 Hz), 8.21 (d, 2H, J = 8.4 Hz), 9.02 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 26.4, 122.1, 125.1, 127.8, 128.0, 128.98, 129.01, 130.2, 135.1, 137.7, 142.2, 147.5, 149.6, 151.8, 197.1. Anal. calcd. for $C_{17}H_{12}ClNO$: C 72.47, H 4.29, N 4.97; found: C 72.36, H 4.34, N 4.90.

4-(4-Benzyloxy-3-fluorophenyl)-7-chloroquinoline (7j)

Chromatography (hexane – ethyl acetate 3:1 volume fraction) provided **7j** as a white solid (1.70 g, 93%), mp 150 to 151 °C. IR: 3014. ^{1}H NMR ($CDCl_3$) δ: 5.26 (s, 2H), 7.18 (m, 2H), 7.27 (br d, 1H, J = 11.5 Hz), 7.30 (d, 1H, J = 4.4 Hz), 7.39 (m, 1H), 7.43–7.53 (m, 5H), 7.89 (d, 1H, J = 9.0 Hz), 8.19 (d, 1H, J = 1.9 Hz), 8.93 (d, 1H, J = 4.4 Hz). ^{13}C NMR ($CDCl_3$) δ: 71.3, 115.5, 117.4, 117.6, 121.3, 125.0, 125.41, 125.45, 127.0, 127.4, 127.7, 128.3, 128.7, 130.5, 130.6, 135.4, 136.1, 147.0, 147.1, 147.3, 149.0, 150.8, 151.3, 153.8. Anal. calcd. for $C_{22}H_{15}ClFNO$: C 72.63, H 4.16, N 3.85; found: C 72.21, H 4.12, N 3.83.

7-Chloro-4-(3-thienyl)quinoline (10)

Chromatography (hexane – ethyl acetate 4:1 volume fraction) provided **10** as a white solid (1.10 g, 89%), mp 74 to 75 °C. IR: 2975. ^{1}H NMR δ: 7.43 (dd, 1H, J = 1.2, 4.9 Hz), 7.49 (d, 1H, J = 4.4 Hz), 7.56 (dd, 1H, J = 2.2, 9.1 Hz), 7.74 (dd, 1H, J = 3.0, 4.9 Hz), 7.80 (m, 1H), 8.10 (m, 2H), 8.92 (d, 1H, J = 4.4 Hz). ^{13}C NMR δ: 121.9, 125.4, 126.2, 127.3, 127.7, 128.0, 129.0, 129.2, 134.9, 138.2, 143.2, 149.7, 151.8. Anal. calcd. for $C_{13}H_8ClNS$: C 63.54, H 3.28, N 5.70; found: C 63.53, H 3.20, N 5.66.

(E)-7-Chloro-4-(1-hexenyl)quinoline (11)

Chromatography (hexane–ether 4:1 volume fraction) provided **11** as a colorless oil (1.05 g, 95%). IR (film): 2957, 2928, 1579. ^{1}H NMR δ: 0.95 (t, 3H, J = 7.3 Hz), 1.42 (m, 2H), 1.53 (m, 2H), 2.36 (br q, 2H, J = 7.0 Hz), 6.59 (dt, 1H, J = 15.6, 7.0 Hz), 7.15 (d, 1H, J = 15.6 Hz), 7.54 (m, 2H), 8.03 (d, 1H, J = 2.2 Hz), 8.21 (d, 1H, J = 9.0 Hz), 8.81 (d, 1H, J = 4.6 Hz). ^{13}C NMR δ: 13.8, 22.5, 31.4, 33.3, 117.7, 124.3, 125.0, 126.1, 127.1, 128.9, 134.7, 139.3, 143.7, 149.6, 151.8. Anal. calcd. for $C_{15}H_{16}ClN$: C 73.31, H 6.56, N 5.70; found: C 73.15, H 6.66, N 5.64.

References

1. N. Miyaura and A. Suzuki. Chem. Rev. **95**, 2457 (1995).
2. S.P. Stanforth. Tetrahedron, **54**, 263 (1998).
3. A. Suzuki. J. Organomet. Chem. **653**, 83 (2002).
4. J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, and M. Lemaire. Chem. Rev. **102**, 1359 (2002).
5. N. Miyaura. Topics Curr. Chem. **219**, 5 (2002).
6. N.M. Ali, A. McKillop, M.B. Mitchell, R.A. Rebelo, and P.J. Wallbank. Tetrahedron, **48**, 8117 (1992).
7. M.A. Ciufolini, J.W. Mitchell, and F. Roschangar. Tetrahedron Lett. **37**, 8281 (1996).
8. O. Lohse, P. Thevenin, and E. Waldvogel. Synlett, 45 (1999).
9. Y. Gong and H.W. Pauls. Synlett, 829 (2000).
10. M. Allegretti, A. Arcadi, F. Marinelli, and L. Nicolini. Synlett, 609 (2001).
11. A.F. Littke and G.C. Fu. Angew. Chem. Int. Ed. **41**, 4176 (2002).
12. D. Dubé, M. Blouin, C. Brideau, C.-C. Chan, S. Desmarais, D. Ethier, J.-P. Falgueyret, R.W. Friesen, M. Girard, Y. Girard, J. Guay, D. Riendeau, P. Tagari, and R.N. Young. Bioorg. Med. Chem. Lett. **8**, 1255 (1998).
13. J.-Y. Legros, G. Primault, and J.-C. Fiaud. Tetrahedron, **57**, 2507 (2001).
14. D. Najiba, J.-F. Carpentier, Y. Castanet, C. Biot, J. Brocard, and A. Mortreux. Tetrahedron Lett. **40**, 3719 (1999).
15. A.S. Bhanu Prasad, T.M. Stevenson, J.R. Citineni, V. Nyzam, and P. Knochel. Tetrahedron, **53**, 7237 (1997).
16. T. Shiota and T. Yamamori. J. Org. Chem. **64**, 453 (1999).
17. J.M. Nolan and D.L. Comins. J. Org. Chem. **68**, 3736 (2003).
18. R.M. Peck, R.K. Preston, and H.J. Creech. J. Am. Chem. Soc. **81**, 3984 (1959).
19. T.I. Wallow and B.M. Novak. J. Org. Chem. **59**, 5034 (1994).
20. C.R. LeBlond, A.T. Andrews, Y. Sun, and J.R. Sowa, Jr. Org. Lett. **3**, 1555 (2001).
21. D. Badone, M. Baroni, R. Cardamone, A. Ielmini, and U. Guzzi. J. Org. Chem. **62**, 7170 (1997).
22. N.E. Leadbeater and M. Marco. J. Org. Chem. **68**, 888 (2003).
23. R.F. Heck. Palladium reagents in organic syntheses. Academic Press, London. 1985. p. 184.
24. G.B. Smith, G.C. Dezeny, D.L. Hughes, A.O. King, and T.R. Verhoeven. J. Org. Chem. **59**, 8151 (1994).
25. A.F. Littke, C. Dai, and G.C. Fu. J. Am. Chem. Soc. **122**, 4020 (2000).
26. A.-S. Castanet, F. Colobert, J.-R. Desmurs, and T. Schlama. J. Mol. Catalysis A Chem. **182–183**, 481 (2002).
27. C. Amatore and A. Jutand. J. Organomet. Chem. **576**, 254 (1999).
28. C. Amatore and A. Jutand. Acc. Chem. Res. **33**, 314 (2000).
29. K. Fagnou and M. Lautens. Angew. Chem. Int. Ed. **41**, 26 (2002).
30. P.M. Maitlis. The organic chemistry of palladium. Vol 1. Academic Press, New York. 1971. Chap 1.
31. S. Tasler and B.H. Lipshutz. J. Org. Chem. **68**, 1190 (2003).