DOI: 10.1002/ejoc.200900597

Cobalt-Catalyzed C–N Bond-Forming Reaction between N-Aromatic 2-Chlorides and Secondary Amines

Gabriel Toma,*[a] Ken-ichi Fujita,[a,b] and Ryohei Yamaguchi*[a]

Keywords: Cobalt / Cross-coupling / C–N bond formation / Nitrogen heterocycles / Amines

Secondary amines react with N-aromatic 2-chlorides in the presence of a catalytic amount of cobalt chloride. When DPPP was added as ligand, the yield was further improved. The N-aromatic-containing tertiary amines formed are interesting due to their potential biological activity. This work represents the first cobalt-catalyzed approach to C–N bond formation involving N-aromatic 2-chlorides and secondary amines having a certain amount of versatility and functional group tolerance.

Introduction

One of the methods employed for the formation of carbon–heteroatom bonds for the synthesis of important compounds of pharmaceutical and biological interest is the transitional-metal cross-coupling methodology.[1] Among carbon–nitrogen bond-forming processes, α-amination of nitrogen-containing heterocycles is of particular interest, because those molecules represent building blocks for the synthesis of biologically active compounds.[2] In Figure 1 some representative 2-pyridine-included bioactive molecules and their purpose are shown. Along with the 2-pyridine moiety, a six-member nitrogen-containing ring is part of the structure of such molecules. That is why we focused our attention on synthesizing molecules containing such six-membered nitrogen-containing rings.

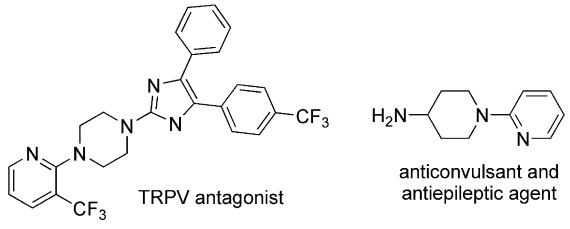


Figure 1. Examples of bioactive molecules including one or more N-containing heterocycles.

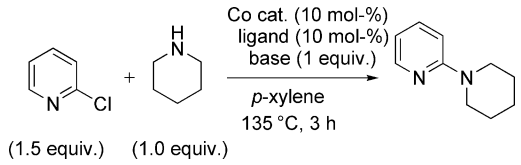
[a] Graduate School of Human and Environmental Studies, Kyoto University,
Kyoto 606-8501, Japan
Fax: +81-75-753-6634
E-mail: tomagabi@f06.mbox.media.kyoto-u.ac.jp
yama@kagaku.mbox.media.kyoto-u.ac.jp
[b] Graduate School of Global Environmental Studies, Kyoto University,
Kyoto 606-8501, Japan

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900597.

Representative procedures previously reported include transition-metal-free microwave procedures[3a] and palladium-catalyzed,[3b] nickel-catalyzed,[3c] and copper-catalyzed[3d] reactions. Reactions performed under microwave irradiation require a large excess of amine and the yields are moderate. As a result of the expensiveness of palladium and complications in the carbon–nitrogen bond-forming procedures reported for nickel catalysts,[4] the necessity of new methodologies involving readily available and nontoxic metals such as cobalt[5] and iron[6] increased. Recent progresses in cobalt catalysis by the Oshima group,[7] the Gosmini group,[8] and other groups[9] mainly regarding cross-coupling reactions show that cobalt-catalyzed methodologies are promising tools of an environmentally friendly nature. Because there are some drawbacks consisting in the use of excess amounts of reducing reagents, involvement of electrochemical techniques, and the use of large amounts of expensive ligands, further development in this field is required. Although a very recent report[5] mentioning a carbon–nitrogen bond-forming reaction by using a cobalt catalyst/DMEDA (*N*,*N*′-dimethylethylenediamine) system showed that aromatic iodides react with a restricted range of nitrogen nucleophiles, a low turnover number (TON; 1.6 to 2.4) for cobalt chloride was reported in the case of aromatic bromides, and the reactivity of heterocyclic halides was not investigated. Herein, we report the first cobalt-catalyzed approach to C–N bond formation involving N-aromatic 2-chlorides and secondary amines having a certain amount of versatility and functional group tolerance.

Results and Discussion

The reaction was screened for different bases and ligands in order to optimize the reaction conditions, and the results are shown in Scheme 1 and Table 1.



Scheme 1. Cobalt-catalyzed coupling of 2-chloropyridine with piperidine.

Table 1. Optimization of the cobalt-catalyzed cross-coupling reaction.

Entry	Base	Ligand	Catalyst	Yield[a] [%]
1	K_3PO_4	none	$CoCl_2$	29
2	K_2CO_3	none	$CoCl_2$	59
3	Na_2CO_3	none	$CoCl_2$	33
4	Li_2CO_3	none	$CoCl_2$	30
5	K_2CO_3	none	$Co(acac)_2$	0
6	K_2CO_3	L-proline	$CoCl_2$	48
7	K_2CO_3	TMEDA	$CoCl_2$	37
8	K_2CO_3	DPPE	$CoCl_2$	56
9	K_2CO_3	DPPP	$CoCl_2$	80
10	K_2CO_3	DPPP	none	trace
11	K_2CO_3	DPPB	$CoCl_2$	53
12	K_2CO_3	PPh_3	$CoCl_2$	61 (65[b])
13[c]	K_2CO_3	DPPP	$CoCl_2$	50
14[c]	K_2CO_3	none	$CoCl_2$	37
15[d]	K_2CO_3	DPPP	$CoCl_2$	5

[a] GC yield by using cumene as internal standard. [b] 20 mol-% ligand was used. [c] 5 mol-% catalyst was used. [d] 1 mol-% catalyst was used, 5 mmol-scale reaction.

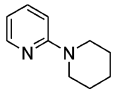
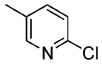
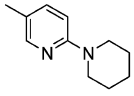
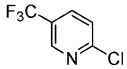
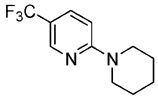
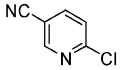
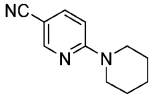
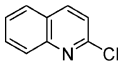
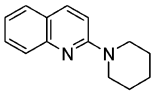
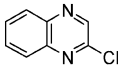
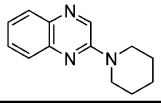
At first, we found that cobalt(II) chloride gave promising results and, therefore, chose to fix it during the optimization of the reaction conditions. When cobalt(II) acetylacetonate was used (Table 1, Entry 5), product formation was not observed by GC analysis. Addition of potassium carbonate showed the highest yield among the bases screened (Table 1, Entries 1–4) and therefore it was further used for ligand screening (Table 1, Entry 2).

Amine ligands (Table 1, Entries 6 and 7) showed a suppressing effect on the reaction, suggesting that the nitrogen atom of 2-chloropyridines may act as a ligand in the reaction and, therefore, amine ligands could decrease the yield.

Phosphane ligands either improved the yield (Table 1, Entries 9 and 12) or did not improve the yield (Table 1, Entries 8 and 11). Triphenylphosphane gave a slightly better yield compared to the ligand-free reaction (61 vs. 59%; Table 1, Entries 12 and 2), whereas DPPP [1,3-bis(diphenylphosphanyl)propane] was the best ligand among those screened, giving 80% yield (Table 1, Entry 9). In the absence of cobalt chloride only a trace amount of product was obtained (Table 1, Entry 10). Attempts to lower the amount of catalyst used were made, and the yield obtained was moderate for 5 mol-% catalyst, but for 1 mol-% catalyst the yield was only 5% (Table 1, Entries 13–15).

The reactions between piperidine and several N-aromatic chlorides are shown in Table 2. As it can be seen from this table, a nitrogen atom next to the carbon atom bearing a chloride group is essential for the reaction to take place (Table 2, Entries 1 and 5). In the case of 2-chloropyridines, the presence of functional groups affected the yield significantly. In the case of an electron-donating group such as methyl, the yield was low (Table 2, Entry 2). In the case of electron-withdrawing groups, the yields were good (75 and 60%; Table 2, Entries 3 and 4) and the functional groups were not altered. Incorporation of a fused benzene ring increased the reactivity compared to 2-chloropyridine; high yields were obtained for 2-chloroquinoline (88%; Table 2, Entry 6) and 2-chloroquinoxaline (91%; Table 2, Entry 7) in the reaction with piperidine.

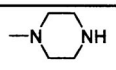
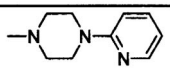
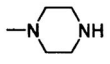
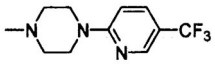
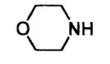
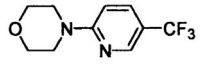
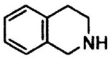
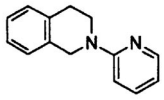
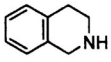
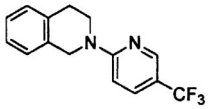
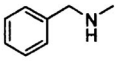
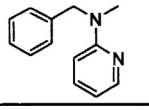
Table 2. Reactions of N-aromatic 2-chlorides with piperidine in the presence of cobalt(II) chloride (10 mol-%) and DPPP (10 mol-%) at 135 °C in *p*-xylene.

Entry	Heteroaromatic chloride	Chloride/ piperidine	Product	Yield[a] [%]
1[b]		1.5:1		72
2[c]		1:1		30
3[b,d]		1:1		75
4[e]		1:1.5		60
5[f]		1:3		n.d.
6[d,e]		1:2		88
7[d,e]		1:2		91

[a] Isolated yield. [b] Reaction time was 4 h and ligand free. [c] 30 mol-% catalyst was used and reaction time was 16 h. [d] 15 mol-% catalyst was used. [e] Reaction time was 3 h. [f] Reaction time was 20 h and reaction temperature was 140 °C. n.d. = not determined.

In Table 3, the reactivity of various amines with 2-chloropyridines under cobalt catalysis is shown. The yield of the reaction between 2-chloropyridine and *N*-methylpiperazine (50%; Table 3, Entry 1) was less than the one where piperidine was employed (80%; Table 1, Entry 9), suggesting that extra binding of another nitrogen atom would not be beneficial for the reaction. Therefore, the reactivity of six-member cyclic amines depended on the kind of heteroatom present, as shown in the case of *N*-methylpiperidine and morpholine. The yield was 83% in the case of morpholine

Table 3. Reactions of 2-chloropyridine and 2-chloro-5-trifluoromethylpyridine with miscellaneous amines in the presence of cobalt(II) chloride (10 mol-%) and DPPP (10 mol-%) at 135 °C in *p*-xylene.

Entry	Amine	Chloride/amine	Product	Yield [%]
1[a]		1.5:1		50[b]
2		1:1		55[c]
3[d]		1:1		83[c]
4		1.5:1		68[b]
5		1:1		75[c,e]
6		1.5:1		86[c,f]

[a] Reaction time was 3 h. [b] GC yield using cumene as internal standard. [c] Isolated yield. [d] Reaction time was 4 h. [e] 15 mol-% cobalt chloride, ligand free. [f] 20 mol-% cobalt chloride and 20 mol-% DPPP were used.

(Table 3, Entry 3), whereas in the case of *N*-methylpiperazine it was only 55% (Table 3, Entry 2). A fused piperidine also reacted despite the slight steric hindrance to give good yields (68 and 75%; Table 3, Entries 4 and 5). A noncyclic amine also reacted under the same conditions as shown in Entry 6 to give the desired product in high yield (86%; Table 3, Entry 6). Studies related to the reaction time were made, but further extension of the reaction time did not give better results. Although the most relevant results are shown here, other substrates were also tested and the scope and limitations of the reaction is to be published in a future full paper along with a more detailed investigation of the reaction mechanism.

Conclusions

In summary, we have developed a new methodology to prepare N-aromatic-containing tertiary amines that are useful building blocks for bioactive molecules. Although significant progress has been made during the past few years in cobalt chemistry, the use of N-aromatic 2-chloro compounds in C–N bond-forming reactions is reported for the first time in this paper. Among the bases and ligands screened, potassium carbonate and DPPP gave the best results. The mechanism of the reaction will be studied in the near future.

Experimental Section

General Procedure: To an oven-dried Schlenk tube that was flushed with argon was consecutively added N-aromatic 2-chloride (1–1.5 mmol), secondary amine (1–2 mmol), base (1 mmol), cobalt(II) chloride (10 mol-%), phosphane ligand (10 mol-%), and *p*-xylene (0.5 mL). The mixture was allowed to stir at 135 °C for 3 h in an oil bath. After cooling the Schlenk tube to room temperature, cumene was added as an internal standard and dichloromethane as a solvent before GC analysis was performed. Isolation was done by column chromatography on silica gel or alumina (hexane/ether). Product identification was done by NMR spectroscopy, GC–MS, and elemental analysis.

Supporting Information (see footnote on the first page of this article): Full characterization data of the products.

[1] a) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544 and references cited therein; b) H. Shinokubo, K. Oshima, *Eur. J. Org. Chem.* **2004**, 2081–2091.
[2] a) A. Correa, O. G. Mancheno, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108–1117; b) B. D. Sherry, A. Furstner, *Acc. Chem. Res.* **2008**, *41*, 1500–1511; c) V. K. Gore, V. V. Ma, R. Tamir, N. R. Gavva, J. J. S. Treanor, M. H. Norman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5825–5830.
[3] a) S. Narayan, T. Seelhammer, R. E. Gawley, *Tetrahedron Lett.* **2004**, *45*, 757–759; for reviews: P. Appukkuttan, E. Van der Eycken, *Eur. J. Org. Chem.* **2008**, 1133–1155; b) A. Tewari, M. Hein, A. Zapf, M. Beller, *Tetrahedron* **2005**, *61*, 9705–9709; M. S. Viciu, R. A. Kelly III, E. D. Stevens, F. Naud, M. Studer, S. P. Nolan, *Org. Lett.* **2003**, *5*, 1479–1482; S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck, J. F. Hartwig, *Org. Lett.* **2000**, *2*, 1423–1426; c) C. Desmarets, R. Schneider, Y. Fort, *J. Org. Chem.* **2002**, *67*, 3029–3036; G. Manolikakes, A. Gavryushin, P. Knochel, *J. Org. Chem.* **2008**, *73*, 1429–1434; d) H. Zhang, Q. Cai, D. Ma, *J. Org. Chem.* **2005**, *70*, 5164–5173.
[4] a) E. Brenner, R. Schneider, Y. Fort, *Tetrahedron* **2002**, *58*, 6913–6924 and references cited there; b) C. Desmarets, R. Scheider, Y. Fort, *J. Org. Chem.* **2002**, *67*, 3029–3036.
[5] Y.-C. Teo, G.-L. Chua, *Chem. Eur. J.* **2009**, *15*, 3072–3075.
[6] a) D. Guo, H. Huang, J. Xu, H. Jiang, H. Liu, *Org. Lett.* **2008**, *10*, 4513–4516; b) A. Correa, C. Bolm, *Angew. Chem. Int. Ed.* **2007**, *46*, 8862–8865.
[7] a) H. Ohmiya, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 1886–1889 and references cited there; b) H. Ohmiya, K. Wakabayashi, H. Yorimitsu, K. Oshima, *Tetrahedron* **2006**, *62*, 2207–2213.
[8] a) C. Gosmini, J.-M. Begouin, A. Moncomble, *Chem. Commun.* **2008**, 3221–3233 and references cited therein; b) M. Amatore, C. Gosmini, *Angew. Chem. Int. Ed.* **2008**, *47*, 2089–2092.
[9] a) P. Shukla, Y.-C. Hsu, C.-H. Cheng, *J. Org. Chem.* **2006**, *71*, 655–658; b) B. Sezen, D. Sames, *Org. Lett.* **2003**, *5*, 3607–3610; c) G. Dunet, P. Knochel, *Synlett* **2007**, *9*, 1383–1386 and references cited there; d) G. Cahiez, C. Chaboche, C. Duplais, A. Moyeux, *Org. Lett.* **2009**, *11*, 277–280; e) E. Shirakawa, T. Sato, Y. Imazaki, T. Kimura, T. Hayashi, *Chem. Commun.* **2007**, 4513–4515; f) M. Lombardo, S. Licciulli, F. Pasi, G. Angelici, C. Trombini, *Adv. Synth. Catal.* **2005**, *347*, 2015–2018; g) A. Kuno, N. Saino, T. Kamachi, S. Okamoto, *Tetrahedron Lett.* **2006**, *47*, 2591–2594 and references cited therein.

Received: June 1, 2009
Published Online: August 10, 2009

