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Amination and amidation of aryl iodides catalyzed by copper(I)–phenanthroline complexes

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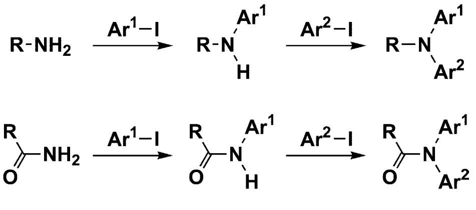
Abstract—Four kinds of copper(I)–phenanthroline complexes ($[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$, $[\mathrm{Cu^I(phen)Cl}]_2$, $[\mathrm{Cu^I(phen)_2}]\mathrm{BF_4}$, and $\mathrm{Cu^I(phen)PPh_3Cl}$) were prepared and used as catalysts for amination and amidation of aryl iodide to investigate the influence on the yields of products due to differences of the structures. These complexes were found to work as catalysts on these reactions and showed that the differences of structures of copper(I) complexes significantly influenced the yield of aryl-nitrogen bond forming processes.

Arylamines and arylamides are prevalent and important compounds in biological, pharmaceutical, and electronic materials.[1–6] Their extensive importance has developed many synthetic methods for the formation of aryl-nitrogen bonds. Both classical Ullmann coupling processes[7,8] and the related Goldberg coupling reaction[9,10] have been commonly used in laboratory and industrial scale in spite of necessity to use high temperature, highly polar solvents, and large amounts of copper reagents (Scheme 1).



Scheme 1.

During the last decade, significant advances have occurred in the cross-coupling methodology for aryl-nitrogen bond forming process, Pd catalyzed reaction of aryl halides such as Hartwig–Buchwald coupling became the more commonly used and excellent methods in laboratory scale.[11,12] However, copper mediated coupling is still the reaction of choice for large and industrial-scale production owing to an economic attractiveness and various types of copper-catalyzed systems have been developed and reported.[13–16]

When we followed these copper-catalyzed systems, we often felt the difficulty of reproducibility because there were many factors, which influenced the properties and yields of coupling reactions: hygroscopic degree, grain size, valency, stability, and solubility of copper reagents; selection of solvents and ligands; ligands/copper reagents ratio; basicity, hygroscopic degree, grain size of bases; how to combine their factors. Furthermore, in general, ligands and copper reagents are added separately into the reaction systems without making a copper complex except a few examples.[17,18] However, investigating what structures of copper complexes have higher activity for the coupling reaction is considered to lead to understand the mechanism of the reaction and proper molecular design for more active catalysts.

Since Goodbrand and Hu reported 1,10-phenanthroline (phen) produced significant rate accelerations for Ullmann condensation,[13] we have been interested in the function of 1,10-phenanthroline. It is considered that 1,10-phenanthroline makes some complexes with copper salts and the complexes work as catalysts though the real active species are unknown (Scheme 2).

Keywords: Amination; Amidation; N-Arylation; Phenanthroline; Copper; Complex; Catalysis.

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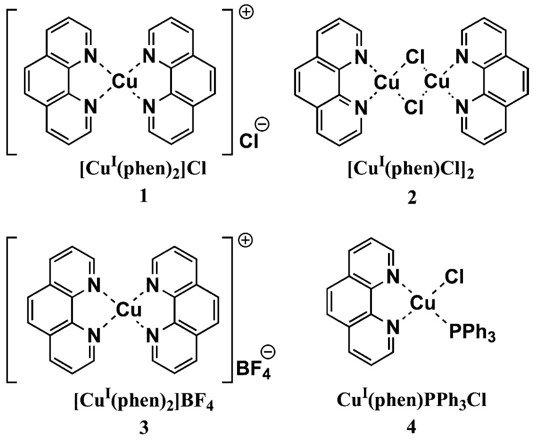


Scheme 2.

Kitagawa and Munakata reported the synthesis and properties of binuclear $[\mathrm{Cu^I(phen)X}]_2$ complexes and mononuclear $[\mathrm{Cu^I(phen)_2}]\mathrm{X}$ complexes and that there are some differences in their properties and reactivity, for example, binuclear $[\mathrm{Cu^I(phen)X}]_2$ complexes reversibly react with CO whereas mononuclear $[\mathrm{Cu^I(phen)_2}]\mathrm{X}$ complexes do not react with CO.[19] We intended to use some well-defined copper complexes having 1,10-phenanthroline as catalysts for aryl-nitrogen bond forming processes and investigate the influence on the yields of coupling products due to differences of the structures.

In this study, four kinds of copper(I)–phenanthroline complexes $[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1**,[19] $[\mathrm{Cu^I(phen)Cl}]_2$ **2**,[19] $[\mathrm{Cu^I(phen)_2}]\mathrm{BF_4}$ **3**,[20] and $\mathrm{Cu^I(phen)PPh_3Cl}$ **4**[21] are prepared according to previous papers and used as catalysts for the synthesis of arylamines and arylamides.

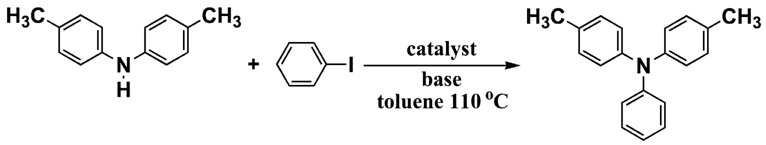
N-Arylation of *p*,*p*′-ditolylamine with iodobenzene catalyzed by 8 mol % of four complexes with respect to the amine was performed in toluene at 110 °C and is shown in Table 1.[22] These four complexes were found to work as good catalysts for this reaction and $[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** was the most effective complex among them (Table 1, entries 1–4). It is very interesting that two similar structures of copper complexes $[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** and $[\mathrm{Cu^I(phen)_2}]\mathrm{BF_4}$ **3** had different activity for the N-arylation as catalysts. As a reason, it is considered that the coordination ability of $\mathrm{Cl^-}$ is higher than that of $\mathrm{BF_4^-}$ so that $[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** has five coordinated Cu-center though $[\mathrm{Cu^I(phen)_2}]\mathrm{BF_4}$ **3** has four coordinated Cu-center with $\mathrm{BF_4^-}$ ion as a counter anion. In case that 10 mol % of $\mathrm{Cu^ICl}$[23] and 50 mol % of 1,10-phenanthroline with respect to the amine were added separately into the systems (Table 1, entry 8), the yield was 42% and lower than those of $[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** or $[\mathrm{Cu^I(phen)Cl}]_2$ **2** though there was a possibility of generation of them in situ.

The influence of bases on the yields of 4,4′-dimethyltriphenylamine in the presence of $[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** as an optimum catalyst was investigated to find that NaO^{t}Bu was the most effective and using milder bases such as $\mathrm{K_3PO_4}$, $\mathrm{K_2CO_3}$, and $\mathrm{Cs_2CO_3}$ significantly resulted in low yields (Table 1, entries 5–7). The similar tendency was observed in case of using the other complexes as catalysts.

Amidation of iodobenzene with benzamide was also performed by using these copper(I) complexes in a similar manner of amination and is shown in Table 2.[24]

As a result, all copper(I) complexes were found to catalyze the amidation (Table 2, entries 1–3) by using $\mathrm{K_3PO_4}$[25] as a base. To our knowledge, this is the first example of amidation of aryl halides catalyzed by copper(I) complexes. Using strong base such as NaO^{t}Bu resulted in no reaction in contrast to the results of

Table 1. Amination of iodobenzene with various copper(I) complexes and bases



Entry	Catalyst (mol %)	Base[a]	Reaction time (h)	LC yield (%)
1	$[\mathrm{Cu^I(phen)_2}]\mathrm{BF_4}$ **3** (8)	NaO^{t}Bu	5	59
2	$\mathrm{Cu^I(phen)PPh_3Cl}$ **4** (8)	NaO^{t}Bu	5	36
3	$[\mathrm{Cu^I(phen)Cl}]_2$ **2** (4[b])	NaO^{t}Bu	5	62
4	$[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** (8)	NaO^{t}Bu	5	80 (75[c])
5	$[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** (8)	$\mathrm{K_3PO_4}$	20	9
6	$[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** (8)	$\mathrm{K_2CO_3}$	20	8
7	$[\mathrm{Cu^I(phen)_2}]\mathrm{Cl}$ **1** (8)	$\mathrm{Cs_2CO_3}$	20	6
8	$\mathrm{Cu^ICl}$/phen (10/50)	NaO^{t}Bu	5	42[d]

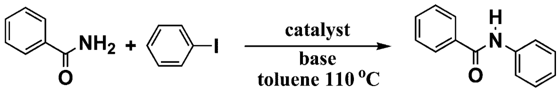
[a] All bases except NaO^{t}Bu were ground with an agate mortar and dried on heating up to 100 °C in vacuo before using.

[b] Total amount of copper(I) ion is 8 mol % with respect to an amine.

[c] Isolated yield obtained by column chromatography on silica gel using *n*-hexane–toluene (7/3) as eluent.

[d] As 2,2′-bipyridine is one of typical bidentate ligands, the effect was compared with that of phenanthroline in the similar condition ($\mathrm{Cu^ICl}$/bipiridine = 10/50, base: NaO^{t}Bu, reaction time 5 h; LC yield 26%).

Table 2. Amidation of iodobenzene with various copper(I) complexes and bases



Entry	Catalyst (mol %)	Base[a]	Reaction time (h)	LC yield (%)
1	$[Cu^I(phen)_2]BF_4$ **3** (8)	K_3PO_4	20	87
2	$[Cu^I(phen)Cl]_2$ **2** (4)	K_3PO_4	20	92
3	$[Cu^I(phen)_2]Cl$ **1** (8)	K_3PO_4	20	94 (90[b])
4	$[Cu^I(phen)_2]Cl$ **1** (8)	K_2CO_3	20	72
5	$[Cu^I(phen)_2]Cl$ **1** (8)	Cs_2CO_3	20	11
6	$[Cu^I(phen)_2]Cl$ **1** (8)	NaO^tBu	20	0
7	Cu^ICl/phen (10/50)	K_3PO_4	20	70

[a] All bases were treated in the same way of amination (see Table 1).

[b] Isolated yield obtained by column chromatography on silica gel using *n*-hexane–EtOAc (1/1) as eluent.

amination (Table 2, entry 6). Since the proton of amide is more acidic than that of amine, it is considered that using strong base lead to the formation of an excess of the deprotonated amide to give a non-reactive cuprate complex, which impedes desired catalytic cycle of amidation as Buchwald and co-workers explained in their reports of amidation on their systems.[26]

In conclusion, copper(I)–1,10-phenanthroline complexes $[Cu^I(phen)_2]Cl$ **1**, $[Cu^I(phen)Cl]_2$ **2**, $[Cu^I(phen)_2]BF_4$ **3**, and $Cu^I(phen)PPh_3Cl$ **4** were prepared and used as the catalysts for amination and amidation of iodobenzene with *p*,*p*′-ditolylamine and benzamide, respectively. These complexes were found to work as the catalysts on these reactions and showed that the differences of structures among these complexes significantly influenced the yield of carbon–nitrogen bond forming processes. To our knowledge, amidation of aryl iodides catalyzed by copper(I) complexes was the first example. In case that Cu^ICl and 1,10-phenanthroline were added separately into the systems, the yield of amination was lower than those of $[Cu^I(phen)_2]Cl$ **1** or $[Cu^I(phen)Cl]_2$ **2** though there was a possibility of generation of them in situ.

Though the mechanism and correlation between activity and structures of catalysts could still not be completely elucidated from these results, investigating what structures of copper complexes have higher activity for the coupling reaction is important for proper molecular design of more active catalysts. We are still in the process of studying the mechanism and developing the systems for large and industrial-scale production of arylamines and arylamides and will be reporting on them in the near future.

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22. Typical procedure of amination is as follows: Under nitrogen atmosphere, 1 mmol of *p*,*p*′-ditolylamine, 1 mmol of iodobenzene, 2 mmol of base, and 8 mol % of a catalyst with respect to an amine were added in 10 mL of dry toluene, followed by heating to the reflux temperature of 110 °C, stirring at the same temperature for definite time (5 or 20 h), and cooling down to room temperature to stop the reaction. The reaction mixture was filtrated with disposable ODS cartridge column and diluted to a definite volume with acetonitrile, followed by determination of chemical yields with HPLC analysis. HPLC: Nacalai Cosmosil 5C18 MSII, 4.6 × 150 mm column. Mobile phase: A, acetonitrile; B, water; A/B 85:15.
23. Cu^ICl was prepared by reduction of $Cu^{II}Cl_2$ with sodium sulfite, see: Keller, R. L.; Wycoff, H. D. *Inorg. Synth.* **1945**, *2*, 1.

24. Amidation were performed in the same way of amination by using 1 mmol of benzamide, 1 mmol of iodobenzene, 2 mmol of base, and 0.08 mmol of a catalyst (8 mol % with respect to an amide) (see Ref. 22). Dilution of the reaction mixture after reaction was carried out with methanol instead of acetonitrile, followed by HPLC analysis. HPLC: Nacalai Cosmosil 5C18 MSII 4.6 × 150 mm column. Mobile phase: A, 5 mM of aqueous KH_2PO_4 solution adjusted by 5 mM of H_3PO_4; B, methanol; A/B 55:45.
25. K_3PO_4 was found to be the most effective base on this reaction, but thorough drying of this reagent is necessary before using to give good results. Insufficient drying of K_3PO_4 was found to give rise to significant depression of chemical yields and reproducibility on this reaction.
26. Buchwald and co-workers have reported a proposed reaction mechanism in case of using strong base as a scheme below, see: Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.