C–C Coupling

DOI: 10.1002/anie.200903500

Rhodium/N-Heterocyclic Carbene Catalyzed Direct Intermolecular Arylation of sp^2 and sp^3 C–H Bonds with Chelation Assistance**

*Min Kim, Jaesung Kwak, and Sukbok Chang**

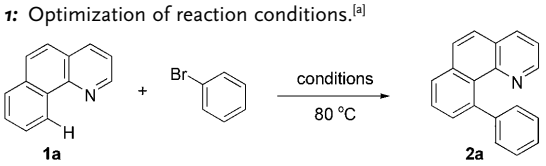
Dedicated to Professor Bong Rae Cho on the occasion of his 60th birthday

Transition metal catalyzed cross-coupling reactions are one of the most important methods utilized for the carbon–carbon bond formation.[1] Biaryl compounds are an important structural motif in either organic synthesis and materials or medicinal chemistry,[2] and they are synthesized most conveniently by various types of cross-coupling reactions.[3] In recent years, however, a new approach involving direct arylation has been intensively investigated; in this approach aryl halides react with non-functionalized arenes by C–H bond activation.[4] Although palladium catalysts have been most widely employed in the direct arylation of arenes,[5] other metal species were also examined, including Ru, Fe, Ni, and Cu, albeit with different degrees of success.[6] In contrast, rhodium complexes have been investigated as efficient and selective catalysts for the C–H bond functionalization in recent years.[7–9]

During our studies in the C–H functionalization of arenes,[10] we wondered whether N-heterocyclic carbene (NHC) ligands could display notable effects on the catalytic activity of rhodium species in the direct arylation reactions. Although it is well-known that NHCs often exhibit dramatic effects upon the catalytic activities of some metal species such as Pd, Ni, and Ru,[11] the study of the rhodium-mediated reactions has not been extensively investigated.[12]

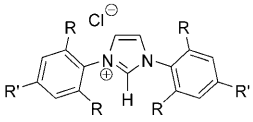
At the outset of our studies, benzo[*h*]quinoline (**1a**) was used as a model substrate to react with bromobenzene in the presence of various catalytic rhodium systems (Table 1). Whereas a low conversion was observed with a dimeric [{Rh(cod)Cl}$_2$] species alone at 80 °C (Table 1, entry 1), the addition of a NHC ligand precursor (IMes·HCl) and PCy_3 in the presence of *t*BuONa provided increased efficiency (Table 1, entries 2–3). Additional improvement was observed when a pregenerated [Rh(cod)(IMes)Cl] catalyst was used (Table 1, entry 4), but the conversion was still not sufficient for potential synthetic applications. Whereas no reaction was observed using [$Rh_2(OAc)_4$] alone (Table 1, entry 5), the addition of IMes·HCl resulted in a dramatic increase of the reaction efficiency leading to 10-phenylbenzo[*h*]quinoline (**2a**) within six hours at 80 °C in toluene (Table 1, entry 6). The structures of the employed NHCs displayed significant effects upon the activity of the resultant rhodium catalyst, as demonstrated in entry 7 of Table 1.

Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst system (mol%)	*t* [h]	Conv. [%][b]
1	[{Rh(cod)Cl}$_2$] (1.5)	6	10
2	[{Rh(cod)Cl}$_2$] (1.5)/IMes·HCl (3)/	6	14
3	[{Rh(cod)Cl}$_2$] (1.5)/IMes·HCl (3)/PCy_3 (5)	2	39
4	[Rh(cod)(IMes)Cl] (3)/PCy_3 (5)	2	63
5	[$Rh_2(OAc)_4$] (2.5)	12	<1
6	[$Rh_2(OAc)_4$] (2.5)/IMes·HCl (5)	6	>99
7	[$Rh_2(OAc)_4$] (2.5)/IPr·HCl (5)	6	<1
8	[$Rh_2(OAc)_4$] (1.5)/IMes·HCl (3)	2	14
9	[$Rh_2(OAc)_4$] (1.5)/IMes·HCl (3)/PCy_3 (5)	2	>99
10	[$Rh_2(OAc)_4$(IMes)] (1.5)/PCy_3 (5)	2	59
11	[$Rh_2(OAc)_4$] (1.5)/PCy_3 (5)	2	5
12	$RhCl_3$ (3)/IMes·HCl (6)/PCy_3 (10)	2	<1
13	$Pd(OAc)_2$ (3)/IMes·HCl (6)/PCy_3 (10)	2	<1

[a] Reaction conditions: **1a** (0.5 mmol), bromobenzene (1.5 equiv), and *t*BuONa (1.5 equiv) in toluene (0.33 mL) at 80 °C. [b] Determined using GC methods (internal standard: 1,3-benzodioxole). cod = 1,5-cyclooctadiene, Cy = cyclohexyl.



IMes · HCl: R = Me, R' = Me

IPr · HCl: R = *i*Pr, R' = H

When the amount of the rhodium species was additionally reduced, the additive effect of external phosphine was quite pronounced (compare entries 8 and 9 in Table 1). Interestingly, in this case, a pregenerated [$Rh_2(OAc)_4$(IMes)] species displayed a reduced efficiency when compared to the in situ catalyst system (compare entries 9 and 10 in Table 1). In addition, phosphine alone did not improve the reaction efficiency (Table 1, entry 11). Not surprisingly, a rhodium(III) species did not show any catalytic activity (Table 1, entry 12). Additionally, a corresponding palladium system was inactive for the arylation (Table 1, entry 13). Notably, the developed reaction conditions are much milder when compared to those previously reported with other metal species, such as Pd, Ru, Fe, and Ni, for the same transformation.[5,6]

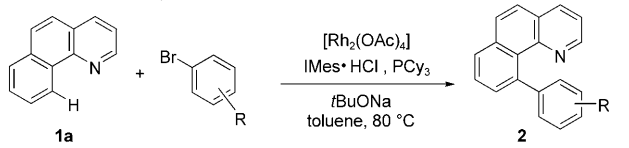
[*] M. Kim, J. Kwak, Prof. Dr. S. Chang
Department of Chemistry
Korea Advanced Institute of Science and Technology (KAIST)
Daejeon, 305-701 (Republic of Korea)
Fax: (+82) 42-350-2810
E-mail: sbchang@kaist.ac.kr

[**] This research was supported by the Korea Research Foundation (KRF-2008-C00024, Star Faculty Program)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903500.

Under the optimized reaction conditions identified above, a range of substituted bromoarenes were readily reacted with benzo[*h*]quinoline (**1a**, Table 2). In general, whereas bromobenzenes bearing electron-withdrawing substituents react with **1a** in excellent yields, electron-donating groups slightly slowed the reaction rate. In contrast, the present procedure was not effective with chlorobenzene, leading to less than 5% product yield from the reaction with **1a**; this is frequently observed in the direct arylation using other metal species such as Pd, Ru, or Ni.[13]

Table 2: Direct arylation of **1a** with various bromobenzenes.[a]

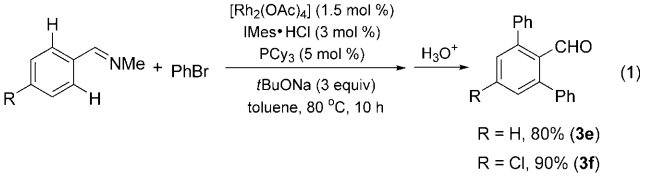


Entry	R	*t* [h]	Yield [%][b]
1	H	2	98
2	4-F	2	99
3	4-CF_3	2	98
4	4-Me	4	91
5[c]	4-Et	4	85
6[c]	4-MeO	4	56
7[c]	3,5-dimethyl	4	75

[a] Reaction conditions: **1a** (0.5 mmol), bromobenzene (1.5 equiv), *t*BuONa (1.5 equiv), $[Rh_2(OAc)_4]$ (1.5 mol%), IMes·HCl (3 mol%), and PCy_3 (5 mol%) in toluene (0.33 mL) at 80°C. [b] Yield of isolated product yield. [c] Toluene (0.5 mL) was used.

The scope of N-heteroaromatic compounds was examined next in reactions with bromobenzene (Scheme 2). When 2-phenylpyridine was reacted with 1.5 equivalents of bromobenzene under the optimized conditions, a mixture of 2-(2-phenyl)phenylpyridine and 2-(2,6-diphenyl)phenylpyridine was obtained in a 3:1 ratio. Upon increasing the amount of bromobenzene used to three equivalents, the diarylated compound **3a** was produced almost exclusively, by using higher loading of the rhodium catalyst and a longer reaction time (10 h, 80°C). In addition to the pyridyl group, pyrazole and oxazoline moieties also displayed similar directing effects in the arylation reaction, and the corresponding diarylated products (**3b**, **3c**, and **3d**, respectively) were obtained in excellent yields.

When *N*-methylbenzylidenamine was subjected to the reaction conditions, 2,6-diphenylbenzaldehyde (**3e**) was isolated in high yield after acidic hydrolysis, thereby suggesting that an imino moiety can also serve as an effective directing group in the arylation [Eq. (1)].[14] In addition, the diarylation of an aldimine compound bearing a labile group (R = Cl) proceeded smoothly to afford **3f** in high yield, thereby demonstrating a high degree of functional group compatibility of the present procedure.



(1)

In the metal-mediated C–H bond activation, the proton abstraction path is a well-established mechanistic proposal. In particular, Echavarren and Fagnou proposed a base-assisted hydrogen atom abstraction route in the palladium-catalyzed arylation.[15] In addition, Dixneuf and co-workers suggested a similar pathway in the ruthenium-catalyzed arylation reaction, which was supported by DFT calculations.[16] The analogous proton abstraction mechanism was also proposed in the rhodium-catalyzed direct arylation using acid chlorides or acid anhydrides.[9]

We initiated our mechanistic investigation with an in situ NMR study to observe any plausible metallacyclic intermediates.[17] The change of the ^{1}H NMR spectra of benzo[*h*]quinoline (**1a**) was monitored over time at 55°C as it reacted with a stoichiometric amount of $[Rh_2(OAc)_4]$, IMes·HCl, and *t*BuONa in $[D_4]$MeOH (Figure 1).[18] A signal for the proton at the C10 position (●) of **1a** gradually decreased over time,

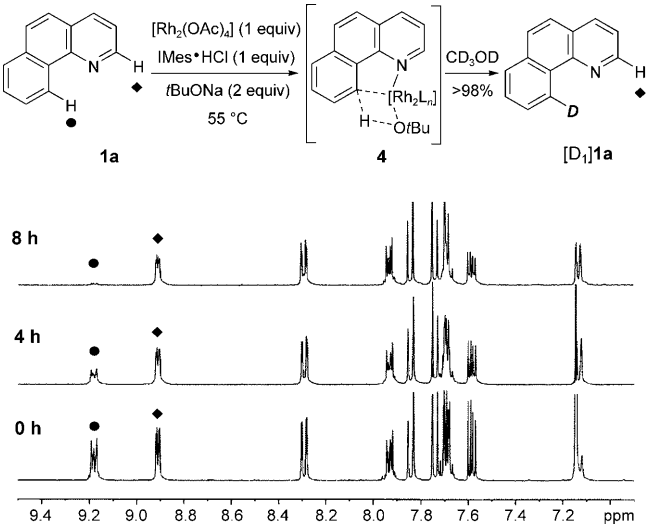
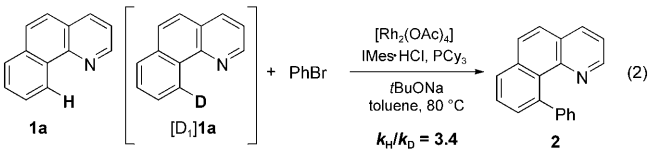


Figure 1. Rhodium/base-mediated proton exchange with deuterium at C10 of **1a**.

eventually leading to a complete exchange of the proton with deuterium within eight hours.[17] In contrast, no exchange was observed for the same reaction run in the absence of either an external base or rhodium species,[19] suggesting that the base-assisted proton abstraction takes place with the help of metal coordination such as that shown in **4** (Figure 1).[20]

A competition experiment was also performed to obtain kinetic isotope effects between two compounds **1a** and $[D_1]$**1a** [Eq. (2)]. Significant intermolecular kinetic isotope effects



(2)

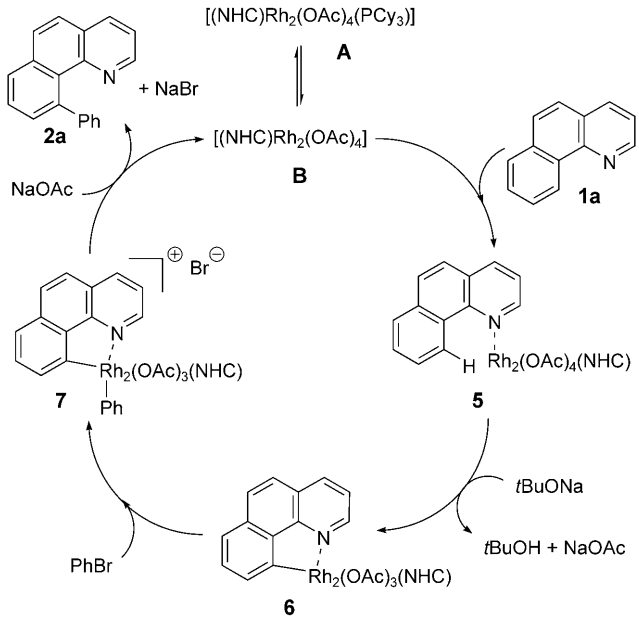
($k_H/k_D = 3.4$ at 30% conversion after 45 min) were observed.[19]

On the basis of the above studies and the precedented reports,[9,15,16] a mechanistic proposal of the present rhodium-catalyzed arylation is depicted in Scheme 1. Since the dimeric rhodium precursor $[Rh_2(OAc)_4]$ has two axial positions which serve as binding sites to external ligands or solvent,[21] it can be assumed that the added electron-rich NHC and phosphine ligands are initially coordinated to two different rhodium metal centers, leading to the complex $[(NHC)Rh_2(OAC)_4(PCy_3)]$ (**A**). A similar explanation was recently reported by Hermann et al., in which the role of an added phosphine ligand in the Rh/NHC-catalyzed hydrogenation reaction was assumed to stabilize the active species.[22] Indeed, structures of certain NHC-bound dirhodium tetraacetate complexes were previously characterized, and the species have been utilized as efficient catalysts in various reactions such as C–H insertion, allylic oxidation, and arylation of aldehydes.[23] In analogy, we also presume that the active catalytic species is the bimetallic species **B**, in which only one rhodium center is bound to one NHC upon release of PCy_3 from **A**. This reasoning stems from the fact that the known procedure of generating NHC-bound dirhodium(II) complexes is quite similar to our present conditions and that the mono-NHC species $[(NHC)Rh_2(OAc)_4]$ was found to be the active catalysts in previous examples.[23]

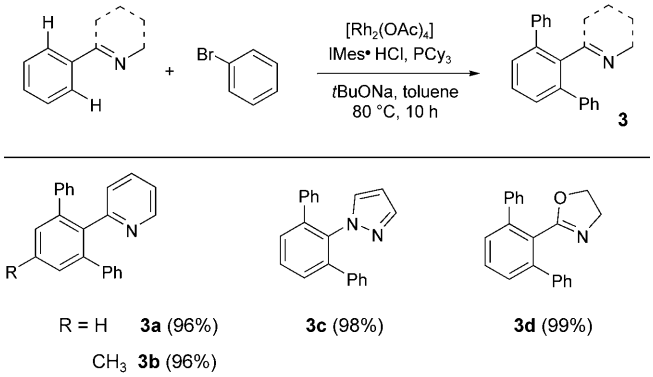
One possibility is that one rhodium center of **B**, not bound to a NHC ligand, binds first to the nitrogen atom of the substrate **1a**, leading to the cheated complex **5**. The subsequent process is proposed to be a proton abstraction by the action of an external base, sodium *tert*-butoxide in this case, to afford a five-membered metallacycle intermediate **6** upon release of one molecule of anionic acetate ligand. Oxidative addition of bromobenzene by the Rh^{II} center of **6** would generate a chelated cationic rhodium species **7**.[24] It is envisioned that the rhodium metal center responsible for the redox cycle is operative between Rh^{II}–Rh^{IV}[23] although most known Rh-mediated reactions involve Rh^{I}–Rh^{III} catalytic systems.[7–9] Reductive elimination of the phenyl rhodium intermediate **7** and reassociation of one acetate ligand will deliver the arylated product **2a** along with the generation of $[(NHC)Rh_2(OAc)_4]$ (**B**) for entry into the subsequent catalytic cycles.

However, the involvement of alternative pathways can also be considered, in which an oxidative addition of the rhodium species **B** into bromobenzene occurs first, and then the base-assisted proton abstraction path affords the same intermediate **7**.[24]

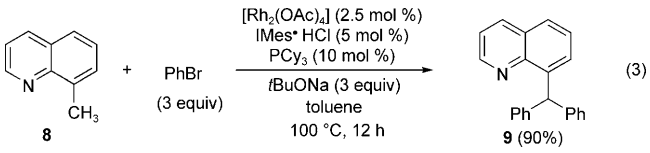
The present rhodium-catalyzed arylation protocol could be readily extended into the C–H functionalization of benzylic sp^3 and vinyl sp^2 C–H bonds [Eq. (3)–(6)]. When 8-methylquinoline (**8**) was reacted with three equivalents of bromobenzene in the presence of the rhodium catalyst system at 100 °C, a diarylated product, 8-(diphenylmethyl)quinoline (**9**), was obtained in high yield [Eq. (3)].[25] A facile installation of an aryl group at the β position relative to a 2-pyridyl group of 2-vinylpyridine was readily achieved to give 2-[(*E*)-2-phenylethenyl]pyridine (**11**) [Eq. (4)]. The reaction was highly selective in that only one phenyl group was introduced

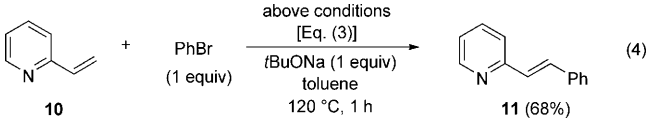


Scheme 1. Proposed mechanistic pathway.



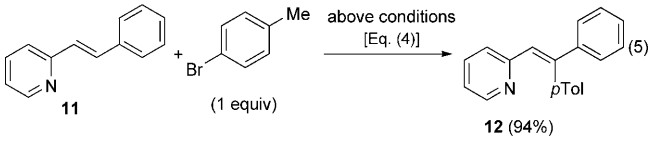
Scheme 2. Rhodium-catalyzed *ortho*-bisarylation with bromobenzene. Reaction conditions: heteroarene (0.35 mmol), bromobenzene (3.0 equiv), *t*BuONa (3.0 equiv), $[Rh_2(OAc)_4]$ (2.5 mol%), IMes·HCl (5 mol%), and PCy_3 (10 mol%) in toluene (0.7 mL) for 10 h at 80 °C. The reported yields are those of the isolated products.



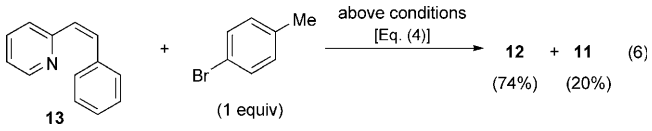


at the β-vinyl position with complete stereoselectivity under the optimized reaction conditions, albeit at higher temperatures.[26]

Interestingly, we observe that the arylation of (2-phenylethenyl)pyridine proceeded stereoselectively to afford only the (*Z*)-product **12** [Eq. (5)]. The stereochemical outcome is



in agreement with a mechanistic proposal that the reaction proceeds by the 2-pyridyl group directed C–H bond activation of olefins, which is in contrast with the Heck-type route that will lead to the *E*-isomeric product as demonstrated by Inoue and co-workers and Ackermann et al.[27] It was also found that the *Z* double bond of **13** was isomerized during the course of the reaction to the *E*-isomer **11** [Eq. (6)]. As a



result, it can be postulated that **13** is first converted into **11** under the conditions and then the chelation-assisted β-proton abstraction lead to the *Z*-product **12**.[28] In addition, the observation of this isomerization can rationalize the stereochemical outcome of [Eq. (4)], in which (*Z*)-(2-phenylethenyl)pyridine (**13**) is presumably formed first and then subsequent isomerization occurs to afford the *E*-product **11**.

In conclusion, we have developed a new protocol of the rhodium-catalyzed chelation-assisted direct arylation at the sp^3 and sp^2 C–H bonds. The reactivity of rhodium catalyst was dramatically increased by the simultaneous employment of electron-rich N-heterocyclic carbene and PCy_3 ligands. Mechanistic studies revealed that the arylation on aromatic sp^2 C–H bonds takes place by a proton abstraction pathway. Synthetic applications of the present method are underway, which will be reported in due course.

Experimental Section

Representative procedure: Bromobenzene (118 mg, 0.75 mmol), sodium *tert*-butoxide (72 mg, 0.75 mmol), $[Rh_2(OAc)_4]$ (3.3 mg, 0.0075 mmol), 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (5.1 mg, 0.015 mmol), and PCy_3 (39 mg, 0.025 mmol) were added to a solution of benzo[*h*]quinoline (**1a**, 90 mg, 0.5 mmol) in toluene (0.33 mL). The reaction mixture, which was contained in a screw-top vial, was vigorously stirred for 2 h at 80 °C and then filtered through a Celite pad washing with ethyl acetate (15 mL). Combined organic layers were evaporated and the resulting residue was purified using silica gel column chromatography (EtOAc/*n*-hexane 1:10) to afford 10-phenylbenzo[*h*]quinoline (**2a**, 125 mg, 98%).

Received: June 29, 2009
Revised: September 24, 2009
Published online: October 23, 2009

Keywords: chelation assistance · direct arylation · homogeneous catalysis · N-heterocyclic carbenes · rhodium

[1] *Cross-Coupling Reactions* (Ed.: N. Miyaura), Springer, Berlin, **2002**.
[2] D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893.
[3] a) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; b) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.
[4] a) L.-C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253; b) J.-Q. Yu, R. Giri, X. Chen, *Org. Biomol. Chem.* **2006**, *4*, 4041; c) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; d) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *40*, 35; e) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35.
[5] For selected recent examples of the palladium-catalyzed direct arylations, see: a) T. Okazawa, T. Satoh, M. Miura, M. Nomura, *J. Am. Chem. Soc.* **2002**, *124*, 5286; b) L.-C. Campeau, M. Parisien, M. Leblanc, K. Fagnou, *J. Am. Chem. Soc.* **2004**, *126*, 9186; c) O. Daugulis, V. G. Zaitsev, *Angew. Chem.* **2005**, *117*, 4114; *Angew. Chem. Int. Ed.* **2005**, *44*, 4046; d) L. Ackermann, A. Althammer, S. Fenner, *Angew. Chem.* **2009**, *121*, 207; *Angew. Chem. Int. Ed.* **2009**, *48*, 201.
[6] a) L. Ackermann, A. Althammer, R. Born, *Angew. Chem.* **2006**, *118*, 2681; *Angew. Chem. Int. Ed.* **2006**, *45*, 2619; b) H.-Q. Do, R. M. K. Khan, O. Daugulis, *J. Am. Chem. Soc.* **2008**, *130*, 15185.
[7] a) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996; b) S. Proch, R. Kempe, *Angew. Chem.* **2007**, *119*, 3196; *Angew. Chem. Int. Ed.* **2007**, *46*, 3135.
[8] J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013, and references therein.
[9] X. Zhao, Z. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 8136.
[10] a) S. Ko, Y. Na, S. Chang, *J. Am. Chem. Soc.* **2002**, *124*, 750; b) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, *33*, 302; c) J. M. Lee, E. J. Park, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 7824; d) S. H. Cho, S. J. Hwang, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 9254; e) S. J. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158; f) E. J. Park, S. H. Kim, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 17268.
[11] S. P. Nolan, *N-Heterocyclic Carbene in Synthesis*, Wiley-VCH, Weinheim, **2006**.
[12] a) J. Wolf, A. Labande, J.-C. Daran, R. Poli, *Eur. J. Inorg. Chem.* **2007**, 5069; b) L. Zhang, J. Wu, *Adv. Synth. Catal.* **2008**, *350*, 2409; c) W. Gil, A. M. Trzeciak, J. J. Ziółkowski, *Organometallics* **2008**, *27*, 4131; d) M. S. Jeletic, M. T. Jan, I Ghiviriga, K. A. Abboud, A. S. Veige, *Dalton Trans.* **2009**, 2764.
[13] A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.
[14] a) S. Oi, Y. Ogino, S. Fukita, Y. Inoue, *Org. Lett.* **2002**, *4*, 1783; b) S.-G. Lim, J.-A. Ahn, C.-H. Jun, *Org. Lett.* **2004**, *6*, 4687.
[15] a) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066; b) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754.
[16] I. Özdemir, S. Demir, B. Çetinkaya, C. Gourlaouen, F. Maseras, C. Bruneau, P. H. Dixneuf, *J. Am. Chem. Soc.* **2008**, *130*, 1156.
[17] For examples of benzo[*h*]quinoline palladacyclic complexes, see: a) D. C. Powers, T. Ritter, *Nat. Chem.* **2009**, *1*, 302; b) K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2007**, *129*, 11904. For examples of Rh-metallacycles of benzo[*h*]quinoline, see: c) S. Chen. Y. Li, J. Zhao, X. Li, *Inorg. Chem.* **2009**, *48*, 1198; d) L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414.

[18] When [D_8]toluene was employed for the NMR study, reproducible results could not be obtained presumably because of the poor solubility of the reaction mixture in the solvent. A similar H/D exchange phenomenon was also obtained with [Rh(cod)(IMes)Cl] (see the Supporting Information for details).
[19] See the Supporting Information for details.
[20] a) S. H. Wiedemann, J. C. Lewis, J. A. Ellman, R. Bergman, *J. Am. Chem. Soc.* **2006**, *128*, 2452; b) D. García-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880.
[21] J. P. Snyder, A. Padwa, T. Stengel, A. J. Arduengo III, A. Jockisch, H.-L. Kim, *J. Am. Chem. Soc.* **2001**, *123*, 11318.
[22] W. A. Herrmann, G. D. Frey, E. Herdtweck, M. Steinbeck, *Adv. Synth. Catal.* **2007**, *349*, 1677.
[23] a) F. A. Cotton, E. A. Hillard, C. A. Murillo, *J. Am. Chem. Soc.* **2002**, *124*, 5658; b) S. J. Na, B. Y. Lee, N.-N. Bui, S.-i. M. H.-Y. Jang, *J. Organomet. Chem.* **2007**, *692*, 5523; c) P. M. P. Gois, A. F. Trindade, L. F. Verios, V. André, M. T. Duarte, C. A. M. Afonso, S. Caddick, F. G. N. Cloke, *Angew. Chem.* **2007**, *119*, 5852; *Angew. Chem. Int. Ed.* **2007**, *46*, 5750.
[24] Rhodium(I) salts are generally known to be quite reluctant to engage in the oxidative addition addition of aryl halides although there are reported cases: a) V. V. Grushin, W. J. Marshall, *J. Am. Chem. Soc.* **2004**, *126*, 3068; b) S. Chen, Y. Li, J. Zhao, X. Li, *Inorg. Chem.* **2009**, *48*, 1198.
[25] a) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330; b) D. Shabashov, O. Daugulis, *Org. Lett.* **2005**, *7*, 3657.
[26] Interestingly, but not surprisingly, no reaction took place under the same conditions when styrene was employed instead of 2-vinylpyridine.
[27] For selected examples of ruthenium-catalyzed direct arylations of 2-alkenylpyridines, see: a) S. Oi, K. Sakai, Y. Inoue, *Org. Lett.* **2005**, *7*, 4009; b) L. Ackermann, R. Born, P. Alvarez-Bercedo, *Angew. Chem.* **2007**, *119*, 6482; *Angew. Chem. Int. Ed.* **2007**, *46*, 6364.
[28] We would like to thank one referee for suggesting the reaction of Equation (6) with regard to the mechanistic pathways.

