Amination of the Ortho C–H Bonds by the $Cu(OAc)_2$-mediated Reaction of 2-Phenylpyridines with Anilines

Takeshi Uemura, Shinya Imoto, and Naoto Chatani*
Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871

(Received May 17, 2006; CL-060585; E-mail: chatani@chem.eng.osaka-u.ac.jp)

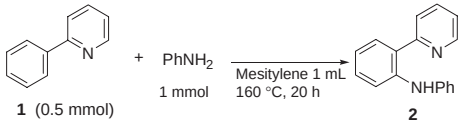
The reaction of 2-phenylpyridines with anilines in the presence of $Cu(OAc)_2$ as a promoter results in selective mono-amination of the ortho C–H bonds in 2-phenylpyridines to give amine derivatives in high yields per the conversion. This is the rare example of the functionalization of C–H bonds to C–N bonds.

Development of transition metal-catalyzed selective functionalization of C–H bonds is a challenge of intensive current interest.[1] A chelation methodology in which ketone, ester, pyridine, and oxazoline function as the directing group is now recognized as one of the most promising methods for the functionalization of not only C–H bonds[2] but also other bonds, such as C–O,[3] C–C,[4] C–F,[5] and O–H bonds.[6] Currently, most of the examples involving functionalization of C–H bonds by the utilization of the chelation methodology result in the formation of C–C bonds. However, less attention has been focused on the formation of carbon–heteroatom bonds from C–H bonds until now, compared with extensively studied C–C bond formation reactions. Quite recently, some reports involving such a formation of carbon–heteroatom from C–H bonds have appeared in literatures. We found that silylation of sp^2 and benzylic C–H bonds with hydrosilanes is achieved by ruthenium complexes.[7] Sanford reported on the formation of C–O and C–halogen bonds via a Pd(IV) intermediates.[8] Yu et al. also reported the Pd(II)-catalyzed ionidation of sp^3 C–H bonds using I_2 and $PhI(OAc)_2$ as oxidants.[9]

The formation of C–N bonds has been the subject of intense studies. The majority of the formation of C–N bonds involves a coupling of aryl halides with amines mediated by copper or palladium complexes.[10] Few examples of the transformation of C–H bonds to C–N bonds by utilizing a chelation strategy exists thus far. Recently, Buchwald et al. reported the formation of intramolecular C–N bond via a C–H bond activation of 2-phenylbenzacetanilides catalyzed by Pd(II) species to produce acetocarbazoles.[11] We now wish to report on the chelation-assisted *intermolecular* amination of the ortho C–H bonds of 2-phenylpyridines with anilines mediated by $Cu(OAc)_2$.[12]

Our initial idea involved the ortho-palladation via an electrophilic substitution of Pd(II) complexes with 2-phenylpyridines, reaction with amines, reductive elimination, followed by reoxidation of the resulting Pd(0) to Pd(II) by Cu(II). When 2-phenylpyridine (**1**) was treated with aniline (1 mmol) in the presence of $PdCl_2$ and $Cu(OAc)_2$ in toluene at 160 °C for 20 h, a trace amount of ortho-amination product **2** was formed. Encouraged by this result, much effort has been made to optimize the reaction conditions by using alternate directing group and changing transition metals, amines, solvents, and temperatures employed. Finally, We were pleased to find that $Cu(OAc)_2$ alone is active in the amination of C–H bonds as a promoter. $Cu(OAc)_2$ is superior to other Cu salts, such as CuCl, CuI, Cu(OTf), $CuBr_2$, CuO, and $Cu(OCOCF_3)_2$ as the promoter for the amination. The reaction of 2-phenylpyridine (**1**, 0.5 mmol), aniline (1 mmol) in the presence of $Cu(OAc)_2$ (1 mmol) in mesitylene (1 mL) at 160 °C for 20 h gave amination product **2** in 27% yield, **1** being recovered in 65% yield (Entry 1 in Table 1). The yield of **2** was improved when a two-batch-wise addition of $Cu(OAc)_2$ was employed (Entry 2). A comparable yield was obtained when the reaction was carried out for 2 h (Entry 3). However, a three-batch-wise addition was not effective (Entry 4). Although the conversion was not high, the reaction system was clean and no byproducts were formed. It was found that the inhibition by the product is responsible for the incomplete conversion. In fact, the addition of product in the reaction system retarded the reaction.

Table 1. Ortho-amination of 2-phenylpyridine (**1**) with aniline

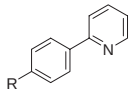
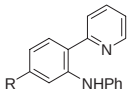
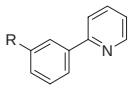
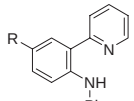
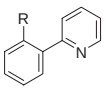
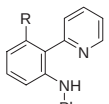
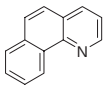
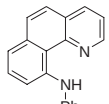


1 (0.5 mmol) **2**

Entry	$Cu(OAc)_2$	**2**/%	Recovered **1**/%
1	1 mmol	27	65
2	0.6 mmol × 2	55	44
3	0.6 mmol × 2 (2 h)	47	50
4	0.6 mmol × 3 (2 h)	42	48

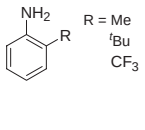
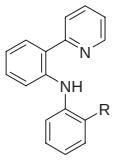
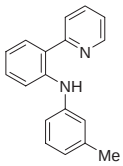
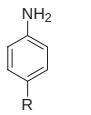
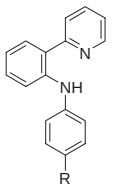
The results on the reaction of some 2-arylpyridines are shown in Table 2. The electronic nature and position of substituents on the phenyl ring had a significant effect on the efficiency

Table 2. Ortho-amination of 2-phenylpyridines with aniline[a]

2-Arylpyridine		Product	Yield/%[b]
	R = Me CF_3 OMe		**3** 43 (57) **4** 30 (67) **5** 40 (45)
	R = Me CF_3 OMe		**6** 17 (65) **7** 14 (80) trace
	R = Me CF_3 OMe		trace trace **8** 40 (46)
			**9** 27 (67)

[a]Reaction conditions: substrate (0.5 mmol), aniline (1 mmol), $Cu(OAc)_2$ (0.6 mmol × 2), mesitylene (1 mL), 160 °C for 2 h. [b]A number in parenthesis is the yield of the recovered substrate.

Table 3. Ortho-amination of 2-phenylpyridine (**1**) with anilines[a]

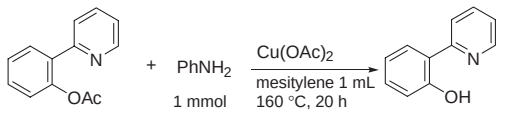
Aniline	Product	Yield/%[b]
 R = Me, ^{t}Bu, CF_3		**10** 41 (50) **11** 30 (67) **12** 24 (32)
		**13** 31 (68)
 R = Me, CF_3		**14** 28 (67) **15** 49 (32)

[a]Reaction conditions: substrate (0.5 mmol), aniline (1 mmol), $Cu(OAc)_2$ (0.6 mmol × 2), mesitylene (1 mL), 160 °C for 2 h. [b]A number in parenthesis is the yield of the recovered substrate.

of the reaction. The presence of a substituent, such as a methyl or trifluoromethyl group, on the ortho position retarded the reaction, however the presence of methoxy group did not affect the efficiency of the reaction.

The effect of structures of anilines was next examined (Table 3). Unlike the effect of a substituent on the phenyl ring in 2-arylpyridines, as shown in Table 2, the significant steric effect of the ortho substituent on aniline was not observed even in the case of *tert*-butyl group. The use of methoxy-substituted aniline gave no reaction, irrespective of the position of the methoxy group. Methoxy-substituted anilines were converted to unisolable products owing to electron transfer from anilines to copper(II) salt.

The reaction mechanism is not clear at the present time.[13] One can propose that selective acetoxylation by $Cu(OAc)_2$ takes place at the ortho C–H bonds and then the resulting acetoxylation product undergoes the $Cu(OAc)_2$-promoted amination under the reaction conditions employed. This possibility can be excluded by the following experiment. When independently prepared acetate **16** was exposed under reaction conditions, **16** underwent aminolysis to give **17** in 47% yield, but no amination product **2** was observed (Scheme 1).



16 **17** 47%

Scheme 1.

In summary, we demonstrated the chelation-assisted intermolecular amination of the ortho C–H bonds in 2-phenylpyridines mediated by copper salt. While the reaction requires stoichiometric amounts of $Cu(OAc)_2$ and the conversion is not high, the reaction does not require expensive metals and ancillary ligands, and the yields per the conversion are quite high, indicating no byproduct formation.

This work was supported by Kansai Research Foundation for Technology Promotion.

References and Notes

1 For recent reviews, see: F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826; M. Miura, M. Nomura, *Top. Curr. Chem.* **2002**, *219*, 211; F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077.
2 For recent examples, see: J. H. Yoon, T. J. Park, J. H. Lee, J. Yoo, C.-H. Jun, *Org. Lett.* **2005**, *7*, 2889; R. K. Thalji, K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *J. Org. Chem.* **2005**, *70*, 6775; F. Kakiuchi, Y. Matsuura, S. Kan, N. Chatani, *J. Am. Chem. Soc.* **2005**, *127*, 5936; V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; Y. Kuninobu, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2005**, *127*, 13498; X. Chen, J.-J. Li, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 78.
3 F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2004**, *126*, 2706.
4 N. Chatani, Y. Ie, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **1999**, *121*, 8645; C.-H. Jun, H. Lee, S.-G. Lim, *J. Am. Chem. Soc.* **2001**, *123*, 751.
5 Y. Ishii, N. Chatani, S. Yorimitsu, S. Murai, *Chem. Lett.* **1998**, 157.
6 K. Yokota, H. Tatamidani, Y. Fukumoto, N. Chatani, *Org. Lett.* **2003**, *5*, 4329; S. Inoue, K. Yokota, H. Tatamidani, Y. Fukumoto, N. Chatani, *Org. Lett.*, **2006**, *8*, 2519.
7 F. Kakiuchi, K. Igi, M. Matsumoto, N. Chatani, S. Murai, *Chem. Lett.* **2001**, 422.
8 A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300; L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542; D. Kalyani, M. S. Sanford, *Org. Lett.* **2005**, *7*, 4149.
9 R. Giri, X. Chen, J.-Q. Yu, *Angew. Chem., Int. Ed.* **2005**, *44*, 2112.
10 A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; S. V. Ley, A. W. Thomas, *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
11 W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560.
12 After our work was finished, we found Yu's work on the Cu(II)-catalyzed functionalization of C–H bonds in 2-phenylpyridines appears in ASAP (released on May 6, 2006) of *J. Am. Chem. Soc.* While their major work is chlorination at ortho C–H bonds in 2-phenylpyridines catalyzed by $CuCl_2$, they also reported one example of amination of C–H bonds using $TsNH_2$ in the presence of a stoichiometric amount of $Cu(OAc)_2$. X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790.
13 One possibility is the intermediacy of unusual cyclometalated Cu complexes, which are generated from **1** and $Cu(OAc)_2$. An alternative mechanism involves SET process from the benzene ring of **1**-coordinated Cu complexes. In both cases, the coordination of the pyridine in **1** is required for the reaction to proceed. In fact, the presence of a methyl group at the 6-position of the pyridine ring resulted in no reaction.

Published on the web (Advance View) June 27, 2006; doi:10.1246/cl.2006.842