JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Rh(NHC)-Catalyzed Direct and Selective Arylation of Quinolines at the 8-Position

Jaesung Kwak, Min Kim, and Sukbok Chang*

Department of Chemistry and Molecular Level Interface Research Center, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Republic of Korea

Supporting Information

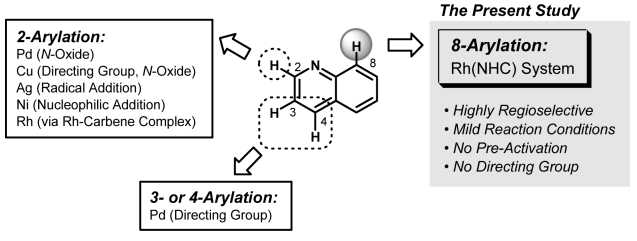
ABSTRACT: A new catalytic protocol for the regioselective direct arylation of quinoline derivatives at the 8-position has been developed. The reaction is catalyzed by a Rh(NHC) system, and the choice of the NHC ligand was most important for achieving high reactivity and selectivity.

Recent progress on the catalytic C−H bond functionalization methods has opened new possibilities for an ideal chemical synthesis enabling straightforward formation of C−C or C−X bonds from cheap and simple molecules.[1] However, it is still difficult to control the position of activated C−H bonds if the substrates have more than one reacting site. Therefore, the development of site-selective C−H bond activation is highly desirable to achieve regioselective C−C or C−X bond formation in subsequent steps.[2]

Quinoline, which is a prominent structural motif found in a wide range of natural products of interesting biological activity,[3] has been derivatized often via transition-metal-catalyzed approaches (Scheme 1).[4−9] In such transformations, high regioselectivity at the 2-position was readily obtained by converting quinolines into their *N*-oxides.[5b,c,6] More recently, catalytic C-2 arylation of unmodified quinolines was achieved by utilizing nickel (Tobisu and Chatani),[7] silver (Baran),[8] or rhodium catalysts (Bergman and Ellman).[9] In addition, Yu developed a novel method of arylation at the 3- or 4-position based on a chelation-assisted strategy, thus requiring an amido group in the 4- or 3-position of quinolines to direct the regioselectivity.[5d]

In spite of the above important contributions, no direct catalytic arylation method has been developed to functionalize quinolines *at the 8-position*.[10] In fact, the conventional method requires the de novo synthesis of 8-halogenated quinolines followed by cross-coupling.[11] In this context, there is a strong desire for the development of a direct catalytic functionalization of unmodified quinolines at the 8-postion. Described herein is *the Rh(NHC)-catalyzed direct 8-arylation of quinolines, representing the first example of complete regiocontrol* to the best of our knowledge.

Scheme 1. Selectivity Controlled Direct Arylation of Quinolines



Recently, we have demonstrated that *N*-heterocyclic carbene (NHC) ligands can play a crucial role in Rh-catalyzed reactions, thus dramatically improving both reactivity and selectivity.[12] During the course of our research aimed at an efficient C−H bond functionalization of heteroarenes,[13] we were intrigued by the feasible effects of NHC ligands on the resultant Rh−NHC catalytic system ultimately to influence the catalytic activity and regioselectivity in the direct arylation of quinoline (Table 1).

While $Rh_2(OAc)_4$ species (5 mol %) exhibited only negligible activity in the absence of ligands (entry 1), the addition of the IMes•HCl ligand (1 equiv) significantly improved the arylation efficiency (entry 2). Importantly, a careful analysis of the obtained products revealed that the arylation took place almost exclusively at the 8-postion of quinoline to afford 8-(*p*-tolyl)quinoline (**2b**) albeit in moderate yield under the employed conditions.[14] Other NHC ligands examined exhibited much lower effects on the catalytic activity, but the selectivity still remained high in favor of 8-arylation over the 2-position (entries 3−5). Interestingly, regioselectivity was diminished upon the use of a bulky NHC ligand (e.g., IAd) although the catalytic activity was improved moderately (entry 6). In addition, no beneficial effect was observed when a phosphine ligand was employed (entry 7).

The structure of an isolated $Rh_2(OAc)_4$(IMes) complex was characterized,[15] and it was confirmed that this pregenerated catalyst performs the arylation with similar reactivity when compared to that obtained under the *in situ* conditions (compare entries 8 and 2). With the use of 2 equiv of quinoline relative to bromoarene, the reaction proceeded more smoothly to afford a synthetically acceptable yield even using a lesser amount of catalyst (entry 9). A dramatic NHC effect was also observed with other sources of Rh catalysts such as $RhCl(PPh_3)_3$, $[Rh(coe)_2Cl]_2$, or $Rh(acac)_3$ species (entries 10−13).[16]

Our result is highly significant in that the Bergman−Ellman Rh-catalyst system for the arylation of quinolines gives only 2-arylated products via Rh-quinoline "carbene" intermediates.[9c,d] Therefore, *our Rh−NHC system is an extremely useful and complementary route to obtain regioisomeric 8-arylquinolines.*

For operational convenience, the protocol of generating a Rh−NHC catalyst *in situ* was set up as the optimized conditions.

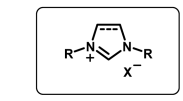
Received: December 28, 2010
Published: February 28, 2011

dx.doi.org/10.1021/ja111670s | *J. Am. Chem. Soc.* 2011, 133, 3780–3783

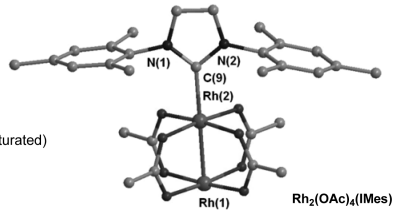
Table 1. Optimization of Reaction Conditions[a]

entry	catalyst system (mol %)	yield (%)[b]	ratio of 2b/3b[c]
1	$Rh_2(OAc)_4$ (5)	3	–
2	$Rh_2(OAc)_4$ (5)/IMes·HCl (5)	58	>99:1
3	$Rh_2(OAc)_4$ (5)/SIMes·HCl (5)	8	29:1
4	$Rh_2(OAc)_4$ (5)/IPr·HCl (5)	4	10:1
5	$Rh_2(OAc)_4$ (5)/IiPr·HBF_4 (5)	7	16:1
6	$Rh_2(OAc)_4$ (5)/IAd·HBF_4 (5)	20	2:1
7	$Rh_2(OAc)_4$ (5)/PCy_3 (5)	5	5:1
8	$Rh_2(OAc)_4$(IMes) (5)	57	>99:1
9	$Rh_2(OAc)_4$ (3)/IMes·HCl (6)[d]	84	>99:1
10	$RhCl(PPh_3)_3$ (10)[e]	8	>1:99
11	$RhCl(PPh_3)_3$ (6)/IMes·HCl (6)[d]	80	79:1
12	$[RhCl(coe)_2]_2$ (3)/IMes·HCl (6)[d]	84	>99:1
13	$Rh(acac)_3$ (6)/IMes·HCl (6)[d]	59	>99:1

[a] Quinoline (**1a**, 0.3 mmol), 4-bromotoluene (0.3 mmol), and *t*-BuONa (2.5 equiv) in toluene (0.3 mL) at 95 °C for 24 h. [b] Yield of **2b** + **3b** determined by ^{1}H NMR using an internal standard. [c] Determined by GC integration. [d] 2 equiv of quinoline were used. [e] Performed at 130 °C without base.

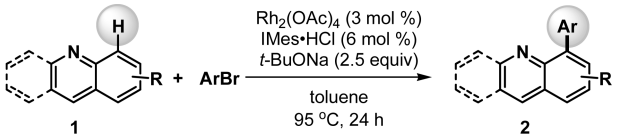


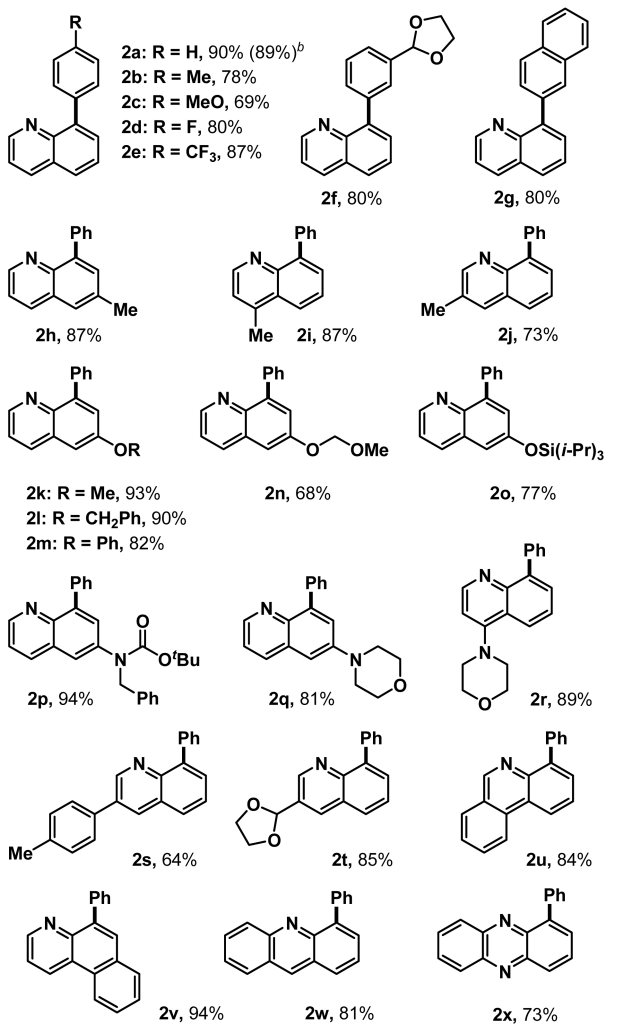
IMes: R = 2,4,6-trimethylphenyl
SIMes: R = 2,4,6-trimethylphenyl (saturated)
IPr: R = 2,6-diisopropylphenyl
I*i*Pr: R = isopropyl
IAd: R = adamantyl



$Rh_2(OAc)_4$(IMes)

Table 2. Scope of Aryl Bromides and Quinoline Derivatives in the Rh(NHC)-Catalyzed Direct Arylation[a]





[a] Reaction conditions: quinolines (**1**, 0.6 mmol), aryl bromides (0.3 mmol), *t*-BuONa (0.75 mmol), $Rh_2(OAc)_4$ (3 mol %), IMes•HCl (6 mol %) in toluene (0.3 mL) at 95 °C for 24 h. [b] Chlorobenzene was used instead of bromobenzene.

In general, a broad range of quinolines and aryl bromides was successfully employed for the selective arylation (Table 2). Electronic variation on bromoarenes little affected the reaction efficiency (**2a**−**2e**). An acetal group was well tolerated (**2f**), and bromonaphthalene could also be used as a facile reactant (**2g**). On the other hand, reaction of *ortho*-substituted aryl bromides (e.g., 2-bromotoluene) was quite sluggish under the present conditions presumably due to steric reasons. Interestingly, when chlorobenzene was employed as a reacting partner instead of bromobenzene, almost the same product yield was obtained under otherwise identical conditions (**2a**, 90% vs 89%).

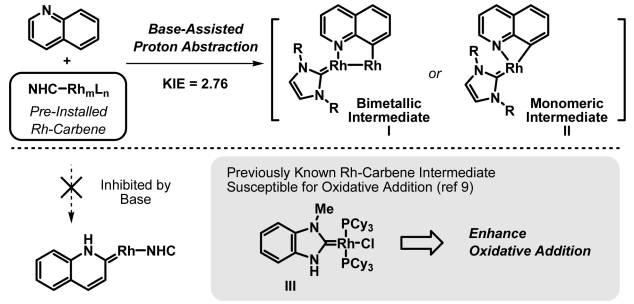
Quinolines substituted with a methyl group at various positions were all efficiently arylated at the 8-position (**2h**−**2j**). Arylation of quinolinyl ethers such as methyl, benzyl, phenyl, or MOM derivatives took place also selectively in high yields (**2k**−**2n**). It was noted that a silyl-protected quinolinol underwent the arylation without a problem (**2o**). Significantly, quinolines bearing amino groups were arylated at the 8-position in excellent yields (**2p**−**2r**). It was observed that polycondensed hetereoarenes such as phenanthridine, benzo[*f*]quinoline, acridine, and phenazine were all arylated with excellent regioselectivity in high yields (**2u**, **2v**, **2w**, and **2x**, respectively).

Ellman et al. elegantly demonstrated that a base inhibits the formation of Rh-carbene species in their Rh(I)-catalyzed direct arylation of heteroarenes.[9c,d] As a result, it is postulated that the generation of such Rh-carbene intermediates is excluded under our present reaction conditions. Instead, it is tentatively proposed that base-assisted concerted proton abstraction and metalation are operative in the present 8-arylation reaction.[17] Intermolecular kinetic isotope effects (*KIE*) were measured from a competition experiment between quinoline (**1a**) and its deuterated derivative (**1a**-d_7), revealing a high value of *KIE* (2.76).[14]

Although more comprehensive studies are required to describe the mechanistic details of the present reaction, especially with regard to the origin of regioselectivity and structure of active catalytic species, we propose that the formation of a bimetallic Rh species bound to an NHC ligand could be responsible for the outcomes (Scheme 2, **I**). In fact, $Rh_2(OAc)_4$-mediated activation

dx.doi.org/10.1021/ja111670s |*J. Am. Chem. Soc.* 2011, 133, 3780–3783

Scheme 2. A Possible Mechanistic Pathway

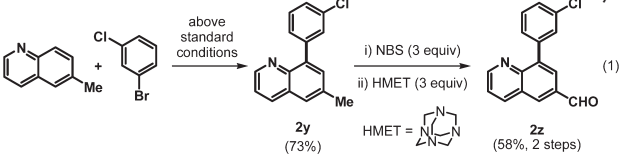


of an *ortho* C−H bond of PPh_3 was known,[18] and a similar type of C−H bond activation has been well documented in a number of different types of metal clusters (e.g., $Ru_3(CO)_{12}$ or $Os_3(CO)_{10}(CH_3CN)_2$).[19] In addition, $Rh_2(NHC)L_n$ species are reported to catalyze a range of reactions while maintaining their dimeric integrity during the course of the catalytic cycle.[12a,15] However, the observation that certain precursors of monomeric rhodium species also showed significant catalytic activity and regioselectivity led us to consider the possibility that the formation of a four-membered rhodacycle involving a monomeric Rh−NHC species (**II**) is also a plausible intermediate.[20]

Although a clear-cut relationship between the reactivity and structure of the NHC ligands cannot be formulated at present, it is postulated that the presence of a bound NHC ligand is essential influencing the subsequent oxidative addition of a rhodium metal center, in the form of either intermediate **I** or **II**, onto a coupling partner, arylbromides. Indeed, it was proposed that Ellman's rhodium-carbene species, such as **III** generated *in situ* from the reaction of *N*-methylbenzimidazole with $[RhCl(coe)_2]_2$ in the presence of PCy_3, has high electron density at the rhodium center allowing subsequent oxidative addition to aryl halides to proceed more readily.[9] For the same reason, we envision that an oxidative addition of intermediate **I** or **II** in our case is also enhanced by the preinstalled Rh-carbene species.[21]

Using the current method, a precursor of potent PDE4 inhibitors could be readily synthesized (eq 1).[22] Regio- and chemoselective arylation of 6-methylquinoline with 1-bromo-3-chlorobenzene was achieved to give the desired product (**2y**) in 73% yield under the above optimized conditions. This result indicates that an aryl−Br bond preferentially reacts with quinoline over the corresponding aryl−Cl bond under the present conditions. Benzylic protons were brominated using excessive NBS, and the resultant mixture of mono- and dibromo intermediates was subsequently oxidized leading to a stable quinoline carbaldehyde (**2z**) in 58% yield over two steps.

In conclusion, we have developed an efficient Rh(NHC)-catalyzed direct arylation of quinolines with an excellent degree of regioselectivity at the 8-position. The choice of NHC ligand in combination with the rhodium catalyst source were found to be essential in achieving high activity and selectivity, allowing a wide range of 8-arylquinoline derivatives to be obtained in high yields for the first time. Detailed mechanistic studies are underway to elucidate the origin of such high regioselectivity and structure of active catalytic species.



■ ASSOCIATED CONTENT

Supporting Information. Experimental details and ^1H and ^{13}C NMR spectra of new compounds, and CIF file of $Rh_2(OAc)_4(IMes)$. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
sbchang@kaist.ac.kr

■ ACKNOWLEDGMENT

Dedicated with respect to Professor Eun Lee for his honorable retirement. This work was supported by the National Research Foundation (Star Faculty Program, KRF-2008-C00024), MIRC (NRF-2010-0001957), and Carbon Dioxide Reduction & Sequestration Research Center (AC3-101). The authors also thank Dr. Seung Hwan Cho for experimental assistance and helpful discussions.

■ REFERENCES

(1) General reviews on the C-H activation: (a) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (b) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (c) Bergman, R. *Nature* **2007**, *446*, 391.

(2) For recent reviews on the selective and direct C−H functionalization, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Campeau, L.-C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q.-N.; Lazareva, A. *Synlett* **2006**, 3382. (d) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (e) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (f) Pascual, S.; de Mendoza, P.; Echavarren, A. M. *Org. Biomol. Chem.* **2007**, *5*, 2727. (g) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (h) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(3) Quinoline bioactivity: (a) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; WILEY-VCH: 2003. (b) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166.

(4) For reviews on the direct catalytic arylations, see: (a) Miura, M.; Satoh, T. *Top. Organomet. Chem.* **2005**, *14*, 55. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) McGlacken, G. P.; Bateman, L. M. *Chem. Rev. Soc.* **2009**, *38*, 2447. (d) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (e) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792.

(5) (a) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291. (d) Wasa, M.; Worrell, B. T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 1275.

(6) Zhao, D.; Wang, W.; Yang, F.; Lan, J.; Yang, L.; Gao, G.; You, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3296.

(7) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070.

(8) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194.

(9) (a) Lewis, J. C.; Wiedemann, S. H.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2004**, *6*, 35. (b) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (c) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**,

130, 14926. (d) Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 7863.

(10) Knochel et al. reported that regioselective deprotonation of quinolines using magnesium bases for the formation of organozinc species: Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525.

(11) Macdonald, D.; Perrier, H.; Liu, S.; Laliberté, F.; Rasori, R.; Robichaud, A.; Masson, P.; Huang, Z. *J. Med. Chem.* **2000**, *43*, 3820.

(12) (a) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8935. (b) Kim, M.; Lee, J.; Lee, H.-Y.; Chang, S. *Adv. Synth. Catal.* **2009**, *351*, 1807. (c) Kim, M.; Chang, S. *Org. Lett.* **2010**, *12*, 1640.

(13) For recent examples, see: (a) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (b) Park, E. J.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 17268. (c) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (d) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. (e) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272. (f) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868.

(14) See the Supporting Information for details.

(15) For previous reports on the use and characterization of dirhodium complexes with axial NHC ligands, see: (a) Gois, P. M. P.; Trindade, A. F.; Veiros, L. F.; André, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 5750. (b) Trindade, A. F.; Gois, P. M. P.; Veiros, L. F.; André, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *J. Org. Chem.* **2008**, *73*, 4076. (c) Na, S. J.; Lee, B. Y.; Bui, N.-N.; Mho, S.-i.; Jang, H.-Y. *J. Organomet. Chem.* **2007**, *692*, 5523.

(16) A $RhCl(PPh_3)_3$/IMes system was previsouly reported to display catalytic activity in the hydroformylation and hydrogenation reaction: (a) Chen, A. C.; Ren, L.; Decken, A.; Crudden, C. M. *Organometallics* **2000**, *19*, 3459. (b) Allen, D. P.; Crudden, C. M.; Calhoun, L. A.; Wang, R. *J. Organomet. Chem.* **2004**, *689*, 3203.

(17) An NH-tautomerized benzoquinoline−iridium complex was converted into a cyclometalated benzoquinoline−iridium complex when the Brønsted base was used. Esteruelas, M. A.; Fernández-Alvarez, F. J.; Oliván, M.; Oñate, E. *Organometallics* **2009**, *28*, 2276.

(18) Chakravarty, A. R.; Cotton, F. A.; Tocher, D. A.; Tocher, J. H. *Organometallics* **1985**, *4*, 8.

(19) (a) Fukuyama, T.; Chatani, N.; Tatsumi, J.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1998**, *120*, 11522. (b) Kabir, S. E.; Kolwaite, D. S.; Rosenberg, E.; Hardcastle, K.; Cresswell, W.; Grindstaff, J. *Organometallics* **1995**, *14*, 3611. (c) Shapley, J. R.; Samkoff, D. E.; Bueno, C.; Churchill, M. R. *Inorg. Chem.* **1982**, *21*, 634.

(20) Mohr, F.; Privér, S. H.; Bhargava, S. K.; Bennett, M. A. *Coord. Chem. Rev.* **2006**, *250*, 1851.

(21) A reverse order of the arylation pathway proceeding through the prior oxidative addition of aryl halides to Rh(I) species followed by the C−H bond activation of quinoline can also be envisioned. In fact, the involvement of ArRh(III) species in the C−H bond activation was previously proposed: (a) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996. (b) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136. (c) Vogler, T.; Studer, A. *Org. Lett.* **2008**, *10*, 129.

(22) Wilhelm, R.; Fatheree, P. R.; Chin, R. L. Quinolines as Type IV Phosphodiesterase Inhibitors. Patent WO 9422852, 1994.