

Evaluation of catalytic activity of copper salts and their removal processes in the three-component coupling reactions*

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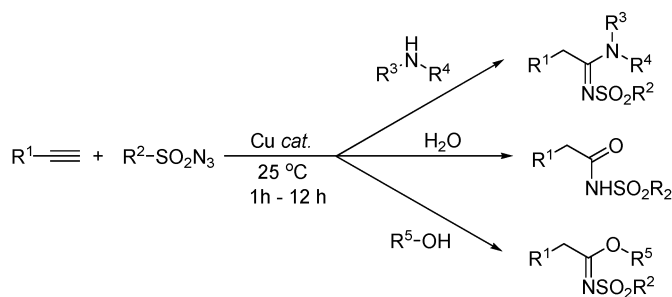
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Abstract: The catalytic activity of a wide range of copper salts, including Cu(I) and Cu(II), has been examined in the Cu-catalyzed three-component coupling reactions of sulfonyl azides, terminal alkynes, and amines, alcohols, or water to afford *N*-sulfonyl amidines, imidates, and amides, respectively. Furthermore, the investigation on the ligand effect in our protocol has revealed that certain types of ligands such as tris(benzyltriazolylmethyl)amine (TBTA) exhibited notable acceleration effects on the coupling reaction. The facile and efficient methods for removing copper salts from reaction mixture were also examined.

Keywords: three-component reactions; amidines; imidates; amides; ligand effects; removal of copper salts.

INTRODUCTION

Multicomponent reactions (MCRs) are a powerful tool for the synthesis of highly functionalized molecules of complexity and diversity in a single operation. The utility of MCRs has drawn much attention especially from the area of combinatorial chemistry and drug discovery [1]. The advantage of MCRs has driven the effort for devising highly efficient and selective process in recent years [2]. As part of this effort to develop new MCRs, we have devised the efficient Cu-catalyzed three-component reactions of 1-alkynes, sulfonyl azides, and amines, alcohols, or water to afford amidines, imidates, and amides, respectively (Scheme 1) [3,4]. The three-component coupling reactions are characterized by high effi-



Scheme 1 Cu-catalyzed three-component coupling reactions.

*Paper based on a presentation at the 14th International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-14), 2–6 August 2007, Nara, Japan. Other presentations are published in this issue, pp. 807–1194.

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ciency and selectivity, a wide substrate scope, mild conditions, and tolerance to various functional groups. In this paper, we give full details of the catalytic activity of copper salts, the ligand effects on the reaction, and several methods for removing residual copper from the reaction mixture.

STUDIES ON THE CATALYTIC ACTIVITIES OF COPPER SALTS

The catalytic activity of various copper salts in our three-component coupling protocol was initially examined. To a stirred mixture of phenylacetylene (0.5 mmol), *p*-toluenesulfonyl azide (0.6 mmol), and copper catalyst (0.05 mmol) in the choice of solvent was slowly added diisopropylamine (0.6 mmol), benzyl alcohol (0.6 mmol), or water (1.3 mmol) at room temperature. Triethylamine (0.6 mmol) was necessary for the synthesis of imidates and amides. The reaction mixture was stirred at room temperature for the indicated period of time.

The results showed that the oxidation state of copper catalyst employed, either Cu(I) or Cu(II), has negligible influence on the efficiency in the synthesis of amidines and imidates (Table 1). However, in the case of hydrolytic amide synthesis, Cu(I) catalysts exhibited higher reactivity than Cu(II) catalysts. It is interesting to note that, while CuCN showed lower efficiency in the amidine and imidate synthesis, it displayed unexpected high reactivity in the amide synthesis. Moreover, the poor activity of Cu(CH₃CN)₄PF₆ in the amide synthesis was ascribed to the high sensitivity of the catalyst toward moisture present in the conditions.

Table 1 Effect of copper salts in the three-component coupling reactions.^a

$$\text{Ph}-\text{C}\equiv\text{C} + \text{Ts}-\text{N}_3 + \text{Nu}-\text{H} \xrightarrow[\text{solvent, 25 }^\circ\text{C}]{\text{Cu (10 mol \%)}} \text{Ph}-\text{C}(\text{Nu})=\text{C}(\text{NTs})$$

Entry	Catalyst	Nu-H		
		(<i>i</i> -Pr) ₂ NH (%) ^b	PhCH ₂ OH (%) ^c	H ₂ O (%) ^c
1	CuI	82	86	94
2	CuCl	85	82	61
3	CuBr·SMe ₂	89	82	67
4	CuCN	69	23	82
5	Cu(CH ₃ CN) ₄ PF ₆	85	56	<5
6	Cu(OTf) ₂	29	55	30
7	CuCl ₂	84	61	30
8	CuBr ₂	85	78	55

^aYield was determined by ¹H NMR relative to an internal standard (1,1,2,2-tetrachloroethane).

^bTHF was used as a solvent and runs for 2 h.

^cCHCl₃ was used as a solvent and runs for 12 h.

LIGAND EFFECTS ON THE CATALYTIC ACTIVITY OF COPPER SALTS

In metal-catalyzed reactions, chelating ligands often display dramatic enhancement in the reactivity and selectivity [5]. To further optimize our reaction conditions, we scrutinized the ligand effects on our three-component coupling reactions by employing various multidentate ligands (20 mol %), which are known to coordinate with copper (Fig. 1).

The results showed that most of the chelating ligands employed reduced the catalytic activity to some extents, resulting in slightly lower conversion, compared to that without the external ligands. Among the ligands employed, however, tris(benzyltriazolylmethyl)amine (TBTA, L7) exhibited significant rate enhancement in the synthesis of amidines and imidates. In fact, TBTA was reported to accelerate the Cu-catalyzed [3+2] cycloaddition reaction of alkyl or aryl azides with 1-alkynes [6]. The lig-

Ligands examined:

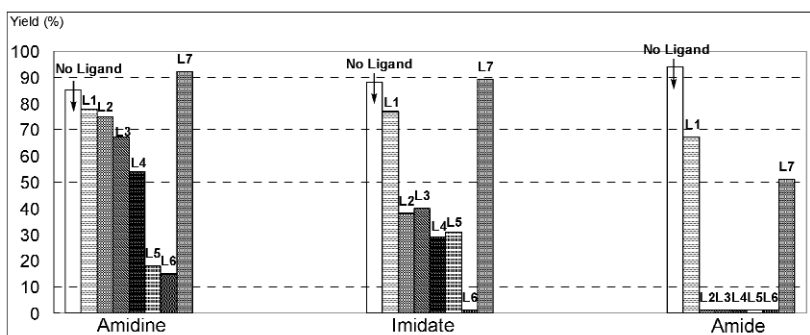
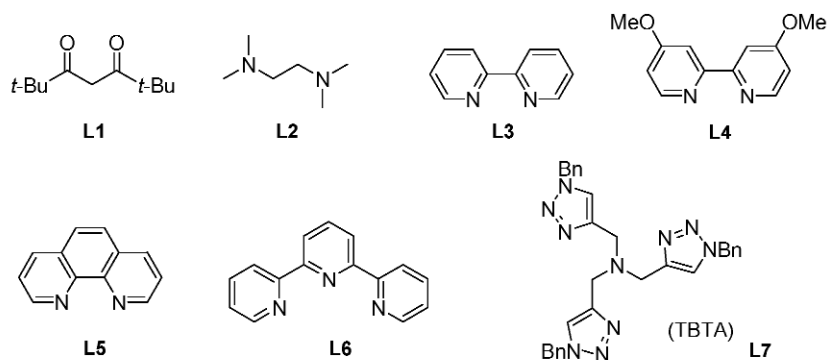


Fig. 1 Ligand effects on the catalytic activity in the three-component coupling reactions.

and effects are presumably due to some changes in the nature of the resulting metal complexes such as solubility, binding affinity to substrates, π/σ bond accepting capability, hybridization state and geometry of the coordinating orbitals, or bite angle of the coordination [7]. Therefore, it can be assumed that in our case, those external ligands examined might have some effects on the electronic and/or steric environment of copper complexes, thus eventually exerting influence on the catalytic activity.

We also obtained a reaction profile in order to understand the effect of ligand on the rate of the reaction (Fig. 2). In the synthesis of amidines with *p*-toluenesulfonyl azide (1.50 mmol), phenylacetylene

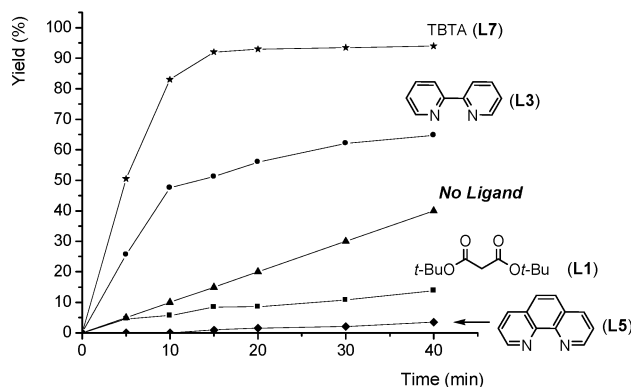
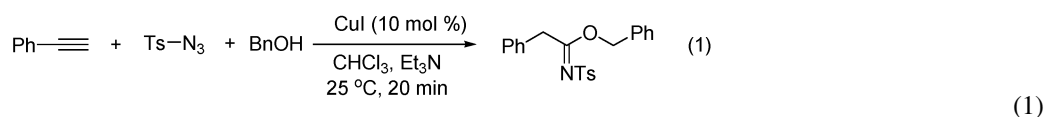


Fig. 2 Kinetic profiles in the Cu-catalyzed three-component coupling reactions.

(1.25 mmol), diisopropylamine (1.50 mmol), and CuI (5 mol %) in tetrahydrofuran (THF), the initial period of reaction in the presence of selected ligands such as **L1**, **L3**, **L5**, and **L7** was monitored by ^1H NMR using an internal standard (1,4-dimethoxybenzene). It turned out that the initial rate was increased only by **L3** and **L7** ligands. Although the presence of **L3** also showed some increase in the reaction rate, the reaction curve reached plateau around 70 % conversion, and no further progress was observed even after prolonged time.

In order to demonstrate more dramatic ligand effects, **L7** (TBTA) was chosen as a representative ligand in the synthesis of imidates, which takes about 12 h to get full conversion using 10 mol % of CuI in the absence of external ligands [3b]. When the reaction was carried out in the presence of 20 mol % of TBTA ligand, full conversion was observed within 20 min, whereas only 7 % of imidate product could be obtained in the absence of **L7** during the same reaction period.



With TBTA (**L7**, 20 mol %): 100 % conversion, 80 % yield

Without TBTA: 20 % conversion, 7 % yield

Recently, we have shown that a plausible intermediate, 5-cuprated *N*-sulfonyltriazone species, could be trapped in the reaction of sulfonyl azides and 1-alkynes under certain conditions, thus leading to triazoles without the ring-opening processes [8]. On the basis of this result, we were also intrigued by potential ligand effects on the synthesis of triazole (Table 2). It turned out that the ligand effect in this case was quite similar to that of amide synthesis: all ligands inhibited the formation of triazole to some extents, and the extents of degree were varied depending on the ligands employed. Among those ligands examined, oxygen-coordinating species (**L1**) and tris-triazole (**L7**, TBTA) exhibited relatively less inhibiting effects (entries 2 and 7, respectively).

Table 2 Ligand effect on the copper-catalyzed synthesis of *N*-sulfonyl-1,2,3-triazoles.^a

$$\text{Ph-C}\equiv\text{C} + \text{Ts-N}_3 \xrightarrow[\text{12 h}]{\text{CuI (10 mol \%), Ligand (12 mol \%), 2,6-lutidine, CHCl}_3, 0^\circ\text{C}} \text{Ph-1,2,3-triazole-N-Ts}$$

Entry	Ligand	Conversion (%) ^b	Yield (%) ^b
1	None	100	80
2	L1	61	59
3	L2	61	<1
4	L3	90	<1
5	L4	91	<1
6	L5	54	<1
7	L6	45	<1
8	L7	79	61

^aPhenylacetylene (0.60 mmol), TsN₃ (0.50 mmol), 2,6-lutidine (0.60 mmol), CuI (0.05 mmol), and ligand (0.06 mmol) in CHCl₃ at 0 °C.

^bDetermined by ^1H NMR relative to an internal standard (1,1,2,2-tetrachloroethane).

REMOVAL PROCESS OF THE RESIDUAL COPPER AFTER THE COUPLING REACTIONS

The chemical and pharmaceutical processes are in dire need of effective removal process of metal species from metal-mediated reactions [9]. In fact, the difficulty of removing metal species in catalytic reactions sometimes enforces chemists to redesign the synthetic schemes in order to avoid those metal-mediated steps being positioned in the late stages. Since amidines, imidates, and amides serve as important pharmacophores as well as prominent structural motifs in numerous bioactive natural and synthetic products, we envisaged that effective removal of copper residual after the three-component reactions would be highly desired for the potential utilities of those compounds especially in medicinal chemistry [10].

A number of purification protocols have been tested for the facile removal of copper species from the amidine synthesis (Table 3). The amount of copper residual in 5 mg of crude amidine product was determined by atomic absorption spectrometry (AAS) [11,12]. Initially, simple filtration of the reaction mixture through a celite pad (procedure 1) resulted in the residual copper content of 36.2 $\mu\text{g}/5\text{ mg}$ of amidine (entry 1). Interestingly, the copper content was significantly reduced down to 2.91 $\mu\text{g}/5\text{ mg}$ if the reaction mixture was filtered through a silica pad (procedure 2, entry 2). Moreover, when the reaction mixture was treated with silica (procedure 3) prior to the filtration through a silica pad (procedure 2), the copper content went further down to 0.42 $\mu\text{g}/5\text{ mg}$ (entry 3). As anticipated, treatment of

Table 3 Residual copper contents after the treatment methods.^a

Entry	Purification methods ^b	Copper residual in product ($\mu\text{g}/5\text{ mg}$) ^c
1	procedure 1	36.2
2	procedure 2	2.91
3	procedure 3 and then procedure 2	0.42
4	procedure 4 and then procedure 2	4.79
5 ^d	procedure 4 and then procedure 2	0.19
6	procedure 5	4.85
7	procedure 6 and then procedure 1	3.55
8	procedure 7 and then procedure 1	0.34
9	procedure 7 and then procedure 2	0.034
10	procedure 8 and then procedure 1	0.11
11	procedure 8 and then procedure 2	0.034

^aPhenylacetylene (0.60 mmol), TsN_3 (0.50 mmol), diisopropylamine (0.60 mmol), CuI (0.05 mmol), and ligand (0.06 mmol) in THF at 25 °C.

^b**procedure 1:** filtration of the reaction mixture through a celite pad (6.0 g);

procedure 2: filtration of the reaction mixture through a silica pad (10.0 g);

procedure 3: treatment of the reaction mixture with silica (0.1 g); **procedure 4:** treatment of the reaction mixture with charcoal (0.2 g); **procedure 5:** quenching of the reaction mixture with 1 N NaOH (3.0 mL); **procedure 6:** quenching of the reaction mixture with saturated aqueous NH_4Cl solution; **procedure 7:** quenching of the reaction mixture with 1 N HCl (3.0 mL); **procedure 8:** quenching of the reaction mixture with sat. NH_4OH solution (3.0 mL).

^cContents of copper species per 5 mg of crude amidine were determined by AAS, and the values are an average of two runs.

^dThe amount of charcoal was 10 times compared to that of entry 4.

the reaction mixture with charcoal turned out to be quite effective for the purification purpose, and the extent of which was dependent on the amounts of charcoal employed (entries 4–5).

We subsequently applied the methods of quenching the reaction mixture reported in literature to examine the efficiency of removing copper residual. For example, when the crude reaction mixture was quenched with aqueous NaOH solution (procedure 5), the copper residual was determined to be 4.85 $\mu\text{g}/5$ mg of amidine product (entry 6). Quenching the reaction mixture with a saturated solution of NH_4Cl (procedure 6) followed by the filtration through a pad of celite reduced the copper content to 3.55 $\mu\text{g}/5$ mg (entry 7). Treatment of the reaction mixture with 1 N aqueous HCl solution (procedure 7) followed by the filtration through a pad of celite was also efficient for the removal of copper residual (entry 8). Filtration through a silica pad turned out to be more effective than that of a celite pad (compare entries 8 and 9). In fact, by the combination of procedures 7 and 2, the contents of copper residual were significantly lowered down to 0.034 $\mu\text{g}/5$ mg. It became clear that quenching the reaction mixture with aqueous NH_4OH solution (procedure 8) was most effective for the removal of copper residual with the combination of filtration through a silica pad (entry 11).

In summary, various copper species were scrutinized to understand the catalytic effect, in terms of efficiency and selectivity of the reactions in the three-component reactions of 1-alkynes, sulfonyl azides, and amines, alcohols, or water. In addition, the investigation of ligand effects has revealed that *N*-chelating ligands are generally inhibiting reaction progresses except for the ligand with triazole functionality, **L7**. A series of experimental procedures for the efficient removal of residual copper contents in amidine products were examined, and the level of residual copper contents could be reduced down to 0.03–0.57 $\mu\text{g}/5$ mg of crude product.

ACKNOWLEDGMENT

This research was supported by a Korea Science and Engineering Foundation (KOSEF) grant funded by the Korea government (MOST, No. R01-2007-000-10618-0) and CMDS at KAIST.

REFERENCES

1. A. Tuch, S. Wallé. In *Handbook of Combinatorial Chemistry*, Vol. 2, K. C. Nicolaou, R. Hanco, W. Hartwig (Eds.), Chap. 23, Wiley-VCH, Weinheim, Germany (2002).
2. For reviews, see: (a) A. Dömling, I. Ugi. *Angew. Chem., Int. Ed.* **39**, 3169 (2000); (b) D. J. Ramon, M. Yus. *Angew. Chem., Int. Ed.* **44**, 1602 (2005); (c) A. Dömling. *Chem. Rev.* **106**, 17 (2006).
3. (a) I. Bae, H. Han, S. Chang. *J. Am. Chem. Soc.* **127**, 2038 (2005); (b) E. J. Yoo, I. Bae, S. H. Cho, H. Han, S. Chang. *Org. Lett.* **8**, 1347 (2006).
4. (a) S. Chang, M. J. Lee, D. Y. Jung, E. J. Yoo, S. H. Cho, S. K. Han. *J. Am. Chem. Soc.* **128**, 12366 (2006); (b) S. H. Cho, E. J. Yoo, I. Bae, S. Chang. *J. Am. Chem. Soc.* **127**, 16046 (2005); (c) S. H. Cho, S. J. Hwang, S. Chang. *Org. Synth.* **85**, 131 (2008); (d) M. P. Cassidy, J. Raushel, V. V. Fokin. *Angew. Chem., Int. Ed.* **45**, 3154 (2006); (e) S. H. Cho, S. Chang. *Angew. Chem., Int. Ed.* **46**, 1897 (2007); (f) S. H. Kim, D. Y. Jung, S. Chang. *J. Org. Chem.* **72**, 9769 (2007); (g) J. Y. Kim, S. H. Kim, S. Chang. *Tetrahedron Lett.* **49**, 1745 (2008); (h) S. H. Cho, S. Chang. *Angew. Chem., Int. Ed.* **47**, 2836 (2008); (i) E. J. Yoo, S. Chang. *Org. Lett.* **10**, 1163 (2008).
5. (a) N. G. Andersen, B. A. Keay. *Chem. Rev.* **101**, 997 (2001); (b) C. Kaes, A. Katz, M. W. Hosseini. *Chem. Rev.* **100**, 3553 (2000); (c) H. McManus, P. J. Guiry. *Chem. Rev.* **104**, 4151 (2004); (d) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire. *Chem. Rev.* **100**, 2159 (2000).
6. (a) T. R. Chan, R. Hilgraf, K. B. Sharpless, V. V. Fokin. *Org. Lett.* **6**, 2853 (2004); (b) M. Whiting, V. V. Fokin. *Angew. Chem., Int. Ed.* **45**, 3157 (2006).

7. (a) H. B. Goodbrand, N. X. Hu. *J. Org. Chem.* **64**, 670 (1999); (b) A. J. Clark, R. P. Filik, G. H. Thomas. *Tetrahedron Lett.* **40**, 4885 (1999); (c) T. Manifar, S. Rohani, T. P. Bender, H. B. Goodbrand, R. Gaynor, M. Saban. *Ind. Eng. Chem. Res.* **44**, 789 (2005).
8. E. J. Yoo, M. Ahlquis, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless, S. Chang. *Angew. Chem., Int. Ed.* **46**, 1730 (2007).
9. (a) N. Galaffu, S. P. Man, R. D. Wilkes, J. R. H. Wilson. *Org. Process Res. Dev.* **11**, 406 (2007); (b) C. J. Welch, J. Albaneze-Walker, W. R. Leonard, M. Biba, J. DaSilva, D. Henderson, B. Laing, D. J. Mathre, S. Spencer, X. Bu, T. Wang. *Org. Process Res. Dev.* **9**, 198 (2005); (c) C. E. Garrett, K. Prasad. *Adv. Synth. Catal.* **346**, 889 (2004).
10. It is known that a high concentration of copper species in human body causes serious damages on liver and kidney: W. Yantasee, Y. Lin, G. E. Fryxell, K. L. Alford, B. J. Busche, C. D. Johnson. *Ind. Eng. Chem. Res.* **43**, 2759 (2004).
11. For recent examples of Ru removal process in catalytic reactions, see: (a) S. H. Hong, R. H. Grubbs. *Org. Lett.* **9**, 1955 (2007); (b) F. Gallou, S. Saim, K. J. Koenig, D. Bochniak, S. T. Horhota, N. K. Yee, C. H. Senanayake. *Org. Process Res. Dev.* **10**, 937 (2006); (c) H. D. Maynard, R. H. Grubbs. *Tetrahedron Lett.* **40**, 4137 (1999); (d) L. A. Paquette, J. D. Schloss, I. Efremov, F. Fabris, F. Gallou, J. Mendez-Andino, J. Yang. *Org. Lett.* **2**, 1259 (2000); (e) J. H. Cho, B. M. Kim, *Org. Lett.* **5**, 531 (2003).
12. For recent examples of Pd removal process in catalytic reactions, see: (a) C. E. Garrett, K. Prasad. *Adv. Synth. Catal.* **346**, 889 (2004); (b) K. Konigsberger, G.-P. Chen, R. R. Wu, M. J. Girgis, K. Prasad, O. Repic, T. J. Blacklock. *Org. Process Res. Dev.* **7**, 733 (2003).