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An efficient protocol for the preparation of amides by copper-catalyzed reactions between nitriles and amines in water

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ABSTRACT

The reactions between nitriles and amines catalyzed by $Cu(OAc)_2$ and 2-piperidinecarboxylic acid were carried out in pure water without any other additives. A variety of substituted amides can be obtained in moderate to good yields up to 90%.

Amides represent an important class of compounds found in numerous bioactive products, such as Sorafenib **1**,[1] Lipitor **2,** and Vyvanse **3** (Scheme 1), which have been widely used for the treatment of cancer, hypercholesterolemia, and juvenile hyperactivity, respectively.

Normally, the classical synthetic protocol to obtain amide is the substitution reaction between carboxylic acid and amine,[2] which usually results in the formation of ammonium salt and generally requires a temperature above 160 °C.[3] Further studies revealed that the reaction temperature could be significantly lowered by using specially designed areneboronic acids[4] or heterogeneous silica catalysts.[5] On the other hand, one of the most common methods for amide synthesis employs activated derivatives of the carboxylic acid, such as esters[6] together with carbodiimides, phosphonium, or uronium salts as additives.[7] Other general procedures for amide synthesis include the well-established name reactions such as Ritter,[8] Schmidt,[9] Beckmann,[10] Ugi,[11] Wolff et al.[12] Besides, catalytic procedures have been developed including oxidative amidation of aldehydes[13] or alcohols,[14] aminocarbonylation of aryl halides[15] or terminal alkynes,[16] rearrangement of oximes and coupling with amines,[13a] cross coupling of amides with aryl and alkenyl halides,[17] and transamidation of amides with amines.[18]

Besides these protocols, a less frequently reported synthetic method is the coupling of nitrile with amine, which has been reported to be performed in the presence of ruthenium[19a] or platinum[19b] catalysts. These reactions were unexceptionally carried out in organic solvents such as DME. In continuation of our work on copper-catalyzed hydrolysis of nitrile to amide[20a] and other coupling reactions in water,[20] herein is reported the reaction of nitrile and amine catalyzed by copper to form amide in water.

The initial studies were focused on the optimization of catalytic conditions based on phenylacetonitrile **1a** and aniline **2a** as model substrates. As shown in Table 1, control experiments indicated the catalyst to be essential for the reaction, and only a trace of product was detected in the absence of ligand or metal (Table 1, entries 1 and 2). Seven different ligands **L1**–**L7** were tested, and 2-piperidinecarboxylic acid **L7** seemed to be superior to others in yield of 71% (Table 1, entries 3–9). It is worthy to note that ammonia **L5** gave only 39% yield, which was reported by us to form high catalytic species with CuI during catalytic nitrile hydrolysis (entry 7).[20a] Comparison of different metal sources indicated $Cu(OAc)_2$ to be better than others including $CuCl_2$, CuO, CuI, $NiCl_2$, and $FeCl_3$ (Table 1, entries 9–14). Reaction temperature was another important factor to affect the results. For example, when the reaction temperature was decreased from 100 to 80 °C, the yields of the desired product dropped from 71% to 50% (Table 1, entries 9 and 15). Meanwhile, when the reaction temperature was increased to 120 °C, the yield of the desired product remained quite stable at 70% (Table 1, entry 16). Finally, the catalyst loading was investigated and 10 mol % was found to be fitful for the catalysis (Table 1, entries 17–19). Thus, the optimal catalytic conditions consist of $Cu(OAc)_2$ (10 mol %) and **L7** (20 mol %) in water (5 mL) at 100 °C for 18 h.

Next, the scope and limitation of this protocol were examined by using other substrates under the optimized reaction conditions.

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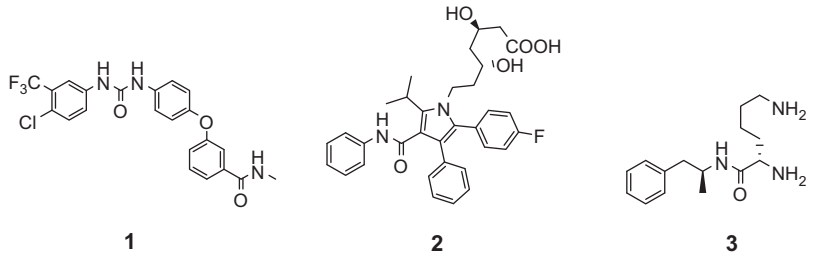
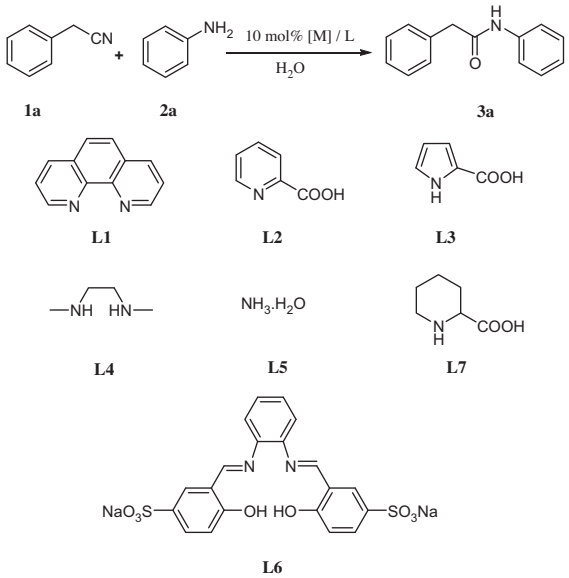


Scheme 1. Selected examples of biologically and therapeutically active amides.

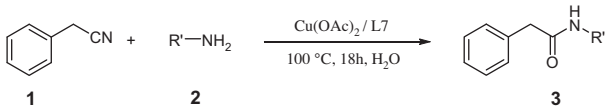
Table 1
Optimization of reaction conditions[a]

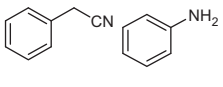
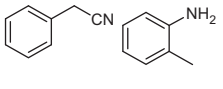
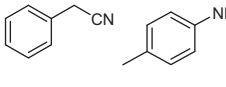
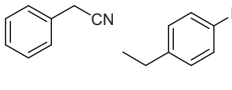
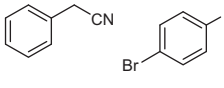
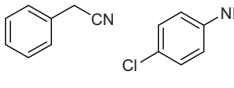
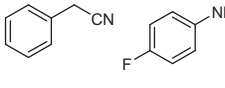
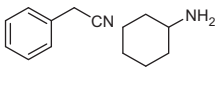
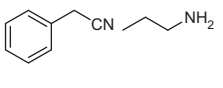
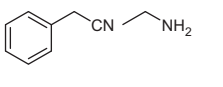


Entry	[M]	Ligand	Yield[b] (%)
1	$Cu(OAc)_2$	—	4
2	—	L7	Trace
3	$Cu(OAc)_2$	L1	16
4	$Cu(OAc)_2$	L2	31
5	$Cu(OAc)_2$	L3	27
6	$Cu(OAc)_2$	L4	22
7	$Cu(OAc)_2$	L5	39[c]
8	$Cu(OAc)_2$	L6	29[d]
9	$Cu(OAc)_2$	L7	71
10	$CuCl_2$	L7	55
11	CuO	L7	29
12	CuI	L7	40
13	$NiCl_2$	L7	23
14	$FeCl_3$	L7	18
15	$Cu(OAc)_2$	L7	50[e]
16	$Cu(OAc)_2$	L7	70[f]
17	$Cu(OAc)_2$	L7	40[g]
18	$Cu(OAc)_2$	L7	56[h]
19	$Cu(OAc)_2$	L7	73[i]

[a] All reactions were carried out by using phenylacetonitrile (1.0 mmol), phenylamine (1.3 mmol), [M] (0.1 mmol), and ligand (0.2 mmol) in H_2O (5 mL) at 100 °C for 18 h.
[b] Isolated yields.
[c] [Cu]/Ligand = 1:4.
[d] [Cu]/Ligand = 1:1.
[e] The reaction temperature was 80 °C.
[f] The reaction temperature was 120 °C.
[g] 2.5 mol % catalyst.
[h] 5 mol % catalyst.
[i] 20 mol % catalyst.

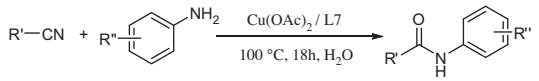
Table 2
Cu-catalyzed reactions between phenylacetonitrile and different amines[a]



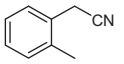
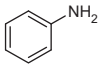
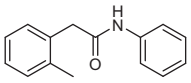
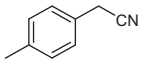
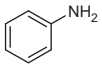
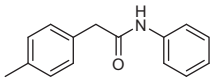
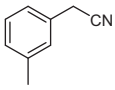
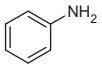
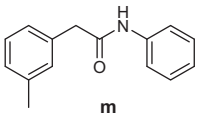
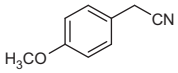
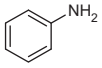
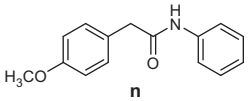
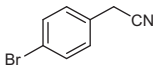
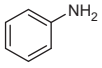
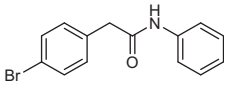
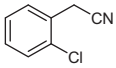
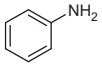
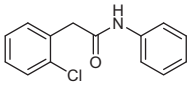
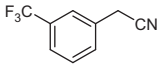
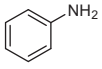
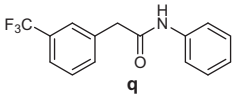
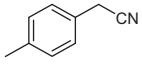
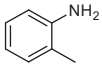
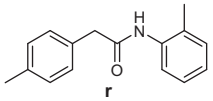
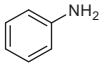
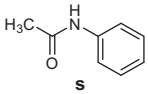
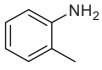
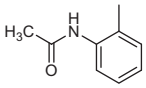
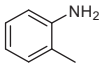
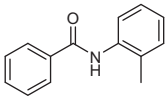
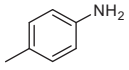
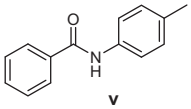
Entry	Nitrile	Aniline	Product	Yield[b] (%)
1			**a**	71
2			**b**	86
3			**c**	83
4			**d**	85
5			**e**	56
6			**f**	69
7			**g**	52
8			**h**	71
9			**i**	75
10			**j**	73

[a] Reaction conditions: **1** (1 mmol), **2** (1.3 mmol), $Cu(OAc)_2$ (0.1 mmol) and 2-piperidinecarboxylic acid (0.2 mmol) in H_2O (5 mL) at 100 °C for 18 h.
[b] Isolated yields.

Table 3
Cu-catalyzed coupling reactions between different nitriles and anilines[a]

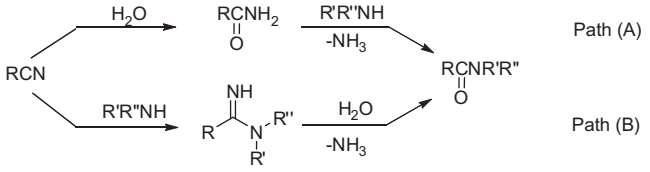


1 **2** **3**

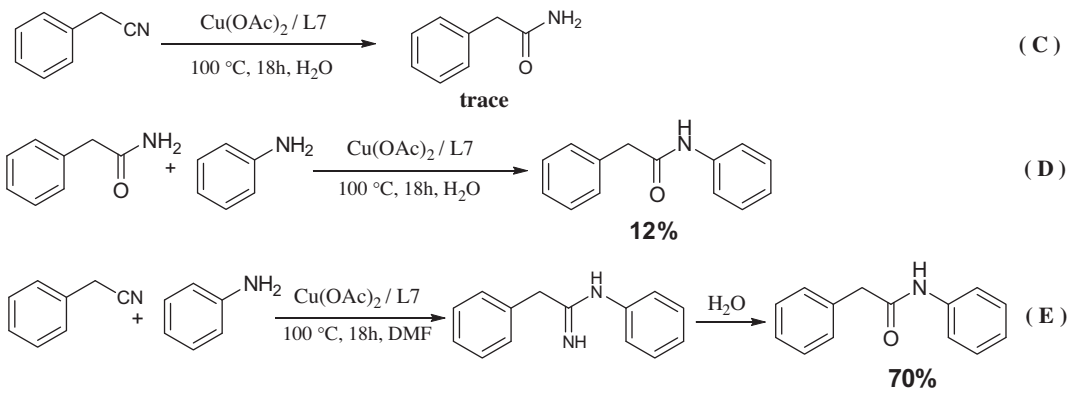
Entry	Nitrile	Amine	Product	Yield[b] %
1			 **k**	86
2			 **l**	83
3			 **m**	80
4			 **n**	82
5			 **o**	51
6			 **p**	64
7			 **q**	50
8			 **r**	90
9			 **s**	67
10			 **t**	71
11			 **u**	50
12			 **v**	53

[a] Reaction conditions: **1** (1 mmol), **2** (1.3 mmol), $Cu(OAc)_2$ (0.1 mmol) and 2-piperidinecarboxylic acid (0.2 mmol) in H_2O (5 mL) at 100 °C for 18 h.
[b] Isolated yields.

As shown in Table 2, the reactions of phenylacetonitrile (**1a**) with a variety of substituted amines could be effectively conducted in yields ranging from 52% to 86%. Anilines bearing electron donating groups resulted in better results than those bearing electron withdrawing groups. For example, 4-methyl and ethylaniline gave the desired products in 83% and 86% yields, while 4-chloro and fluoroaniline resulted in 69% and 52% yields, respectively (Table 2,



Scheme 2. Proposed pathways for amide formation.



Scheme 3. Control experiments of phenylacetonitrile hydrolysis and transamidation of phenylacetamide with aniline.

entries 3, 4 and 6, 7). Furthermore, the catalytic system could also be applied for aliphatic amine such as cyclohexylamine, propylamine, and ethylamine in moderate yields (Table 2, entries 8, 9, and 10).

Meanwhile, similar phenomena could also be found in the case of the reactions between substituted phenylacetonitriles and aniline as shown in Table 3, in which electron-donating substituents also benefited the results.

Furthermore, the steric hindrance of substituents seemed to have less effect on the results. For instance, *ortho*- and *para*-methyl aniline gave 86% and 83% yields (Table 2, entries 2 and 3), while *ortho*- and *para*-phenylacetonitrile also gave similar results (Table 3, entries 1 and 2). And the best result was obtained in the reaction between 4-methyl phenylacetonitrile and 2-methyl aniline to give desired product in 90% yield (Table 3, entry 8). Furthermore, acetonitrile could also be applied for the reactions in yields around 70% (Table 3, entries 9 and 10). On the other hand, benzonitrile could also be reacted with 2-methyl aniline and 4-methyl aniline, affording the corresponding products in 50% and 53% yields, respectively (Table 3, entries 11 and 12).

The catalytic pathway was then studied,[19] and two possible routes might exist as shown in Scheme 2. In path A, nitrile is firstly hydrolyzed to the primary amide based on our former nitrile hydrolysis work,[20] which is then reacted with amine to form amide product. In path B, nitrile is reacted initially with the amines to form an amidine intermediate according to the literature,[21] which is unstable and can be easily hydrolyzed to give corresponding amide and ammonia.[22]

Control experiments as shown in Scheme 3 indicated that path A might not be the major pathway because of low yield to give amide product under the catalytic conditions (Scheme 3C and D). Thus, path B might be the true reaction path, although the direct isolation of amidine failed due to its instability in water.[22] Actually, amidine was detected in the reaction between phenylacetonitrile and aniline in DMF, and was hydrolyzed to be an amide product after the addition of water (Scheme 3E).

In conclusion, an efficient copper-catalyzed protocol for the formation of amide form nitrile and amine has been disclosed.[23] It exhibited several advantages: copper as catalyst instead of expensive metals; water as reaction media instead of organic solvents; neutral reaction conditions without any other additives. This approach represents an important complement to the synthesis of substituted amides and exhibits potential usage in industry. Further work on aqueous catalysis is currently underway in this laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.058.

References and notes

1. Yu, B.; Tang, L. D.; Li, Y. L.; Song, S. H.; Ji, X. L.; Lin, M. S.; Wu, C. F. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 110–114.
2. (a) Colombo, M.; Bossolo, S.; Aramini, A. *J. Comb. Chem.* **2009**, *11*, 335–337; (b) Sarvari, M. H.; Sharghi, H. *J. Org. Chem.* **2006**, *71*, 6652–6654; (c) Shekhar, A. C.; Kumar, A. R.; Sathaiah, G.; Paul, V. L.; Sridhar, M.; Rao, P. S. *Tetrahedron Lett.* **2009**, *50*, 7099–7101.
3. Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827–10852.
4. (a) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem., Int. Ed.* **2008**, *47*, 2876–2879; (b) Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 8645–8657; (c) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196–4197; (d) Ishihara, K.; Ohara, S.; Yamamoto, H. *Macromolecules* **2000**, *33*, 3511–3513; (e) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 1431–1434; (f) Arnold, K.; Batsanov, A. S.; Davies, B.; Whiting, A. *Green Chem.* **2008**, *10*, 124–134; (g) Coghlan, S. W.; Giles, R. L.; Howard, J. A. K.; Patrick, L. G. F.; Probert, M. R.; Smith, G. E.; Whiting, A. *J. Organomet. Chem.* **2005**, *690*, 4784–4793.
5. Comerford, J. W.; Clark, J. H.; Macquarrie, D. J.; Breeden, S. W. *Chem. Commun.* **2009**, 2562–2564.
6. (a) Ranu, B. C.; Dutta, P. *Synth. Commun.* **2003**, *33*, 297–301; (b) Arora, R.; Paul, S.; Gupta, R. *Can. J. Chem.* **2005**, *83*, 1137–1140; (c) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 10039–10044.
7. Valeur, E.; Bradley, M. *Chem. Soc. Rev.* **2009**, *38*, 606–631.
8. (a) Kalkhambkar, R. G.; Waters, S. N.; Laali, K. K. *Tetrahedron Lett.* **2011**, *52*, 867–871; (b) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045–4048.
9. (a) Macleod, F.; Lang, S.; Murphy, J. A. *Synlett* **2010**, 529–534; (b) Yadav, J. S.; Reddy, B. V. S.; Praneeth, K. *Tetrahedron Lett.* **2008**, *49*, 4742–4745.
10. (a) Gnanamgari, D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 922–924; (b) Owston, N. A.; Parker, A. J.; Williams, J. M. J. *Org. Lett.* **2007**, *9*, 3599–3601; (c) Augustine, J. K.; Kumar, R.; Bombrun, A.; Mandal, A. B. *Tetrahedron Lett.* **2011**, *52*, 1074–1077; (d) Chandrasekhar, S.; Gopalaiah, K. *Tetrahedron Lett.* **2003**, *44*, 7437–7439.
11. (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210; (b) Santra, S.; Andreana, P. R. *J. Org. Chem.* **2011**, *76*, 2261–2264; (c) Isaacson, J.; Kobayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1845–1848; (d) Pan, S. C.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3622–3625; (e) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8–21.
12. (a) Meier, H.; Eller, K. P. *Angew. Chem., Int. Ed.* **1975**, *14*, 32–43; (b) Kirmse, W. *Eur. J. Org. Chem.* **2002**, 2193–2256; (c) Julian, R. R.; May, J. A.; Stoltz, B. M.; Beauchamp, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 4478–4486.
13. (a) Yoo, W. J.; Li, C. J. *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065; (b) Bode, J. W.; Sohn, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799; (c) Kovi, K. E.; Wolf, C. *Chem. Eur. J.* **2008**, *14*, 6302–6315; (d) Suto, Y.; Yamagiwa, N.; Torisawa, Y. *Tetrahedron Lett.* **2008**, *49*, 5732–5735; (e) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096–5099.

14. For selected examples of amide formation from amines and alcohols, see: (a) Ghosh, S. C.; Hong, S. H. *Eur. J. Org. Chem.* **2010**, 4266–4270; (b) Dam, J. H.; Osztrovszky, G.; Nordstr, L. U.; Madsen, R. *Chem. Eur. J.* **2010**, *16*, 6820–6827; (c) Wang, Y.; Zhu, D. P.; Tang, L.; Wang, S. J.; Wang, Z. Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 8917–8921; (d) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X. Y.; Honga, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643–2649; (e) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673; (f) Gunanathan, C.; David, Y. B.; Milstein, D. *Science* **2007**, *317*, 790–792.
15. (a) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331; (b) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102–7107; (c) Brennfuhrer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114–4133; (d) Lagerlund, O.; Mantel, M. L. H.; Larhed, M. *Tetrahedron* **2009**, *65*, 7646–7652.
16. (a) Matteoli, U.; Scrivanti, A.; Beghetto, V. *J. Mol. Catal. A: Chem.* **2004**, *213*, 183–186; (b) Lu, S. M.; Alper, H. *J. Am. Chem. Soc.* **2008**, *130*, 6451–6455.
17. (a) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720–16734; (b) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403–406.
18. (a) Calimsiz, S.; Lipton, M. A. *J. Org. Chem.* **2005**, *70*, 6218–6221; (b) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 10003–10008; (c) Zhang, M.; Imm, S.; Bahn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3905–3909.
19. (a) Murahashi, S. I.; Naota, T.; Saito, E. *J. Am. Chem. Soc.* **1986**, *108*, 7846–7847; (b) Cobley, C. J.; van den Heuvel, M.; Abbadi, A.; de Vries, J. G. *Tetrahedron Lett.* **2000**, *41*, 2467–2470; (c) Allen, C. L.; Lapkin, A. A.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 4262–4264.
20. (a) Li, Z.; Wang, L.; Zhou, X. *Adv. Synth. Catal.* **2012**, *354*, 584–588; (b) Wang, Y.; Wu, Z.; Wang, L.; Li, Z.; Zhou, X. *Chem. Eur. J.* **2009**, *15*, 8971–8974; (c) Liang, L.; Li, Z.; Zhou, X. *Org. Lett.* **2009**, *11*, 3294–3297; (d) Wu, Z.; Jiang, Z.; Wu, D.; Xiang, H.; Zhou, X. *Eur. J. Org. Chem.* **2010**, 1854–1857; (e) Wu, Z.; Huang, Q.; Yu, L.; Wu, D.; Li, Z.; Zhou, X. *Eur. J. Org. Chem.* **2011**, 5242–5245; (f) Wu, Z.; Pan, Y.; Zhou, X. *Synthesis* **2011**, 2255–2260.
21. (a) Siegl, W. O. *J. Org. Chem.* **1977**, *42*, 1872–1877; (b) Forsberg, J. H.; Spaziano, V. T.; Balasubramian, T. M.; Lui, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* **1987**, *52*, 1017–1021.
22. Shriner, R. L.; Neumanw, F. W. *Chem. Rev.* **1944**, *35*, 351–425.
23. General experimental procedure: nitrile (1 mmol), amine (1.3 mmol), $Cu(OAc)_2$ (0.1 mmol), and the ligand 2-piperidinecarboxylic acid (0.2 mmol) in water (5 mL) were put into a teflon septum screw-capped tube. The reaction mixture was stirred at 100 °C for 18 h without an inert gas atmosphere, and then cooled to room temperature and extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography to afford the corresponding product.