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Arylation of Heterocycles via Rhodium-Catalyzed C–H Bond Functionalization

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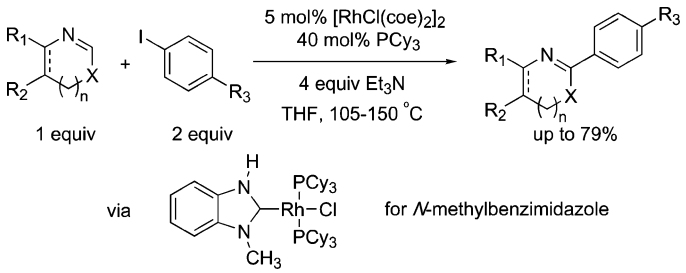
ABSTRACT



A new method for the rhodium-catalyzed arylation of a variety of heterocycles has been developed. The reaction provided moderate to good yields of the arylated products. A preliminary mechanistic investigation of this reaction revealed the intermediacy of an isolable *N*-heterocyclic carbene complex.

Metal-mediated cross-coupling reactions of organometallic reagents and halides constitute an essential class of carbon−carbon bond forming reactions[1] and provide access to a wide array of natural products, pharmaceuticals, ligands, and other materials. However, the organometallic starting materials required for these reactions frequently either are not commercially available or are expensive and result in undesired metal byproducts. Much greater starting material availability and elimination of stoichiometric metal byproducts could theoretically be achieved by the direct cross-coupling of organic compounds through functionalization at a C−H bond. Relatively few examples of this type of intermolecular coupling have been reported.[2] In general, such methods involve *ortho* arylation of benzene derivatives bearing a pendant directing group.[3] A notable exception was reported by Miura et al. in which a number of heterocycles were arylated using a palladium catalyst,[4] and a number of related methods have since emerged.[5] Sames and co-workers have also very recently developed a cobalt catalyst for the arylation of a number of azoles.[6]

Previous work in our laboratories has shown that the C2−H bond of various azoles can be activated by a rhodium-

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(1) (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998. (b) Yamamoto, Y., Negishi, E., Eds. *J. Organomet. Chem.* **1999**, *576*, 1−317 (special edition). (c) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2484. (e) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (f) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835−846.

(2) For reviews, see: (a) Dyker, G. *Chem. Ber.* **1997**, *130*, 1567−1578. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712. (c) Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212−237.

(3) (a) Satoh, T.; Inoh, J.; Kawamura, Y.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2239−2246. (b) Oi, S.; Fukita, S.; Inoue, Y. *Chem. Commun.* **1998**, 2439−2440. (c) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655−2658. (d) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3* (16), 2579−2581. (e) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783−1785. (f) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (g) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112−114.

(4) (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467−473.

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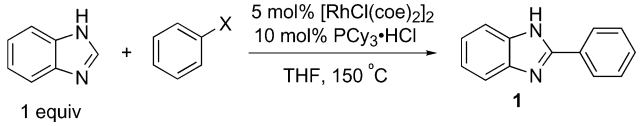
Table 1. Identification of Suitable Coupling Partner[a]



entry	X	equiv	time (h)	conversion (%)[b]
1	$B(OH)_2$	5	15	10
2[c]	$B(OH)_2$	5	13	0
3	$SnMe_3$	1.5	15	0
4	OTf	2	6	0
5	Cl	1.5	18	0
6	Br	1.5	18	10
7	I	1.5	18	15
8[e]	I	1.5	20	16

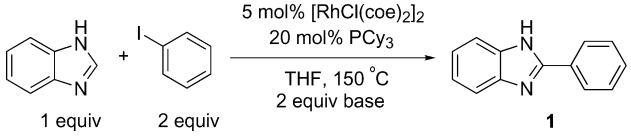
[a] coe = cyclooctene. [b] Conversion to **1** was monitored by GC−MS relative to hexamethyl-benzene internal standard. [c] 5 equiv of K_2CO_3 used. [d] Reaction performed at 105 °C. [e] Free phosphine (PCy_3) used.

(I) catalyst and subsequently coupled to an alkene, yielding the alkylated azole.[7] Investigation into the mechanism of this reaction revealed that the catalysis proceeds via an *N*-heterocyclic carbene (NHC) intermediate.[8] It was hypothesized that such an intermediate might be capable of undergoing other coupling processes, such as arylation.[9]

Initial efforts toward this goal focused on the identification of a suitable coupling partner to accomplish the desired cross-coupling reaction with benzimidazole using optimized conditions from the alkylation reaction (Table 1). Entry 1 shows that phenylboronic acid does indeed provide the desired product, but addition of a Brønsted base (entry 2), in analogy with conventional Suzuki couplings,[1a,e] gave no conversion. Neither trimethyl(phenyl)tin nor phenyl triflate gave encouraging results (entries 3 and 4). The best results in this initial screen were obtained using aryl halides as coupling partners (entries 5−8). The order of reactivity was found to be ArCl < ArBr < ArI. In the case of aryl iodides, product was observed even at the reduced temperature of 105 °C, and the free phosphine was found to be comparable to PCy_3•HCl (entry 8), which had proven advantageous in the alkylation reaction.[7c]

Because HI is the sole byproduct of the coupling reaction, it was thought that this strong acid might be responsible for catalyst decomposition or other deleterious side reactions. Thus, a thorough investigation of the effect of added base on the coupling reaction was undertaken (Table 2). A number of inorganic bases were initially screened (entries 1−4). Lithium carbonate provided a moderate increase in the observed conversion, but other oxygen bases, such as metal oxides, hydroxides, and alkoxides, failed to give further increases in conversion. Nitrogen bases were next screened (entries 5−8), and a positive influence of hindered, tertiary alkylamines was observed. Triethylamine served as an efficient and convenient base, providing the product in 32% conversion in 6 h.

Table 2. Effects of Added Bases on Conversion

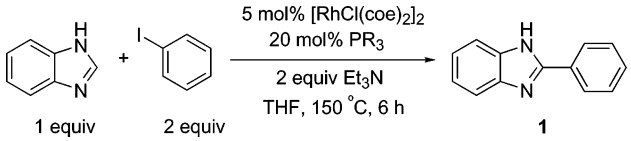


entry	base	time (h)	conversion (%)[a]
1	Li_2CO_3	6	20
2	MgO	6	18
3	NaOH	6	0
4	KO*t*Bu	6	0
5	DMP[b]	20	13
6	PMP[c]	20	9
7	iPr_2EtN	6	33
8	Et_3N	6	32

[a] Conversion to **1** was monitored by GC−MS relative to hexamethyl-benzene internal standard. [b] 2,6-dimethylpyridine. [c] 1,2,2,6,6,-pentamethylpiperidine.

A diverse array of phosphines, having variable steric and electronic properties, were also screened (Table 3). Triaryl phosphines, chelating phosphines, phosphites, and phosphoramidites gave no conversion. A number of hindered trialkylphosphines provided yields comparable to that using tricyclohexylphosphine (entries 2 and 4), but none could provide conversion higher than that originally obtained for tricyclohexylphosphine. Interestingly, conversion was ob-

Table 3. Effects of Phosphine on Conversion



entry	phosphine	conversion (%)[a]
1	PPh_3	0
2	P(*i*-Pr)$_3$	26
3	P(*t*-Bu)$_3$	2
4	P(*t*-Bu)$_2$Me	30
5	$Cy_2P(CH_2)_3PCy_2$	4
6	PCy_3	31
7[b]	PCy_3	50

[a] Conversion to **1** was monitored by GC−MS relative to hexamethyl-benzene internal standard. [b] 0.4 equiv PCy_3, 4 equiv Et_3N, 13 h.

(5) (a) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286−5287. (b) Gallagher, W. P.; Maleczka, R. E. *J. Org. Chem.* **2003**, *68*, 6775−6779. (c) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700−1701. (d) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2003**, *125*, 5274−5275.

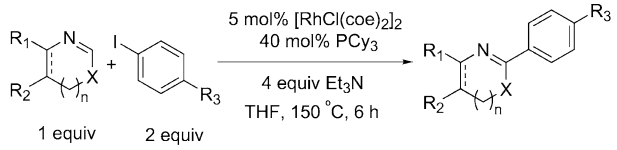
(6) Sezen, B.; Sames, D. *Org. Lett.* **2003**, *5*, 3607−3610.

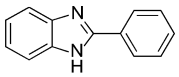
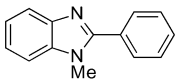
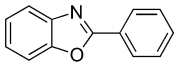
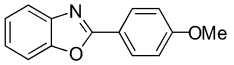
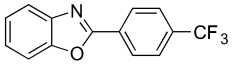
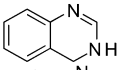
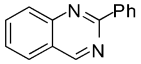
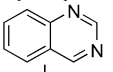
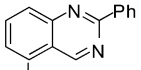
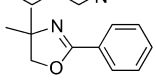
(7) (a) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 2685−2686. (b) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 13964−13965. (c) Tan, K. L.; Vasudevan, A.; Bergman, R. G.; Ellman, J. A.; Souers, A. J. *Org. Lett.* **2003**, *5*, 2131−2134.

(8) Tan, K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202−3203.

(9) McGuiness et al. have shown that NHC complexes can undergo stoichiometric oxidative addition and reductive elimination at a metal center: (a) McGuinness, D. S.; Cavell, K. J.; Skelton, B. W.; White, A. H. *Organometallics* **1999**, *18*, 1596−1605. (b) McGuinness, D. S.; Cavell, K. J.; Yates, B. F.; Skelton, B. W.; White, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 8317−8328.

Table 4. Substrate Generality



Entry	Heterocycle	Product		Yield (%)
1			**1**	56[a]
2			**2**	51[b]
3			**3**	79[b]
4			**4**	73[b]
5			**5**	30[a]
6			**6**	78[a]
7			**6**	0
8			**7**	51[c]

[a] 150 °C, 6 h. [b] 135 °C, 18 h. [c] 105 °C, 18 h.

served to increase with increasing phosphine concentration up to nearly 8 equiv relative to rhodium. Beyond this stoichiometry, a decrease in conversion was observed. Final optimization of reactant stoichiometry provided additional increases in conversion (Table 3, entry 7). Of solvents investigated, only THF and *o*-dichlorobenzene provided good yields of the desired products.

The optimal parameters obtained were applied toward the arylation of a number of different heterocycles with a variety of aryl iodides (Table 4). Of the aromatic heterocycles investigated (entries 1−5), benzoxazole provided the highest yield of arylated product. A trend favoring electron-rich aryl iodides was observed in the coupling to benzoxazole (entries 3−5). Nonaromatic heterocycles also provided good conversion to cross-coupled products.[10] As shown in entry 6, dihydroquinazoline reacted efficiently, providing 2-phenylquinazoline, presumably via cross-coupling followed by dehydrogenation of an initially formed 2-phenyldihydroquinazoline intermediate. Quinazoline provided no conversion to the cross-coupled product after 24 h at 150 °C (entry 7). The oxazoline in entry 8 also gave good conversion to the desired product at the reduced temperature of 105 °C. This result is notable because aryl oxazolines serve as versatile intermediates for the preparation of a range of compounds.[11]

(10) Our group has been investigating the use of nonaromatic substrates in the alkene coupling based on the hypothesized compatibility of these substrates with the proposed carbenoid mechanism (unpublished, ongoing work).

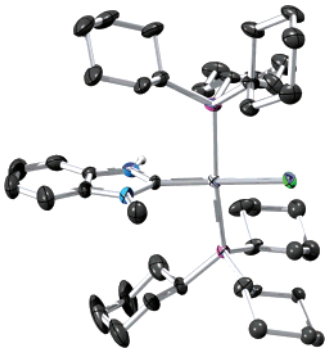


Figure 1. ORTEP drawing of **9**. A molecule of solvent and disorder in two of the cyclohexyl groups (alternate conformers) were omitted for clarity.

To aid in the optimization of the reaction, a preliminary mechanistic study was undertaken. In situ NMR studies of the catalytic reaction of *N*-methylbenzimidazole with iodobenzene revealed the rapid appearance and gradual depletion of ^{1}H and ^{31}P resonances consistent with signals observed for the NHC intermediate proposed in the analogous alkene coupling.[12] Indeed, complex **9** was obtained in 71% yield from the stoichiometric reaction of *N*-methylbenzimidazole with $[RhCl(coe)_2]_2$ and PCy_3.[13] Recrystallization provided X-ray quality crystals for structural characterization (Figure 1).

Complex **9** (0.1 equiv) was shown to be kinetically equivalent to the standard $[RhCl(coe)_2]_2/PCy_3$ system in catalyzing the coupling of *N*-methylbenzimidazole with iodobenzene under the optimized reaction conditions, suggesting its intermediacy in this reaction. Qualitative rate studies of the stoichiometric reaction of **9** with iodobenzene also revealed that this process is inhibited by added phosphine, suggesting that phosphine dissociation occurs prior to oxidative addition of iodobenzene. Additional resonances observed in the in situ ^{1}H NMR spectrum of the stoichiometric reaction indicated the presence of an additional transient carbenoid species.[14]

These preliminary observations suggest the mechanism shown in Scheme 1 for the reaction under investigation.[15]

(11) (a) Michael, R.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837−860. (b) Ie, Y.; Chatani, N.; Ogo, T.; Marshall, D. R.; Fukuyama, T.; Kakiuchi, F.; Murai, S. *J. Org. Chem.* **2000**, *65*, 1475−1488.

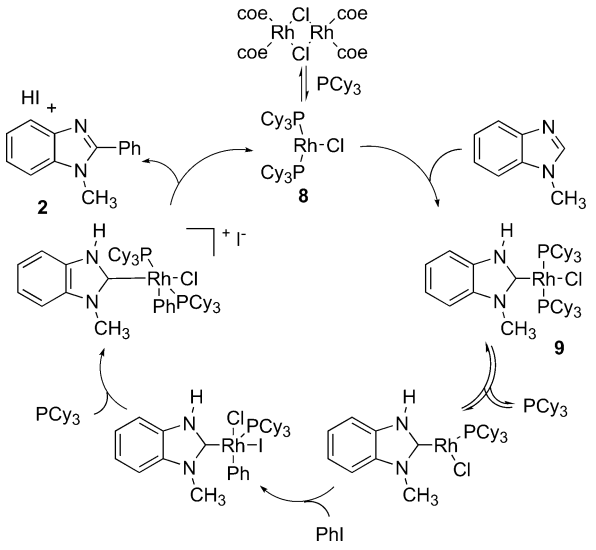
(12) Singlets at 10.19 and 4.16 ppm in the ^{1}H NMR spectrum, corresponding to the N−H and N−CH_3 protons, respectively, and a doublet at 30 ppm in the ^{31}P NMR spectrum were observed.

(13) For reviews of NHCs and their metal complexes, see: (a) Lappert, M. F. *J. Organomet. Chem.* **1988**, *358*, 185−214. (b) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162−2187. (c) Weskamp, T.; Böhm, V. P. W.; Herrmann, W. A. *J. Organomet. Chem.* **2000**, *600*, 12−22.

(14) Additional singlets at 10.28 and 4.19 ppm corresponding to the N−H and N−CH_3 protons, respectively, were observed during the reaction. This complex has not yet been characterized.

(15) Complex **8** is also in equilibrium with its dimer. For relevant studies on $RhCl(PCy_3)_2$, see: (a) Van Gaal, H. L. M.; Van Den Bekerom, F. L. A. *J. Organomet. Chem.* **1977**, *134*, 237−248. (b) Itagaki, H.; Murayama, H.; Saito, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1254−1257. (c) Wang, K.; Rosini, G. P.; Nolan, S. P.; Goldman, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 5082−5088.

Scheme 1. Proposed Mechanism for the Rhodium-Catalyzed Arylation of *N*-Methylbenzimidazole



In addition to the desired product, a large amount of benzene, comprising the mass balance of iodobenzene, formed during the course of the cross-coupling reaction. Addition of neither dihydroanthracene nor 2,6-di-*tert*-butyl-*p*-cresol (BHT, 0.5 equiv) to the reaction mixture increased conversion to either benzene or the desired product, indicating that radical pathways are probably not responsible for the deleterious side reaction.

The ^{1}H NMR spectrum of a solution generated in situ from heating 1 equiv of **8** in d_8-THF contained resonances[16] consistent with those of a bisphosphinochlororhodium(III) hydride[17] and led to the hypothesis that iodobenzene was undergoing competitive hydrodehalogenation.[18] It is therefore proposed that the rhodium center could undergo either cyclometalation[19] or intermolecular C−H activation with one of the cyclohexyl groups of a phosphine ligand.[20] β-Hydride elimination from the metalated species would then give dihydride complex **10**. This species would account for the observed NMR spectroscopic data (Scheme 2). Elimination of HCl followed by addition of PhI and subsequent elimination of the observed PhH would give a bisphosphinorhodium(I) iodide.

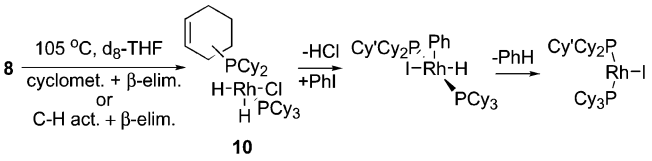
(16) Initially, a doublet of triplets at −23 ppm and a singlet at 5.6 ppm in the ^{1}H NMR spectrum and a doublet at 50.5 ppm in the ^{31}P NMR spectrum were observed. Continued heating of this solution led to formation of two additional doublets at 50.5 and 48.5 ppm in the ^{31}P NMR spectrum. These peaks are consistent with exchange of phosphine on **14** to give a mixture of tricyclohexyl and cyclohexylcyclohexenyl phosphines.

(17) Van Gaal, H. L. M.; Ver Laak, J. M. J.; Posno, T. *Inorg. Chim. Acta* **1977**, *23*, 43−51.

(18) For an extensive review on hydrodehalogenation, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009−4091.

(19) Similar reactivity was observed for $RuH_2(H_2)_2(PCy_3)_2$ upon reaction of this complex with ethylene: Christ, M. L.; Sabo-Etienne, S.; Chaudret, B. *Organometallics* **1995**, *14*, 1082−1084 and references therein.

Scheme 2. Proposed Mechanism for Hydrodehalogenation of PhI



To test this hypothesis, the reactivity of $Rh(Cl)(H)_2(PCy_3)_2$ **11** was studied. Heating 0.1 equiv of **11** with iodobenzene and triethylamine in d_8-THF gave rise to a solution exhibiting a ^{31}P NMR spectrum containing peaks identical to those observed in the spectrum obtained from heating a solution of 0.1 equiv of **8**, iodobenzene, and Et_3N in d_8-THF, indicating a common product mixture for the two reactions. High conversion of iodobenzene to benzene was observed in each case. Notably, comparison of these spectra to that obtained in situ during the catalytic arylation of benzimidazole under optimized reaction conditions revealed the presence of these same peaks. It therefore seems likely that a rhodium hydride of structure similar to that of **10** is responsible for competitive depletion of iodobenzene. Conversion of **8** to a catalytically inactive species would be responsible for the moderate yields obtained.

In conclusion, a new method for the arylation of heterocycles has been developed. The arylation is believed to proceed via a NHC intermediate, which defines the substrate scope of the reaction. Additionally, a competitive hydrodehalogenation reaction was identified. This insight may allow further optimization of yield though use of appropriate phosphine ligands. Continued efforts toward elucidation of the mechanism of this transformation and use of arylboronic acids as coupling partners are also underway.

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Supporting Information Available: Crystallographic data, full experimental details, and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035985E

(20) Itagaki et al. reported formation of **14** (vide infra) from **10** in cyclohexane solution in ref 12b.