ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Ru(II)-Catalyzed *ortho*-C−H Amination of Arenes and Heteroarenes at Room Temperature

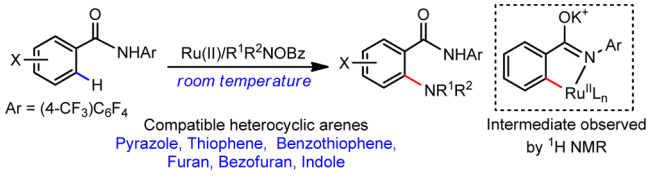
Ming Shang,[†] Shao-Hang Zeng,[†] Shang-Zheng Sun,[†] Hui-Xiong Dai,*[,†] and Jin-Quan Yu*[,†,‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China, and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

hxdai@sioc.ac.cn; yu200@scripps.edu

Received September 2, 2013

ABSTRACT



The Ru(II)-catalyzed *ortho*-C−H amination directed by a weakly coordinating amide auxiliary with *O*-benzoyl hydroxylamines at room temperature has been achieved. This reaction is compatible with heterocycles including pyrazole, thiophene, benzothiophene, furan, benzofuran, and indole.

Aryl- and heteroarylamines are ubiquitous among pharmaceuticals, agrochemical, and organic materials.[1] Therefore, development of efficient synthetic methodologies toward the construction of C−N bonds has attracted considerable attention. Among these methods, the Buchwald−Hartwig amination reaction of aryl halides with amines has been most extensively studied and practiced in both academic and industrial settings.[2] Inspired by a number of seminal reports on Pd-catalyzed intramolecular C−H amination reactions,[3] Pd-catalyzed intermolecular amination of C−H bonds has been developed as an alternative method for preparing arylamines (Scheme 1).[4,5] This new approach could prove especially valuable when access to certain aryl halides in a synthetic sequence are challenging. For example, Pd-catalyzed *ortho*-C−H amination[4] has recently been used to perform a late-stage diversification of an advanced intermediate affording novel analogues of hongoquercin A.[6] While Pd-catalyzed C−H amination using electrophilic *N*-benzoyloxyamines allows for the introduction of a wide range of secondary amines onto simple benzamide substrates, further development of this approach using other transition metal catalysts[7−9] could improve the scope and practicality of this C−H amination

[†] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.
[‡] The Scripps Research Institute.

(1) (a) Hili, R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284. (b) *Amino Group Chemistry, From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2007.

(2) For recent reviews, see: (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338.

(3) For examples of intramolecular Pd-catalyzed C−H amination reactions, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (c) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (d) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (e) Neumann, J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892. (f) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (g) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (h) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.

(4) For Pd-catalyzed intermolecular C−H amination with alkylamines, see: Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652.

(5) For Pd-catalyzed intermolecular C−H amidation, see: (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (b) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (c) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (d) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (e) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (f) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694.

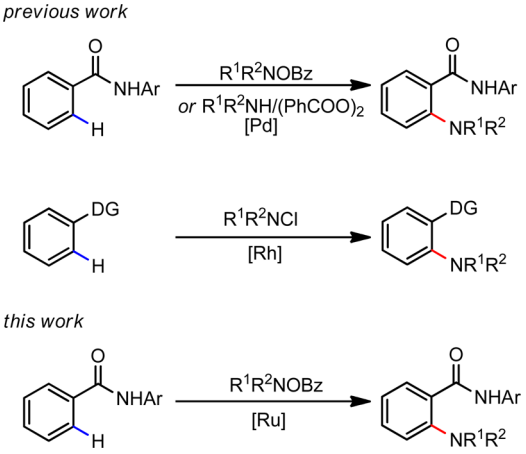
(6) Rosen, B. R.; Simke, L. R.; Thuy-Boun, P. S.; Dixon, D. D.; Yu, J.-Q.; Baran, P. S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7458.

10.1021/ol402515s

reaction. Herein, we report the Ru-catalyzed *ortho*-C−H amination of benzamides with *N*-benzoyloxyamines at room temperature (Scheme 1), demonstrating the superior reactivity of our weakly coorindating directing group with Ru(II) catalysts. The scope of this reaction is substantially broader than our Pd-catalyzed C−H amination reaction[4] with respect to heteroarenes, which typically inhibit C−H activation.

The strong coordination of nitrogen atoms in either the aminating reagents or products to the Pd center could be problematic for developing C−H amination activation reactions assisted by σ-chelation of simple functional groups. We have recently developed an efficient electron-deficient amide auxiliary for C−H activation of carboxylic acid substrates. The origin of the observed reactivity of this auxiliary stems from (a) in situ generation of the imidate allowing for optimum orientation between the directing atom and the target C−H bond required for facile C−H cleavage and (b) the weakly bound arylpalladium intermediates being highly reactive toward electrophilic or nucleophilic reaction partners used for functionalizations. In light of recent progress in Ru(II)-catalyzed C−H functionalizations,[10] we began to investigate whether this auxiliary can be exploited to develop a Ru(II)-catalyzed C−H amination reaction, which will complement our Pd(II)-catalyzed C−H amination reaction in terms of practical operation and scope. Thus, we were pleased to find that C−H amination of *N*-arylbenzamide substrate **1a** with 2 equiv of *N*-benzoyloxyamines **2a** proceeded in the presence of 10 mol % $[RuCl_2(p\text{-cymene})]_2$ and 2 equiv of K_2CO_3 in CH_3CN to give the desired amination product **3a** in 22% yield (Table 1, entry 3).

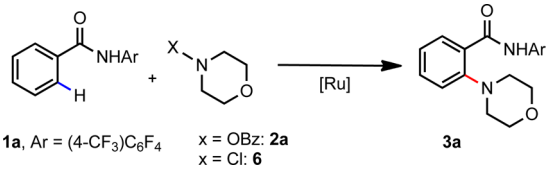
Scheme 1. Transition-Metal-Catalyzed C−H Amination with Electrophilic Amination Reagent



To improve this reaction, we tested other Ru catalysts and found they were not reactive (Table 1, entries 1, 2). An extensive screening of reaction parameters showed that acetone was also a suitable solvent which is not commonly used in Pd-catalyzed C−H activation (Table 1, entry 4). We also found that the oxidant is not required for this reaction [see the Supporting Information]. Extending the reaction time to 36 h afforded a mixture of mono- and diproduct in 44% yield with a 3.4:1 mono/di ratio (entry 6). Attempts to further improve the yield by extending the reaction time was not successful (entry 7).

We were surprised to find that the yield increased to 69% (mono/di = 1.7:1) by running the reaction under Ar (entry 8). To our delight, the yield was further improved to 82% (mono/di = 2.4:1) when the reaction concentration was increased by 2-fold (entry 9). The use of 3 equiv of aminating reagent **2a** afforded the product **3a** in 92% yield (mono/di = 2:1) (entry 10). Finally, switching **2a** to aminating reagent *N*-chloroamines **6** decreased the yield to 25% (entry 12). The use of 5 mol % $[RuCl_2(p\text{-cymene})]_2$ gave a mixture of mono- and diamination products in 54% yield.

Table 1. Optimization of Reaction Conditions[a]



entry	[Ru]	amine	solcent	time (h)	yield (%)[b]
1	$RuH_2(PPh_3)_4$	**2a**	CH_3CN	18	0
2	$RuH_2(CO)(PPh_3)_3$	**2a**	CH_3CN	18	0
3	$[RuCl_2(p\text{-cymene})]_2$	**2a**	CH_3CN	18	22
4	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	18	23
5	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	6	16
6	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	36	34 + 10(di)
7	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	48	35 + 12(di)
8[c]	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	36	44 + 25(di)
9[c,d]	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	36	58 + 24(di)
10[c,e]	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	36	60 + 32(di)
11[c,f]	$[RuCl_2(p\text{-cymene})]_2$	**2a**	acetone	36	42 + 11(di)
12[c]	$[RuCl_2(p\text{-cymene})]_2$	**6**	acetone	36	25 + 6(di)

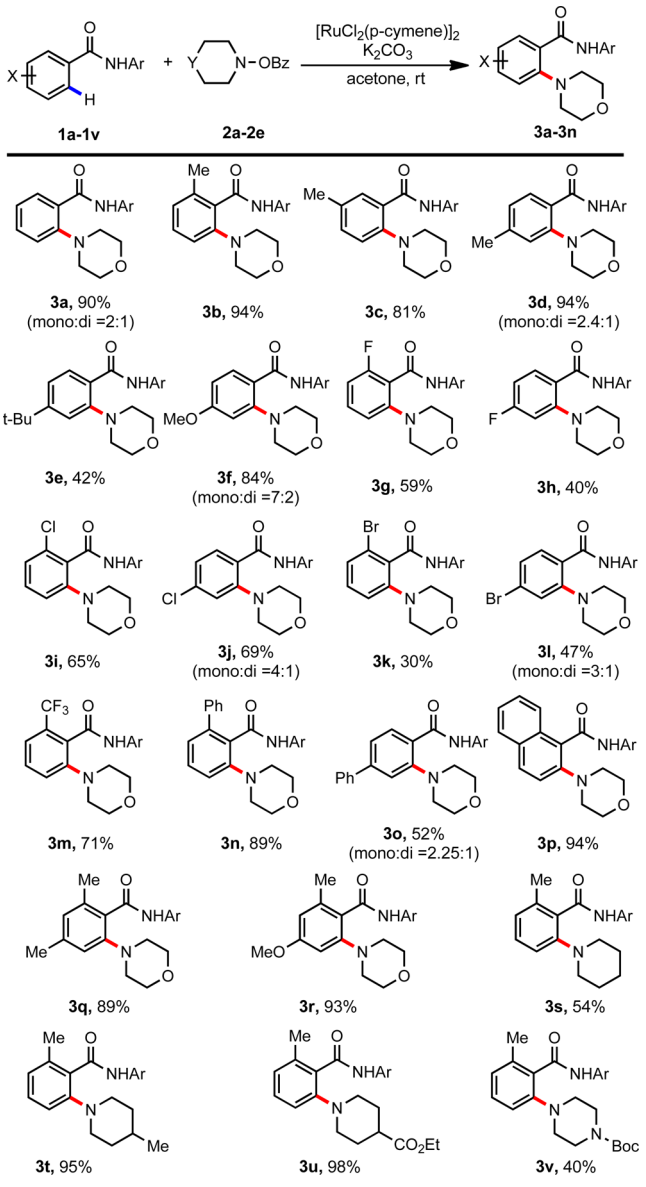
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mmol %), K_2CO_3 (0.4 mmol), solvent (1 mL), air, rt. [b] Yield determined by ^1H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [c] Ar. [d] **1a** (0.2 mmol), **2a** (0.4 mmol). [e] **1a** (0.2 mmol), **2a** (0.6 mmol). [f] **1a** (0.2 mmol), **2a** (0.3 mmol).

(7) For Rh-catalyzed C−H amination reactions: (a) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Org. Lett.* **2012**, *14*, 272. (b) Grohmann, C.; Wang, H.; Glorius, F. *Org. Lett.* **2012**, *14*, 656.

(8) For examples of Cu(II)-catalyzed C−H amination reactions with amides and anilides, see: (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (c) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (d) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (e) Kawano, T.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2010**, *132*, 6900. (f) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217. (g) Cho, S. H.; Yoon, J.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 5996. (h) Tran, L. D.; Roane, J.; Daugulis, O. *Angew. Chem., Int. Ed.* **2013**, *52*, 6043.

(9) For a cobalt-catalyzed C−H amination of azoles via acid-promoted nucleophilic attack, see: Kim, J. Y.; Cho, S. H.; Joseph, J.; Chang, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9899.

Scheme 2. Ru-Catalyzed C−H Amination of Arenes Scope[a,b]

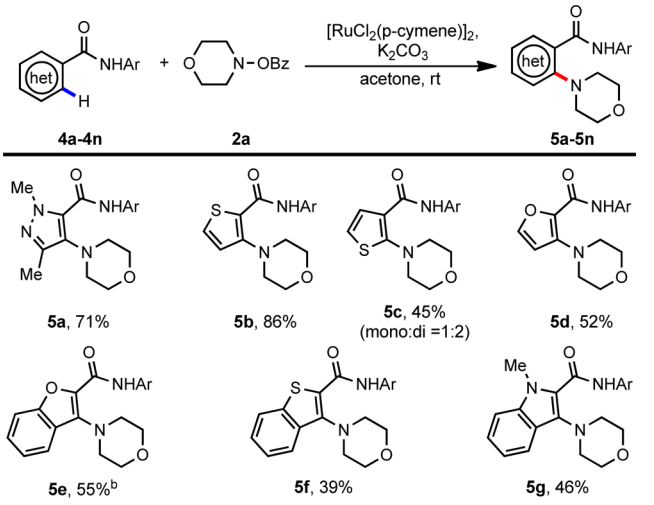


[a] Reaction conditions: **1a-1v** (0.2 mmol), **2a**−**2e** (0.6 mmol), [$RuCl_2$-(*p*-cymene)]$_2$ (10 mmol %), K_2CO_3 (0.4 mmol), Acetone (1 mL), Ar, rt, 36 h. [b] Isolated yield.

With these optimized conditions in hand, we surveyed the substrate scope of this amination reaction (Scheme 2). Amination of arenes bearing methyl substitution at *ortho*-, *meta*-, and *para*-positions gave the desired products in 94%, 81%, and 94% yields respectively (**3b**−**3d**). Sterically bulky *t*-Bu- and electron-donating MeO− substituents on arenes were also tolerated (**3e** and **3f**). Amination of fluorinated and chlorinated arenes proceeded smoothly to give the corresponding products (**3g**−**3j**) in 40−69% yields. Brominated arenes were also compatible in this reaction, albeit giving lower yields (**3k**, **3l**). Amination of arene containing an *ortho*-CF_3 group afforded **3m** in 71% yield. Phenyl-substituted arenes also afforded the desired products in 89% and 52% yields with the *ortho*-substituted substrate being more reactive (**3n** and **3o**). A naphthalene substrate was aminated to give **3p** in excellent yield (94%). Tetrasubstituted arylamines were obtained in good yields using trisubstituted arenes as substrates (**3q** and **3r**). Next, we examined the scope of the amine partners. Various secondary (hetero)cyclic *N*-benzoyloxyamines containing the ester and Boc protecting group was successfully incorporated into arene substrates in 40−98% yields (**3s**−**3v**). However, this reaction is largely limited to six-membered amines. For instance, pyrrolidine is not compatible and amination with diethyl amine gave the desired product in 20% yield.

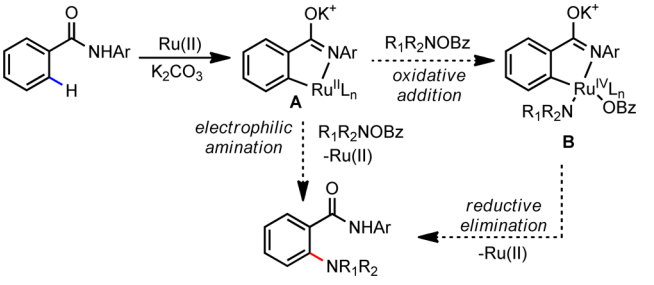
Considering the importance of heteroaryl amines in medicinal chemistry, we examined the compatibility of this amination protocol with a number of heterocyclic substrates. We were pleased to find that amination of

Scheme 3. Ru-Catalyzed C−H Amination of Heteroarenes Scope[a,b]



[a] Reaction conditions: **4a**−**4n** (0.2 mmol), **2a** (0.6 mmol), [$RuCl_2$-(*p*-cymene)]$_2$ (10 mmol %), K_2CO_3 (0.4 mmol), acetone (1 mL), Ar, rt, 36 h. [b] Isolated yield.

Scheme 4. Possible Reaction Pathways with Ru(II) Catalyst



(10) Recent reviews on ruthenium(II)-catalyzed C−H bond functionalization: (a) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744. (b) Ackermann, L. *Acc. Chem. Res.* **2013**, *46*, DOI:10.1021/ar3002798. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (d) Ackermann, L.; Vicente, R. *Top. Curr. Chem.* **2010**, *292*, 211.

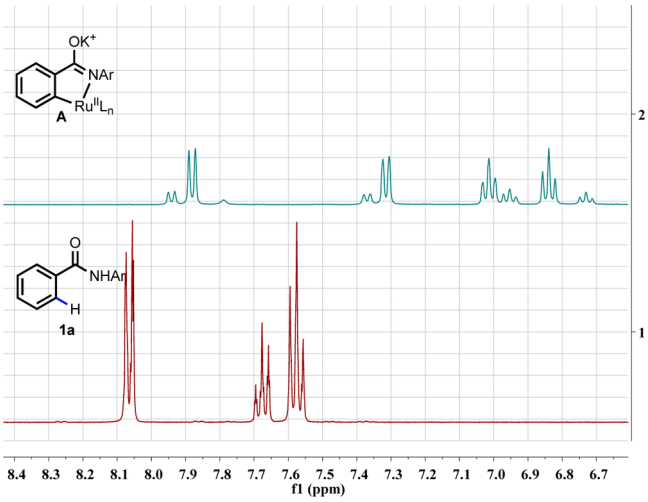


Figure 1. Comparison of ^{1}H NMR of the substrate **1a** and intermediate **A**.

heteroarenes including pyrazole, thiophene, benzothiophene, furan, benzofuran, and indole proceeded smoothly to give the corresponding heteroaryl amines in moderate to good yields (Scheme 3).

Based on a previous Pd-catalyzed C−H amination reaction[4] and Ru(II)-catalyzed C−H functionalizations,[10] we proposed a preliminary pathway for this amination reaction as shown in Scheme 4. First, the arylruthenium(II) intermediate **A** was formed in the presence of base K_2CO_3. **A** was then oxidized to Ru(IV) species **B** by the aminating reagent which underwent reductive elimination to give the desired product. The intermediacy of the Ru(IV) species in C−H arylation was previously studied.[11] At this stage, an electrophilic cleavage of the Ar−Ru(II) bond by the aminating reagents cannot be ruled out.[12] In support of this pathway, we have also characterized the Ar−Ru(II)Ln intermediate **A** by ^{1}H NMR (Figure 1). Ln is mostly likely *p*-cymene(*p*-isopropyltoluene) and carbonate or chloride.

In summary, we have developed a Ru-catalyzed intermolecular C−H amination directed by a weakly coordinating amide auxiliary. This reaction proceeds at room temperature demonstrating the efficacy of a weakly coordinating directing group with Ru(II) catalysts. This new catalytic reaction also provides a potential method for preparing heteroarylamines.

Acknowledgment. We gratefully acknowledge Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, the CAS/SAFEA International Partnership Program for Creative Research Teams, and The Recruitment Program of Global Experts for financial support.

Supporting Information Available. Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) (a) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032. (b) Flegeau, E. F.; Bruneau, C.; Dixneuf, P. H.; Jutand, A. *J. Am. Chem. Soc.* **2011**, *133*, 10161.

(12) (a) Berman, A. M.; Johnson, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 5680. (b) Berman, A. M.; Johnson, J. S. *Synlett* **2005**, 1799. (c) Berman, A. M.; Johnson, J. S.; Nora, G.; Miller, M. J. *Org. Synth.* **2006**, *83*, 31. (d) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219. (e) Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2007**, *9*, 1521.

The authors declare no competing financial interest.