DOI: 10.1002/cjoc.201201121

A Simple and Efficient Copper(II) Complex as a Catalyst for *N*-Arylation of Imidazoles

Yanli Jiao, Nannan Yan, Jianwei Xie,* Xiaowei Ma, Ping Liu, and Bin Dai*

School of Chemistry and Chemical Engineering, the Key Laboratory for Green Processing of Chemical Engineering of Xinjiang Bingtuan, Shihezi University, North 4th Road, Shihezi, Xinjiang 832003, China

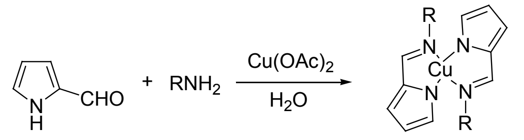
Four inexpensive and air-/moisture-stable pyrrolecarbaldiminato-Cu complexes **1**—**4** were synthesized and evaluated to be a novel class of catalysts for the *N*-arylation of imidazoles with aryl halides. A variety of aryl iodides, bromides and activated aryl chlorides underwent the coupling with imidazoles, promoted by the catalyst **4**, in moderate to good yields without the protection by an inert gas.

Keywords pyrrolecarbaldiminato-Cu complexes, homogeneous catalyst, *N*-arylation, imidazoles, *N*-heterocycles

Introduction

N-Aryl imidazoles are prevalent building blocks of numerous drugs, natural products and energetic materials,[1] and have been exploited as important precursors in the area of *N*-heterocyclic carbine chemistry.[2] Therefore, their preparations have attracted much attention. Traditionally, these compounds were synthesized via S_NAr substitution of imidazoles with activated aryl halides or the classic Ullmann-type coupling reactions,[3] which were often suffered from harsh reaction conditions and stoichiometric amounts of copper reagents. In recent years, the transition-metal (such as palladium, copper, nickel and iron), especially palladium-catalyzed *N*-arylation of imidazoles has achieved remarkable achievements, and shows relative mild reaction conditions, broad substrate scope and excellent functional-group tolerance.[4] However, in comparison with the use of costly palladium and toxic phosphane-containing ligands, it is desirable to develop more effective copper catalytic systems for *N*-arylation of imidazoles. The breakthroughs in this area, which were achieved by two research groups of Buchwald[5] and Taillefer,[6] respectively, have been typically driven by the implementation of new class of ligands and only catalytic amounts of copper metal under mild conditions. Following these pioneering works, several classes of mono- and bidentate chelators have thereby been developed to expedite the reaction rates and lower substantially the reaction temperature of Cu-based C—N coupling reaction.[7] In spite of the significant progress made in the aforementioned transformation, more efficient, air or/and moisture-stable and easy-synthesis ligands or metal-complexes for facilitating these coupling reactions under relatively milder conditions are still in demand.

Scheme 1 Preparation of catalyst **1**—**4** according to the reported method



Catalyst **1** - **4**

1: R = CH_3, 57%; **2**: R = *t*-Bu, 30%; **3**: R = Ph, 47%; **4**: R = Bn, 48%

Since the first report of 2-pyrrolecarbaldimines and its Co and Cu chelates,[8] several pyrrolecarbaldiminato-metal complexes have been synthesized and demonstrated potential applications to various processes, such as C—H activation,[9] ethylene polymerization,[10] neutral luminescent,[11] copper metal CVD (chemical vapour deposition) or ALD (atomic layer deposition) precursors,[12] and so on. However, these series of Cu-complexes, to our knowledge, have seldom been used as the catalysts for the C—N coupling reaction. Moreover, imines have been reported as ligands to improve the reaction efficiency for copper-catalysed Ullmann coupling reaction.[13] Therefore, we reasonably assumed that pyrrolecarbaldiminato-Cu complexes might be a class of effective copper-catalysts for C—N coupling reaction. Herein, we wish to report our results of pyrrolecarbaldiminato-Cu complexes as catalysts for the *N*-arylation of imdazoles. This methodology has several advantages as follows: (1) the catalysts were easily synthesized from cheap starting materials with satisfied yield on a multi-gram scale, and are stable in air and moisture; (2) the reaction condition was relatively

---

* E-mail: cesxjw@gmail.com (Xie, J.); db_tea@shzu.edu.cn (Dai, B.); Tel.: 0086-0993-205-7213; Fax: 0086-0993-205-7270
Received November 14, 2012; accepted December 10, 2012; published online January 8, 2013.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cjoc.201201121 or from the author.

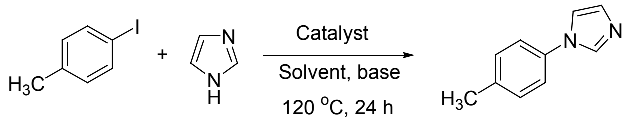
milder and did not require protection by an inert atmosphere; (3) the catalysts worked well for aryl iodides, bromides and electronic-withdrawing aryl chlorides with moderate to good yield.

Results and Discussion

Considering that the electronic effects and steric effects of pyrrolate-imine moieties could play an important role in the catalytic activities, we selectively prepared four typical pyrrolecarbaldiminato-Cu complexes (R=CH_3, *t*-Bu, Ph, and Bn) by reacting the pyrrole-2-carboxaldehyde, corresponding amines, with $Cu(OAc)_2$ *in situ* according to the reported procedures,[12a,14] and the four copper-complexes were characterized by elemental analysis. The synthetic route was shown in Scheme 1. Subsequently, the catalytic activity of the four catalysts was evaluated by using the C—N coupling of 4-iodotoluene with imidazole as a model reaction in the presence of $K_3PO_4 \cdot 3H_2O$ at 120 ℃ for 24 h in DMSO. As expected, the four Cu-complexes all exhibited high catalytic activity for this process, and catalyst **4** was the best, which gave the desired product in 87% isolated yield (Table 1, Entries 1—4). Control experiment conducted in the absence of Cu-complex from the reaction mixture resulted in no product (Table 1, Entry 5).

With the appropriate catalyst in hand, it was reasonable for us to further optimize the other reaction conditions, including solvents, bases, catalyst loading, temperature and reaction times, and the results are listed in Table 1. It was found that DMSO performed as the prime solvent; DMF and toluene were fairish, but were not as good as DMSO; meanwhile, dioxane was not suitable as a solvent (Table 1, Entries 6—8). Investigation into the bases with different basicities revealed that the Cs_2CO_3 demonstrated the best improvement among those screened (NaOH, KOH, K_2CO_3, Cs_2CO_3, and K_3PO_4) to give the corresponding product in 88% yield (Table 1, Entries 9—13). However, $K_3PO_4 \cdot 3H_2O$ was the recommended base as it was less expensive and weaker basicity than Cs_2CO_3. It must be pointed out that the hydrate of K_3PO_4 can dramatically accelerate the arylation of imidazole (Table 1, Entry 4 vs. Entry 9). This could be attributed to that the hydrate of K_3PO_4 increased the rate of the arylation reaction by solubilizing the base in DMSO, and thus facilitating deprotonation of imidazole, which is in good agreement with the reported results.[15] Furthermore, decreasing the loading of catalyst **4** from 10 mol% to 5 mol% led to a decrease of the yield. In addition, reaction time and reaction temperature were also proved to have effects on the reaction, shorter reaction time than 24 h or lower temperature than 120 ℃ can both decelerate the reaction rate and led to lower yields (Table 1, Entries 15, 16). As mentioned above, the combination of Cu-catalyst **4** (10 mol %), $K_3PO_4 \cdot 3H_2O$ (2 equiv.) at 120 ℃ for 24 h in DMSO was chosen as the optimal conditions for *N*-arylation of imidazole with 4-iodotoluene.

Table 1 Screening reaction conditions for *N*-arylation of imidazole with 4-iodotoluene[a]

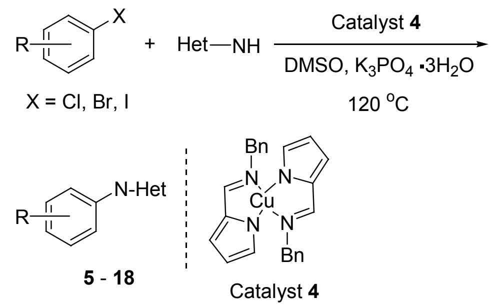


Entry	Catalyst	Solvent	Base	Yield[b]/%
1	1	DMSO	$K_3PO_4 \cdot 3H_2O$	77
2	2	DMSO	$K_3PO_4 \cdot 3H_2O$	73
3	3	DMSO	$K_3PO_4 \cdot 3H_2O$	66
4	4	DMSO	$K_3PO_4 \cdot 3H_2O$	87
5	—	DMSO	$K_3PO_4 \cdot 3H_2O$	0
6	4	DMF	$K_3PO_4 \cdot 3H_2O$	80
7	4	Dioxane	$K_3PO_4 \cdot 3H_2O$	38
8	4	Toluene	$K_3PO_4 \cdot 3H_2O$	70
9	4	DMSO	K_3PO_4	77
10	4	DMSO	NaOH	86
11	4	DMSO	KOH	85
12	4	DMSO	K_2CO_3	81
13	4	DMSO	$CsCO_3$	88
14	4	DMSO	$K_3PO_4 \cdot 3H_2O$	71[c]
15	4	DMSO	$K_3PO_4 \cdot 3H_2O$	76[d]
16	4	DMSO	$K_3PO_4 \cdot 3H_2O$	67[e]

[a] Unless otherwise noted, the reaction was carried out with 4-iodotoluene (0.5 mmol), imidazole (0.75 mmol), catalyst (10 mol%), base (1.0 mmol), and solvent (1 mL) at 120 ℃ for 24 h. [b] Isolated yield. [c] Catalyst (5 mol%). [d] Reaction time: 12 h. [e] Temperature: 100 ℃.

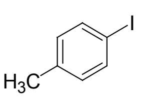
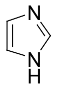
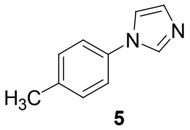
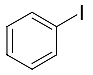
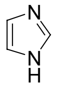
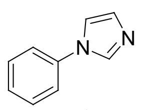
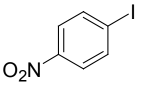
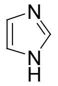
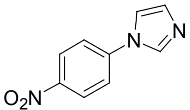
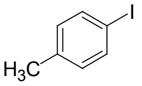
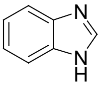
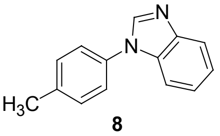
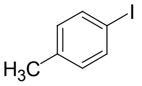
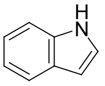
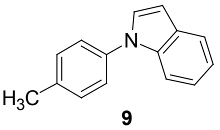
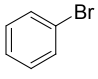
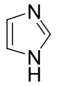
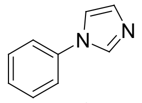
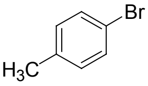
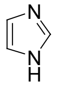
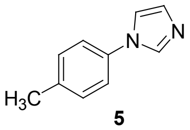
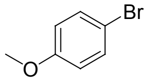
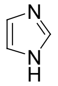
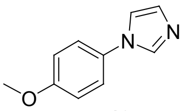
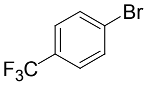
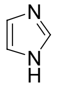
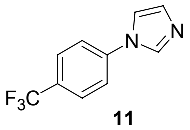
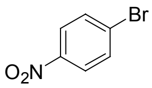
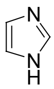
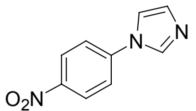
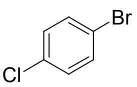
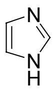
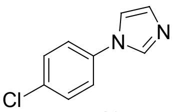
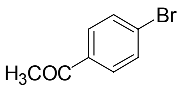
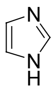
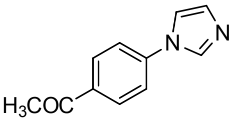
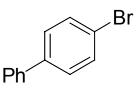
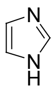
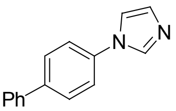
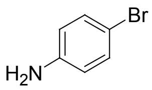
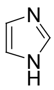
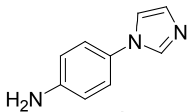
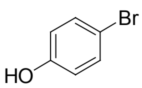
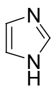
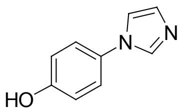
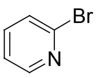
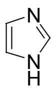
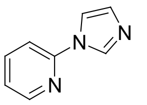
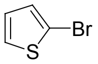
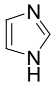
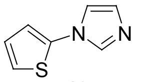
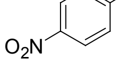
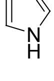
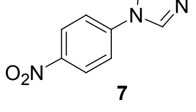
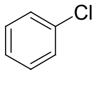
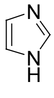
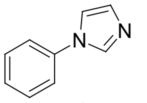
After the best reaction condition was set, the reaction scope and limitations of the catalytic system were then investigated. As shown in Table 2, the good to excellent yields were obtained for the *N*-arylation of imidazole with aryl iodides. To our delight, arylation of other nitrogen-containing heterocycles such as benzimidazole and indole are also efficient with good yield under the standard conditions (Table 2, Entries 1—5). In general, although aryl bromides were less reactive than aryl iodides, satisfactory yields were still obtained for the aryl bromide only with prolonging the reaction time to 36 h. As we can see, the coupling of imidazole with most of electron-rich, electron-neutral, and electron-poor aryl bromides afforded the corresponding products with good to excellent yields. In the case of *p*-bromoanisole, which contains a strongly electron-donating substituent, it is a good substrate, while the 1-bromo-4-(trifluoromethyl) benzene reacts relative slowly (Table 2, Entries 8, 9). Notably, a high level of selectivity was also observed in the amination of aryl bromide bearing another amino or hydroxyl group without formation of diaryl ether or diarylamine products (Table 2, Entries 14, 15). Interestingly, heteroaryl bromides were also coupled with imidazole to afford the desired product in impressive yields (Table 2, Entries 16, 17). In addition, the

Table 2 *N*-Arylation of imidazoles with aryl iodides, bromides and chlorides catalyazed by catalyzed **4**[a]



5 - 18

Catalyst **4**

Entry	ArX	Het-NH	Product	Yield[b]/%
1			 **5**	87
2			 **6**	85
3			 **7**	80
4			 **8**	88
5			 **9**	73
6			 **6**	70
7			 **5**	72
8			 **10**	81
9			 **11**	62
10			 **7**	80
11			 **12**	65
12			 **13**	70
13			 **14**	82
14			 **15**	79
15			 **16**	56
16			 **17**	80
17			 **18**	46
18			 **7**	50
19			 **6**	trace

[a] Reaction conditions: ArX (0.5 mmol), imidazoles (0.75 mmol), catalyst **4** (10 mol%), K_3PO_4•$3H_2O$ (1.0 mmol), and DMSO (1 mL), 120 ℃, 24 h (X=I) or 36 h (X=Br and Cl). [b] Isolated yield.

reaction of electron-deficient aryl chloride such as

1-chloro-4-nitrobenzene with imidazole was also successful and provided the desired product in moderate yield (Table 2, Entry 18). However, only trace *N*-arylation product was observed under the experimental condition, when chlorobenzene was used as the substrate (Table 2, Entry 19).

Conclusions

In summary, we have developed a general, mild and experimental method for the arylation of imidazoles with aryl iodides, bromides and electron-withdrawing aryl chlorides, promoted by inexpensive, air- and moisture-stable pyrrolecarbaldiminato-Cu complexes without the protection of an inert gas. Further application of these copper(II) complexes catalyzed organic reactions is currently ongoing in our laboratory.

Acknowledgement

We acknowledge the National Basic Research Program of China (973 Program) (No. 2012CB722603) and Start-Up Foundation for Young Scientists of Shihezi University (Nos. RCZX201012, RCZX201014, RCZX201015) for their financial support.

References

[1] For selected reviews and examples, see: (a) Jacobs, C.; Frotscher, M.; Dannhardt, G.; Hartmann, R. W. *J. Med. Chem.* **2000**, *43*, 1841; (b) Zhong, J. *Nat. Prod. Rep.* **2005**, *22*, 196; (c) Kison, C.; Opatz, T. *Chem. Eur. J.* **2009**, *15*, 843; (d) Gao, H.; Shreeve, J. M. *Chem. Rev.* **2011**, *111*, 7377; (e) Fujishima, S.; Yasui, R.; Miki, T.; Ojida, A.; Hamachi, I. *J. Am. Chem. Soc.* **2012**, *134*, 3961.

[2] (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606; (b) Benhamou, L.; Chardon, E.; Lavigne, G.; Bellemin-Laponnaz, S.; César, V. *Chem. Rev.* **2011**, *111*, 2705.

[3] (a) Ohmori, J.; Shimizu-Sasamata, M.; Okada, M.; Sakamoto, S. *J. Med. Chem.* **1996**, *39*, 3971; (b) Antonini, I.; Cristalli, G.; Franchetti, P.; Grifantini, M.; Martelli, S. *Synthesis* **1983**, 47; (c) Lo, Y. S.; Nolan, J. C.; Maren, T. H.; Welstead, W. J. Jr.; Gripshover, D. F.; Shamblee, D. A. *J. Med. Chem.* **1992**, *35*, 4790; (d) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657.

[4] For some selected reviews, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954; (b) Wang, Y.; Zeng, J.; Cui, X. *Chin. J. Org. Chem.* **2010**, *30*, 181 (in Chinese); (c) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27; (d) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57.

[5] (a) Buchwald, S. L.; Klapars, A.; Antilla, J. C.; Job, G. E.; Wolter, M.; Kwong, F. Y.; Nordmann, G.; Hennessy, E. J. *WO 02/085838* (Priority number *US 0286286*, **2001**); (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727.

[6] Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Ouali, A. *Fr 2833947-WO 0353225* (Priority number *Fr 16547*, **2001**).

[7] For some selected examples, see: (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421; (b) Lu, Z.; Twieg, R. *Tetrahedron Lett.* **2005**, *46*, 2997; (c) Rao, H.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2005**, *70*, 8107; (d) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164; (e) Chen, Y.; Chen, H. *Org. Lett.* **2006**, *8*, 5609; (f) Yang, M.; Liu, F. *J. Org. Chem.* **2007**, *72*, 8969; (g) Suresh, P.; Pitchuman, K. *J. Org. Chem.* **2008**, *73*, 9121; (h) Wang, D.; Ding, K. *Chem. Commun.* **2009**, 1891; (i) Zhao, H.; Fu, H.; Qiao, R. *J. Org. Chem.* **2010**, *75*, 3311; (j) Hu, Z.; Ye, W.; Zou, H.; Yu, Y. *Synth. Commun.* **2010**, *40*, 222; (k) Thakur, K. G.; Srinivas, K. S.; Chiranjeevi, K.; Sekar, G. *Green Chem.* **2011**, *13*, 2326; (l) Xie, R.; Fu, H.; Ling, Y. *Chem. Commun.* **2011**, *47*, 8976; (m) Wang, D.; Zhang, F.; Kuang, D.; Yu, J.; Li, J. *Green Chem.* **2012**, *14*, 1268; (n) Zhang, J. X.; Yin, H. Q; Han, S. Q. *Chin. J. Org. Chem.* **2012**, *32*, 1429 (in Chinese); (o) Yang, X.; Xing, H.; Zhang, Y.; Lai, Y.; Zhang, Y.; Jiang, Y.; Ma, D. *Chin. J. Chem.* **2012**, *30*, 875.

[8] Emmert, B.; Diehl, K.; Gollwitzer, F. *Ber. Dtsch. Chem. Ges.* **1926**, *62B*, 1733.

[9] Iverson, C. N.; Carter, C. A. G.; Baker, R. T.; Scollard, J. D.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2003**, *125*, 12674.

[10] (a) Yoshida, Y.; Matsui, S.; Takagi, Y.; Mitani, M.; Nakano, T.; Tanaka, H.; Kashiwa, N.; Fujita, T. *Organometallics* **2001**, *20*, 4793; (b) Matsui, S.; Spaniol, T. P.; Takagi, Y.; Yoshida, Y.; Okuda, J. *J. Chem. Soc., Dalton Trans.* **2002**, 4529.

[11] Crestani, M. G.; Manbeck, G. F.; Brennessel, W. W.; McCormick, T. M.; Eisenberg, R. *Inorg. Chem.* **2011**, *50*, 7172.

[12] (a) Grushin, V. V.; Marshall, W. J. *Adv. Synth. Catal.* **2004**, *346*, 1457; (b) Vidjayacoumar, B.; Emslie, D. J. H.; Blackwell, J. M.; Clendenning, S. B.; Britten, J. F. *Chem. Mater.* **2010**, *22*, 4854.

[13] (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607; (b) Liu, Y.-H.; Chen, C.; Yang, L.-M. *Tetrahedron Lett.* **2006**, *47*, 9275; (c) Wang, Y.; Wu, Z. Q.; Wang, L. X.; Li, Z. K.; Zhou, X. G. *Chem. Eur. J.* **2009**, *15*, 8971.

[14] Wansapura, C. M.; Juyoung, C.; Simpson, J. L.; Szymanski, D.; Eaton, G. R.; Eaton, S. S.; Fox, S. *J. Coord. Chem.* **2003**, *56*, 975.

[15] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(Pan, B.; Fan, Y.)