ORGANIC LETTERS

2011
Vol. 13, No. 9
2368–2371

Rhodium(NHC)-Catalyzed *O*-Arylation of Aryl Bromides

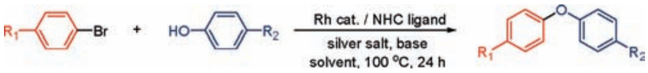
Hyun Jin Kim, Min Kim, and Sukbok Chang*

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

sbchang@kaist.ac.kr

Received March 7, 2011

ABSTRACT



The first example of the rhodium-catalyzed *O*-arylation of aryl bromides is reported. While the right combination of rhodium species and *N*-heterocyclic carbene (NHC) offered an effective catalytic system enabling the arylation to proceed, the choice of NHC was determined to be most important. The developed *O*-arylation protocol has a wide range of substrate scope, high functional group tolerance, and flexibility allowing a complementary route to either *N*- or *O*-arylation depending on the choice of NHC.

A variety of natural products and synthetic intermediates contain a biaryl ether linkage in their structures.[1] Therefore, intensive efforts have been devoted to developing more efficient and practical routes to prepare the biaryl ether bond starting from simple precursors. A conventional procedure used to provide the ether linkage is the Ullmann type reaction,[2] which has been widely utilized in organic synthesis and other areas. Although the protocol offers *O*-arylated products in good yields, there are several limitations such as high reaction temperatures and the requirement of stoichiometric amounts of a copper species. This aspect has led to the development of more useful catalytic procedures by key contributions from the Buchwald[3] and Hartwig groups.[4]

The success of the catalytic protocols can be attributed to the right combination of metal precursors and suitable ligands. For instance, copper species in the presence of amino acids are shown to exhibit dramatically improved catalytic activity in the *O*-arylation.[5] Diamine or other types of compounds[6] have also been utilized as highly efficient ligands in combination with a copper species for efficient reactions. Heterogenized systems of copper catalysts have also been introduced for the *O*-arylation.[7] On the other hand, sterically bulky phosphines were revealed to be crucial for achieving high activity in the Pd-catalyzed ether bond formation.[3b] In addition, some promising protocols of metal-free *O*-arylation have been reported in recent years.[8]

Despite the above mentioned significant progress, there is still room for further improvement especially with respect to substrate scope, functional group compatibility, or synthetic utility. Recently, we have demonstrated that the unique catalytic activity of rhodium species can be obtained by a combination of suitable *N*-heterocyclic carbene (NHC) ligands in the C–C or C–N bond formation.[9] In our continuing efforts to develop more efficient and practical metal-catalyzed organic transformations,[10] we report herein

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(1) (a) Saywer, J. S. *Tetrahedron* **2000**, *56*, 5045. (b) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004.

(2) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (b) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271. (c) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (e) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

(3) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369.

(4) (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (b) Mann, G.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 5413.

(5) (a) Cai, Q.; Zou, B.; Ma, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1276. (b) Cai, Q.; Ma, D. *Org. Lett.* **2003**, *5*, 3799.

(6) (a) Cristau, H.-J.; Cellier, P. P.; Hamada, S.; Spindler, J.-F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913. (b) Ouali, A.; Spindler, J.-F.; Cristau, H.-J.; Taillefer, M. *Adv. Synth. Catal.* **2009**, *348*, 499.

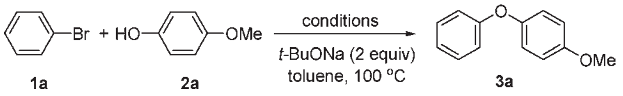
(7) (a) Benyahya, S.; Monnier, F.; Wong Chi Man, M.; Bied, C.; Ouzzani, F.; Taillefer, M. *Green Chem.* **2009**, *11*, 1121. (b) Sreedhar, B.; Arundhathi, R.; Reddy, P. L.; Kantam, M. L. *J. Org. Chem.* **1996**, *61*, 1133.

(8) (a) Yuan, Y.; Thome, I.; Kim, S. H.; Chen, D.; Beyer, A.; Bonnamour, J.; Zuidema, E.; Chang, S.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 2892. (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *6*, 99. (c) Bates, R. B.; Janda, K. D. *J. Org. Chem.* **1982**, *47*, 4374.

10.1021/ol200603c

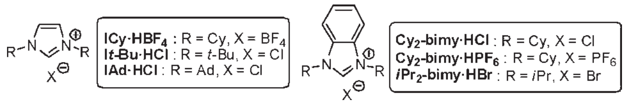
the first example of the Rh(NHC)-catalyzed *O*-arylation of aryl bromides.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalytic systems	*t* (h)	yield (%)[b]
1	$Rh_2(OAc)_4$	24	0
2	$Rh_2(OAc)_4$ + ICy·HBF_4	12	50
3	$Rh_2(OAc)_4$ + PCy_3	12	0
4	$Rh_2(OAc)_4$ + ICy·HBF_4 + PCy_3	12	55
5	$RhCl_3$ + ICy·HBF_4	24	0
6	$Rh_2(OAc)_4$ + ICy·HBF_4	24	70
7	$Rh_2(OAc)_4$ + I*t*-Bu·HCl	24	0
8	$Rh_2(OAc)_4$ + IAd·HCl	24	0
9	$Rh_2(OAc)_4$ + IMes·HCl	24	0
10	$Rh_2(OAc)_4$ + Cy_2-bimy·HPF_6	24	95
11	$[RhCl(cod)]_2$ + Cy_2-bimy·HPF_6	24	40
12	$[RhCl(cod)]_2$ + *i*Pr_2-bimy·HBr	24	66
13[c]	$Rh_2(OAc)_4$ + Cy_2-bimy·HPF_6 + $AgPF_6$	24	95
14[c]	$[RhCl(cod)]_2$ + *i*Pr_2-bimy·HBr + $AgSbF_6$	24	95
15[d]	Rh(cod)(*i*Pr_2-bimy)Br + $AgSbF_6$	24	93

[a] Conditions: **1** (0.2 mmol), **2** (0.3 mmol), rhodium catalyst (10 mol %), NHC ligand (2 equiv to Rh), *t*-BuONa (2 equiv to **1**), and toluene (0.2 mL). [b] ^1H NMR yield (internal standard: 1,1,2,2-tetrachloroethane). [c] Rhodium catalyst (3 mol %), NHC ligand (10 mol %), $AgPF_6$ (10 mol %). [d] 5 mol % of Rh-NHC and 10 mol % of Ag salt were employed.



Using bromobenzene (**1a**) and 4-methoxyphenol (**2a**) as coupling partners, optimization of the intermolecular *O*-arylation procedure was first investigated (Table 1). While the reaction was completely ineffective uisng only the $Rh_2(OAc)_4$ catalyst (10 mol %) in the absence of ligands (entry 1), the addition of certain NHC ligands provided much improved results. For instance, an NHC ligand derived from *N*,*N*-dicyclohexylimidazolium accelerated the *O*-arylation reaction to afford (4-methoxyphenyl)-phenyl ether (**3a**) in 50% NMR yield (entry 2). While a phosphine ligand alone was ineffective (entry 3), the combined use of NHC and phosphine ligands did not furnish more enhanced results (entry 4) compared to the conditions using the ICy NHC ligand alone (entry 2).

Not surprisingly, the type of employed rhodium precursors was highly important for an efficient *O*-arylation as seen in entry 5. A prolonged reaction time increased the product yield (entry 6). Using $Rh_2(OAc)_4$ as a metal precursor, various NHCs were subsequently screened to reveal that, as anticipated, *N*-substituents of the imidazolium skeleton significantly influenced the efficiency. For instance, the introduction of bulkier *N*-substituents such as I*t*-Bu or IAd resulted in an inhibition of the reaction (entries 7 and 8, respectively). In addition, the use of IMes in combination with $Rh_2(OAc)_4$, one of our successful systems utilized in the C−C bond formation,[9b] was also ineffective (entry 9).

Interestingly, an NHC ligand (Cy_2-bimy) derived from benzimidazolium salts was determined to be more effective than the corresponding imidazolyl derivative (compare entries 10 and 6). It should be noted that the benzimidazolium salts are readily prepared as a stable solid in one step starting from the corresponding benzimidazoles.[11a] Considering the fact that NHCs derived from benzimidazolium salts have rarely been utilized in transitions metal catalysis,[11] the present result would provide important insight for further investigations of NHCs in other reactions. While a monomeric Rh-NHC species[12] obtained from the use of $[RhCl(cod)]_2$ instead of $Rh_2(OAc)_4$ in combination with the Cy_2-bimy ligand provided only a moderate yield (entry 11), another NHC derived from an *i*Pr_2-benzimidazolium skeleton was more promising (e.g., entry 12).[13]

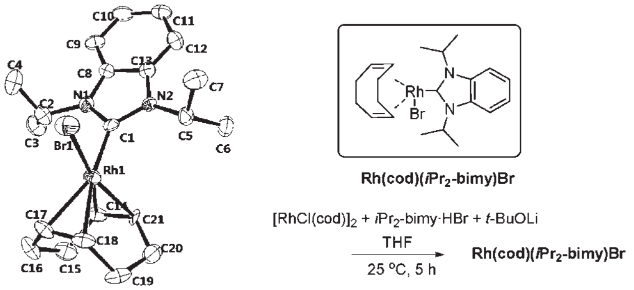


Figure 1. Crystallographic structure of Rh(cod)(*i*Pr_2-bimy)Br.

It was observed that cationic Rh species generated *in situ* by the addition of a silver species into the reaction mixture was highly active,[14] giving excellent product yields even

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(9) (a) Kim, M.; Lee, J.; Lee, H.-Y.; Chang, S. *Adv. Synth. Catal.* **2009**, *351*, 1807. (b) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8935. (c) Kim, M.; Chang, S. *Org. Lett.* **2010**, *12*, 1640. (d) Kwak, J.; Kim, M.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 3780.

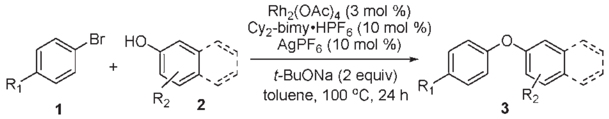
(10) (a) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Hwang, S. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 16158. (d) Hwang, S. J.; Kim, H. J.; Chang, S. *Org. Lett.* **2009**, *11*, 4588. (e) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127. (f) Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899. (g) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868. (h) Kim, J.; Chang, S. *J. Am. Chem. Soc.* **2010**, *132*, 10272.

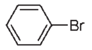
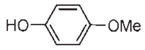
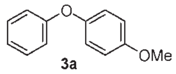
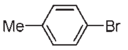
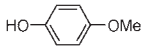
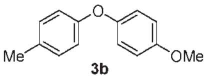
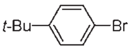
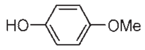
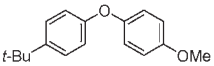
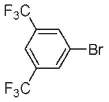
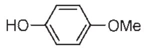
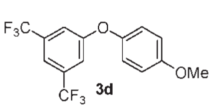
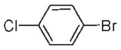
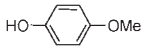
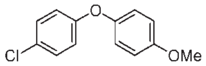
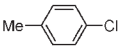
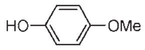
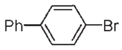
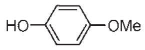
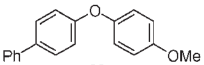
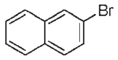
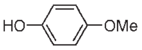
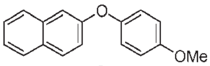
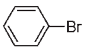
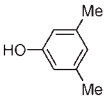
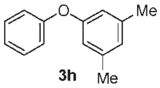
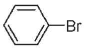
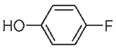
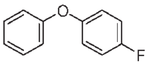
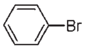
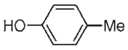
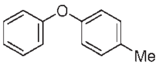
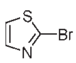
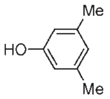
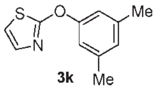
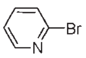
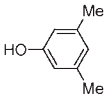
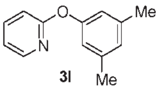
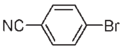
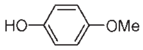
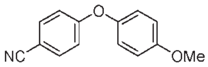
(11) (a) Huynh, H. V.; Han, Y.; Ho, J. H. H.; Tan, G. K. *Organometallics* **2006**, *25*, 3267. (b) Gung, B. W.; Bailey, L. N.; Craft, D. T.; Barnes, C. L.; Kirschbaum, K. *Organometallics* **2010**, *29*, 3450.

(12) The structure of isolated Rh(cod)(NHC) complexes has been characterized: (a) Türkmen, H.; Pape, T.; Hahn, F. E.; Çetinkaya, B. *Eur. J. Inorg. Chem.* **2008**, 5418. (b) Li, J.; Stewart, I. C.; Grubbs, R. H. *Organometallics* **2010**, *29*, 3765.

(13) Gaillard, S.; Nun, P.; Slawin, A. M. Z.; Nolan, S. P. *Organometallics* **2010**, *29*, 5402.

Table 2. *O*-Arylation of Aryl Bromides with Various Phenols[a,b]



entry	aryl bromide	phenol	product	yield (%)[b]
1			 **3a**	90
2			 **3b**	50
3			 **3c**	50
4			 **3d**	74
5			 **3e**	83
6			**3b**	25
7			 **3f**	60
8			 **3g**	80
9			 **3h**	75
10			 **3i**	38
11			 **3j**	70
12			 **3k**	70
13			 **3l**	80
14				<5[c]

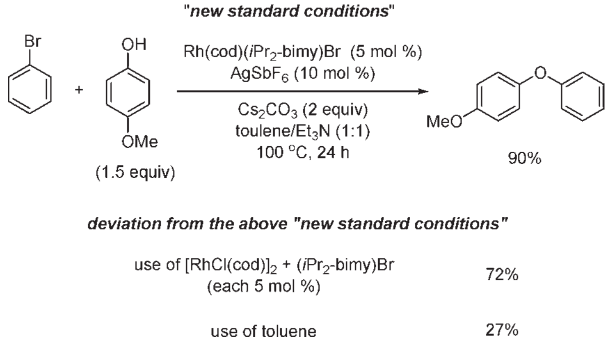
[a] Conditions: **1** (0.2 mmol), **2** (0.3 mmol), $Rh_2(OAc)_4$ (3 mol %), Cy_2-bimy·HPF_6 (10 mol %), $AgPF_6$ (10 mol %), *t*-BuONa (2 equiv to **1**), and toluene (0.2 mL) at 100 °C for 24 h. [b] Isolated yield. [c] ^{1}H NMR yield.

with less amounts of a $Rh_2(OAc)_4$ precursor (3 mol %, entry 13). Likewise, the use of an *in situ* generated monomeric cationic Rh-NHC species, Rh(cod)(*i*Pr_2-bimy)/PF_6, significantly improved the reaction efficiency when compared to the corresponding neutral catalyst (entries 12 and 14). A stable neutral complex of Rh(cod)(*i*Pr_2-bimy)Br was isolated, and its structure was unambiguously characterized (Figure 1). As expected, the catalytic activity of the isolated Rh-NHC species was observed to be as high as the neutral precursor if it was converted to the corresponding cationic species (entries 14 and 15).

Under the optimized conditions using $Rh_2(OAc)_4$-(Cy_2-bimy) as a catalyst, a range of substrates was employed in the *O*-arylation reaction (Table 2). Electronic variation on aryl bromides did not much influence the reaction efficiency (entries 2–5). When 4-bromochlorobenzene was employed, a selective *O*-arylation took place preferentially at the aryl-Br bond in good yield (entry 5). When 4-methylchlorobenzene was examined, a poor product yield of **3b** was obtained under the identical conditions (entry 6). Not only 4-bromobiphenyl but also 2-naphtyl bromide were readily reacted with 4-methoxyphenol to afford polyaryl and fused aromatic ether compounds (entries 7 and 8, respectively).

On the other hand, it was observed that electronic variation on the phenol counterpart was more sensitive to the reaction efficiency. For instance, whereas the reaction of phenols bearing electron-rich substituents smoothly produced an ether linkage, electron-deficient phenols underwent the arylation with lower efficiency (compare entries 9 and 10). Notably, *O*-arylation of heteroaryl bromides proceeded without difficulty. For example, 2-bromothiazole and 2-bromopyridine were readily reacted with phenols to furnish the desired ethers in synthetically acceptable yields (entries 12 and 13, respectively). Since the reaction conditions require a strong base (*t*-BuONa) in more than stoichiometric amounts, several functional groups were found to be incompatible. For instance, poor reactivity was observed in the reaction of 4-bromobenzonitrile with *p*-methoxyphenol with the recovery of the unchanged phenol being more than 90% (entry 14).

Scheme 1. Optimization of New Standard Reaction Conditions



In order to overcome the poor functional group tolerance observed under the above conditions, we tried to replace *t*-BuONa with milder bases (Scheme 1). After extensive screenings, we found that the use of Cs_2CO_3 in

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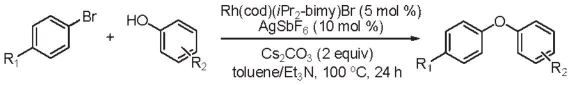
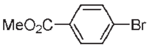
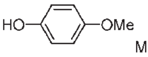
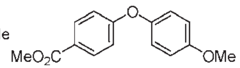
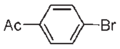
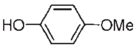
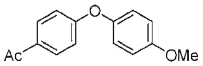
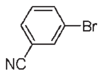
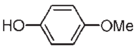
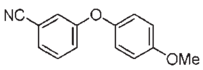
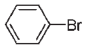
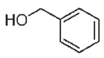
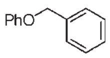
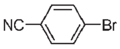
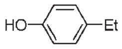
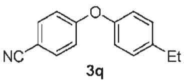
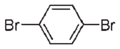
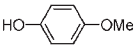
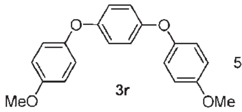
(14) Fructos, M. R.; de Fremont, P.; Nolan, S. P.; Diaz-Requejo, M. M.; Perez, P. J. *Organometallics* **2006**, *25*, 2237.

a cosolvent of toluene and triethylamine (1:1)[15] afforded a comparable result when compared to that using *t*-BuONa (compare the new standard conditions of Scheme 1 and entry 1 of Table 2).[15] Interestingly, a pregenerated Rh-NHC species, Rh(cod)(*i*Pr_2-bimy)Br, was more effective for the reaction than the *in situ* generation procedure adding a Rh precursor and NHC ligand separately. This result may be ascribed to a postulate that the formation of a Rh-NHC complex is less efficient under the new conditions using a milder base.

Table 3. *O*-Arylation Using Cs_2CO_3 as a Mild Base[a,b]



entry	aryl bromide	alcohol	product	yield (%)[b]
1			 **3m**	90
2			 **3n**	85
3			 **3o**	77
4[c]			 **3p**	60
5			 **3q**	70
6[c]			 **3r**	50

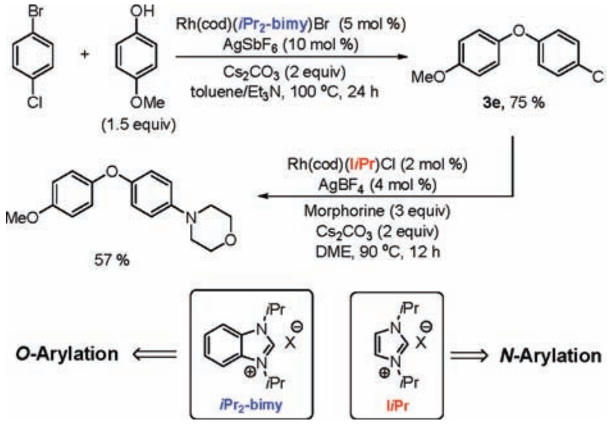
[a] Conditions: **1** (0.2 mmol), **2** (0.3 mmol), Rh(cod)(*i*Pr_2-bimy)Br (5 mol %), $AgSbF_6$ (10 mol %), Cs_2CO_3 (2 equiv to **1**), toluene (0.2 mL), and Et_3N (0.2 mL) at 100 °C for 24 h. [b] Isolated yield. [c] See the Supporting Information for details.

Under the newly developed conditions, the substrate scope was next examined especially with regard to functional group tolerance (Table 3). To our delight, it was observed that a wide range of labile organic groups were compatible under the new reaction protocol.

Indeed, sensitive functional groups such as an ester, acetyl, or cyano moiety were completely intact (entries 1, 2, and 3, respectively), which were not tolerated under the former conditions using *t*-BuONa as a base. It is noted that benzyl alcohol was readily arylated to give the desired benzyl phenyl ether (**3p**) in an acceptable yield (entry 4). However, simple aliphatic alcohols did not undergo etherification under the present conditions. When 1,4-dibromobenzene was reacted with a phenol, a double *O*-arylation took place leading to a symmetric diaryl ether (**3r**) in moderate yield (entry 6).

In line with our recent report,[9c] it was demonstrated that a suitable choice of NHC ligands can lead to chemoselective *O*- or *N*-arylation under otherwise similar Rh-catalyzed conditions (Scheme 2). A facile *O*-arylation of 4-bromochlorobenzene with 4-methoxyphenol was achieved by the action of a Rh-(*i*Pr_2-bimy) catalyst to give an aryl ether (**3e**) in good yield. Subsequent *N*-aryltion at the aryl−Cl bond of **3e** proceeded smoothly using a Rh-(I*i*Pr) system, which was previously shown to be effective for the *N*-arylation reaction reported by us.[9c]

Scheme 2. Tandem C−O and C−N Bond Formations



In conclusion, we have presented the first example of a Rh(NHC)-catalyzed *O*-arylation reaction. A suitable choice of both rhodium species and NHC ligands was crucial for achieving high catalytic activity. A wide range in substrate scope and high functional group tolerance were observed using the developed *O*-arylation procedure.

Acknowledgment. This work was supported by the National Research Foundation (Star Faculty Program, KRF-2008-C00024) and MIRC (NRF-2010-0001957). We acknowledge the Korea Basic Science Institute for the mass analysis and crystal analysis. We also thank Mr. Kyungseok Jeong for advice on crystal structure analysis.

Supporting Information Available. Experimental details, and ^1H and ^{13}C NMR spectra of new compounds, and CIF file of Rh(cod)(*i*Pr_2-bimy)Br. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] This set of conditions was previously employed by Buchwald et al. in the Pd-catalyzed C−O coupling reaction: Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146.