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Rhodium(NHC)-Catalyzed Amination of Aryl Bromides

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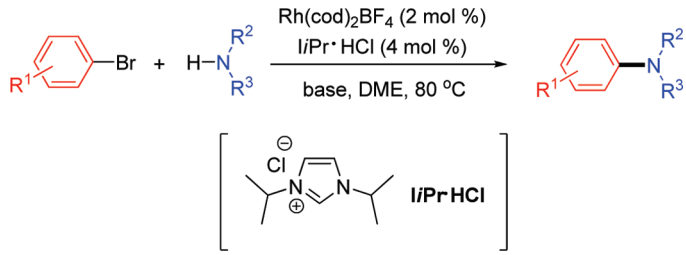
ABSTRACT



A rhodium-catalyzed amination reaction of aryl halides with amines has been developed with the use of a N-heterocyclic carbene (NHC) ligand (I*i*Pr = 1,3-diisopropylimidazol-2-ylidene). The active metal species responsible for the reaction progress was identified. The developed procedure of the Rh-catalyzed*N*-arylation is convenient to carry out under mild reaction conditions displaying a wide range of substrate scope and high degree of functional group tolerance.

Metal-facilitated C−N bond formation has been significantly advanced in recent years.[1] In particular, the palladium-[2] or copper-catalyzed[3] *N*-arylation of aryl halides with amines is most extensively explored. The catalytic amination reaction has been comprehensively studied to reveal its mechanistic and synthetic aspects.[4] Despite these achievements, there is still room for the exploration of new catalytic systems that can display different views of reactivity, functional group tolerance, and diversity.[5]

On the other hand, rhodium-catalyzed C−N bond formation has flourished mainly by the advent of hydroamination of alkenes/alkynes,[6] C−H amination via nitrene transfer,[7] and C−H amination via decomposition of azide moieties.[8]

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(4) (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584.

(5) For selected examples of *N*-arylation with metal species other than Pd or Cu, see: Ni catalysis: (a) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (b) Gradel, B.; Brenner, E.; Schneider, R. L.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 5689. (c) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311. (d) Gao, C. Y.; Cao, X. B.; Yang, L. M. *Org. Biomol. Chem.* **2009**, *7*, 3922. Fe catalysis: (e) Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 8862. (f) Correa, A.; Mancheno, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (g) Correa, A.; Carril, M.; Bolm, C. *Chem.−Eur. J.* **2008**, *14*, 10919. (h) Guo, D. L.; Huang, H.; Xu, J. Y.; Jiang, H. L.; Liu, H. *Org. Lett.* **2008**, *10*, 4513. Co catalysis: (i) Toma, G.; Fujita, K.; Yamaguchi, R. *Eur. J. Org. Chem.* **2009**, 4586. (j) Teo, Y. C.; Chua, G. L. *Chem.−Eur. J.* **2009**, *15*, 3072.

(6) (a) Beller, M.; Eichberger, M.; Trauthwein, H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2225. (b) Hartung, C. G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* **2001**, *66*, 6339. (c) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608. (d) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042. (e) Fukumoto, Y.; Asai, H.; Shimizu, M.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 13792. (f) Liu, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 1570.

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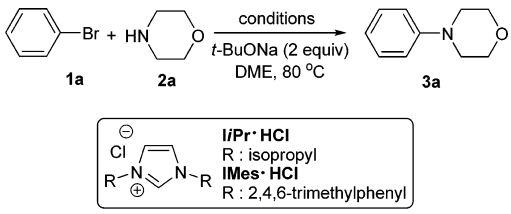
During the course of our studies on the C−N bond formation reactions,[9] we were interested in the new reactivity of N-heterocyclic carbene (NHC)-bound rhodium complexes in the *N*-arylation reaction.[10] Described herein is our study on the development and scope of a Rh(NHC)-catalyzed amination of aryl bromides with amines.

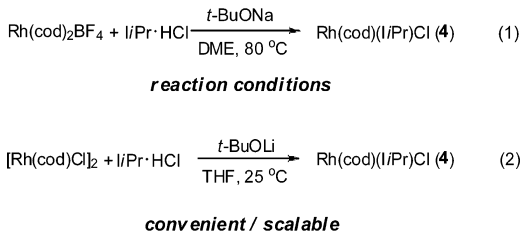
With the use of bromobenzene (**1a**) and morpholine (**2a**) as test substrates, optimization of an intermolecular *N*-arylation was first tried (Table 1). While no conversion was observed with rhodium species in the absence of NHC (entries 1−2), addition of a *N*,*N*′-diisopropyl NHC precursor (I*i*Pr·HCl) resulted in a full conversion at 80 °C in the presence of *t*-BuONa (entry 3). It turned out that structure of NHCs displayed significant effects on the resulting Rh catalyst's activity as demonstrated in entry 4. It was interesting that no reaction was observed when tricyclohexylphosphine was employed as an external ligand instead of I*i*Pr (entry 5).

Table 1. Optimization of the Reaction Conditions[a]



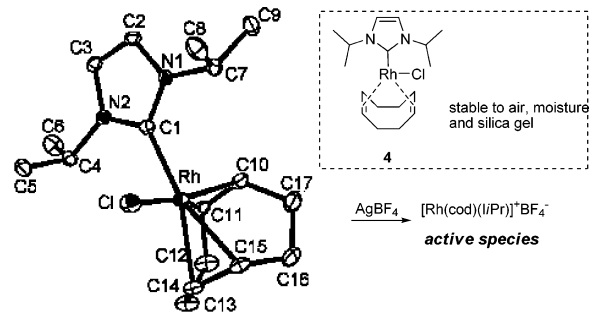
entry	conditions	time (h)	convn (%)[b]
1	$RhCl(PPh_3)_3$	24	<1
2	$Rh(cod)_2BF_4$	24	<1
3	$Rh(cod)_2BF_4$ + I*i*Pr·HCl	12	>99
4	$Rh(cod)_2BF_4$ + IMes·HCl	12	<1
5	$Rh(cod)_2BF_4$ + PCy_3	12	<1
6	Rh(cod)(I*i*Pr)Cl (**4**)	12	50
7[c]	Rh(cod)(I*i*Pr)Cl (**4**) + $AgBF_4$	12	>99
8[c]	$[Rh(cod)Cl]_2$ + I*i*Pr·HCl + $AgBF_4$	12	>99

[a] Conditions: **1a** (0.2 mmol), **2a** (3 equiv), Rh species (2 mol %), additive (4 mol %), *t*-BuONa (2 equiv), and 1.2-dimethoxyethane (0.2 mL) at 80 °C. [b] GC-MS conversion with 1,3-benzodioxole as an internal standard. [c] $AgBF_4$ (10 mol %) was used.



A neutral NHC-bound rhodium species Rh(cod)(I*i*Pr)Cl (**4**) could be isolated under the reaction conditions (eq 2) and its structure was confirmed by ^1H and ^{13}C NMR, and an X-ray crystallographic analysis (Scheme 1).[11] It should be mentioned that the stable Rh complex **4** could also be prepared in a large scale by a more convenient procedure at ambient conditions (eq 2).[11]

Scheme 1. Crystallographic Structure of Rh(cod)(I*i*Pr)Cl (**4**)



While the *isolated* Rh species **4** turned out to be less reactive for the *N*-arylation reaction (entry 6), the reactivity was significantly increased upon the addition of catalytic amounts of $AgBF_4$ salt (entry 7), strongly suggesting that *the active species would be the corresponding cationic complex [Rh(cod)(IiPr)]*$^+$. A full conversion was also achieved with use of a Rh precursor and NHC upon the addition of a silver salt (entry 8).[12]

Under the optimized conditions, the substrate scope was subsequently investigated (Table 2). In general, electronic variation on aryl bromides bearing different types of substituents displayed negligible effects on the reaction efficiency (**3a**−**e**). Not only polyaryl but also heteroaryl bromides smoothly underwent the amination reaction to afford the desired *N*-morpholinyl (hetero)arene derivatives in high yields (**3f**−**h**).

While anilines having either neutral or electron-withdrawing substituents were facile reactants (**3i**−**j**), reaction of electron-rich anilines gave a rather moderate yield (**3k**). On the other hand, excellent product yields were obtained from the reaction of bromobenzene with a wide range of aliphatic amines such as benzyl (**3*l***), *n*-pentyl (**3m**), cyclohexyl (**3n**), *β*-substituted alkyl (**3o**), or pyrrolidine (**3p**) moieties with high efficiency. It should be mentioned that, in contrast to

(8) Shen, M.; Leslie, B. E.; Driver, T. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5056.

(9) (a) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687. (b) Lee, J. M.; Ahn, D.-S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. *J. Am. Chem. Soc.* **2006**, *128*, 12954. (c) Chang, S.; Lee, M. J.; Jung, D. Y.; Yoo, E. J.; Cho, S. H.; Han, S. K. *J. Am. Chem. Soc.* **2006**, *128*, 12366. (d) Han, H.; Park, S. B.; Kim, S. K.; Chang, S. *J. Org. Chem.* **2008**, *73*, 2862. (e) Kim, J.; Lee, S. Y.; Lee, J.; Do, Y.; Chang, S. *J. Org. Chem.* **2008**, *73*, 9454. (f) Kim, J.; Chang, S. *Chem. Commun.* **2008**, 3052. (g) Cho, S. H.; Kim, J. Y.; Lee, S. Y.; Chang, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9127.

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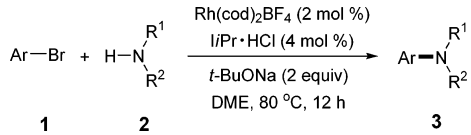
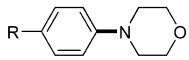
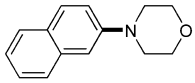
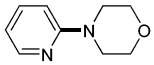
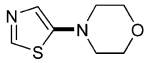
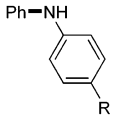
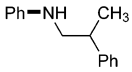
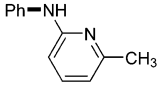
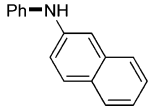
(11) See the Supporting Information for details.

(12) While the amination reaction took place smoothly and reproducibly when the in situ generated $Rh(cod)_2BF_4$ species was used, reactions with the rhodium complex purchased commercially showed rather unreproducible results especially in the case of secondary amines. This can be attributed to the purity of certain bottles of the Rh species (confirmed by ICP-AES analysis). For a similar example of the effects of purity of commercial products on the reaction efficiency, see: Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070.

Table 2. Amination of Aryl Bromides with Various Amines[a,b]



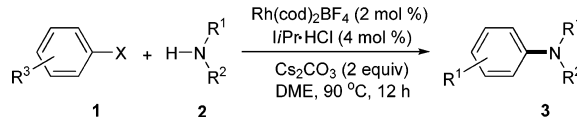
entry	product		yield (%)[b]
1		R = H (**3a**)	93%
2		CH_3 (**3b**)	96%
3		*t*-Bu (**3c**)	93%
4		CH_3O (**3d**)	74%
5		CF_3 (**3e**)	98%
6		**3f**	93%
7		**3g**	80%
8		**3h**	89%
9		R = H (**3i**)	77%
10		Cl (**3j**)	81%
11		CH_3O (**3k**)	51%
12		R = $PhCH_2$ (**3l**)	92%
13		*n*-C_5H_{11} (**3m**)	89%
14		cyclohexyl (**3n**)	92%
15		**3o**	93%
16		**3p**	95%
17		**3q**	90%
18		**3r**	94%

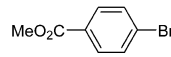
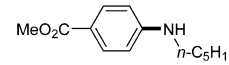
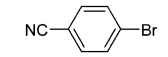
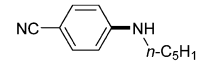
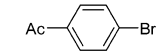
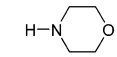
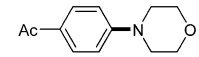
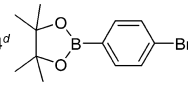
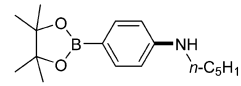
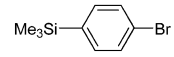
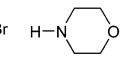
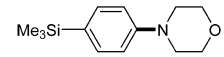
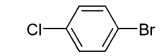
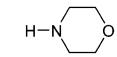
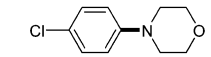
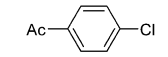
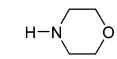
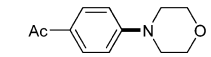
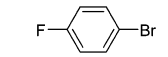
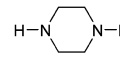
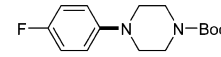
[a] Conditions: **1** (0.4 mmol), **2** (3 equiv), $Rh(cod)_2BF_4$ (2 mol %), I*i*Pr·HCl (4 mol %), and *t*-BuONa (2 equiv) in 1,2-dimethoxyethane (0.4 mL) at 80 °C for 12 h. [b] Isolated yield.

some cases of palladium catalysis,[13] *over arylation of primary amines was not observed at all in the present Rh-catalyzed amination route.*

Due to the fact that the use of a strong base such as *t*-BuONa may lead to a relatively low level of functional group tolerance as seen in the Pd-catalyzed *N*-arylation,[2a] we scrutinized a milder base to replace *t*-BuONa. Among various organic and inorganic bases examined, it was found that, similar to the Pd systems,[14] the employment of Cs_2CO_3 as a base greatly improved the functional group compatibility of the reaction (Table 3).

Table 3. Amination with Cs_2CO_3 as a Mild Base[a,b]



entry	aryl halide	amine	product	yield (%)[b]
1		$H_2N-n-C_5H_{11}$		**3s**, 95
2[c]		$H_2N-n-C_5H_{11}$		**3t**, 88
3				**3u**, 85
4[d]		$H_2N-n-C_5H_{11}$		**3v**, 72
5				**3w**, 98
6				**3x**, 83
7[c]				**3u**, 95
8				**3y**, 82

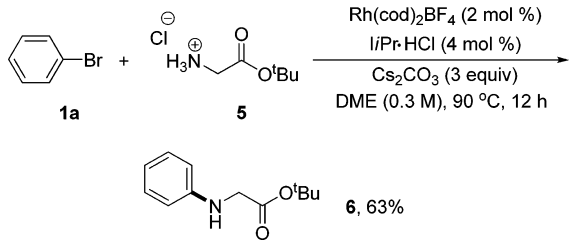
[a] Conditions: **1** (0.4 mmol), **2** (3 equiv), $Rh(cod)_2BF_4$ (2 mol %), I*i*Pr·HCl (4 mol %), and Cs_2CO_3 (2 equiv) in 1,2-dimethoxyethane (0.4 mL) at 90 °C for 12 h. [b] Isolated yield. [c] The reaction was conducted at 120 °C. [d] **2** (1.5 equiv) and *t*-BuONa (1.5 equiv) were used for 6 h.

We were pleased to observe a high degree of functional group tolerance under the new conditions employing Cs_2CO_3. In fact, various base-labile groups such as ester, nitrile, or ketone were tolerated to afford the desired aniline derivatives in high yields albeit at slightly higher temperatures (entries 1−3). It is also noteworthy that the pinacolboronate group was intact in the Rh-catalyzed amination (entry 4) while such substrate could be problematic in the Pd-catalyzed reaction. In addition, a silyl group was completely compatible to the reaction conditions (entry 5).

(13) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369. (b) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327.

(14) (a) Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359. (b) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (c) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.

Scheme 2. *N*-Arylation of Amino Acid Ester



It is notable to achieve a selective amination on an arylbromo moiety in the presence of a chloro group (entry 6) although the *N*-arylation of activated chloroarenes was also possible albeit at 120 °C (entry 7). In addition, labile functional groups such as Boc-protected piperazine underwent the *N*-arylation without difficulty (entry 8).

Additionally, the arylation protocol was briefly examined to see whether the scope can be extended in arylation of amino acid esters. It was observed that the reaction of bromobenzene with glycine *tert*-butyl ester hydrochloride proceeded smoothly under the developed conditions to afford *N*-phenyl glycine *tert*-butyl ester with synthetically acceptable yield (Scheme 2).

In summary, we have disclosed, to the best of our knowledge, the first example of the Rh(NHC)-catalyzed amination of aryl halides. The reaction is convenient to carry out under mild conditions displaying a wide range of substrate scope and high degree of functional group tolerance. Detailed studies on the mechanistic aspects and synthetic applications are now in progress.

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Supporting Information Available: Experimental procedure and characterization data including copies of ^{1}H and ^{13}C NMR spectra of obtained compounds and CIF file of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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