SHORT COMMUNICATION

EurJOC European Journal of Organic Chemistry

DOI: 10.1002/ejoc.201301868

Copper-Catalyzed Regioselective Synthesis of *N*-Aryl Amides from Aldoximes and Aryl Halides

Niranjan Panda,*[a] Raghavender Mothkuri,[a][‡] and Dinesh Kumar Nayak[a][‡]

Keywords: Homogeneous catalysis / Rearrangement / Copper / Aldoximes / Amides

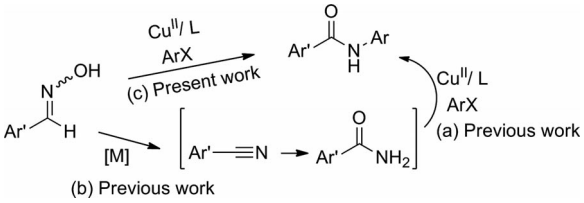
Ligand-assisted copper-catalyzed reaction of aldoximes with aryl halides is described for the regioselective synthesis of *N*-aryl amides. This protocol is simple and compatible with a wide range of functional groups attached to the aryl ring of the halides as well as aldoximes.

Introduction

Carboxamides are pivotal building blocks in many pharmaceuticals and biologically active natural products.[1] Furthermore, they are potential precursors in organic synthesis as well as major constituents of high-performance materials.[2] The classical method for amide synthesis includes the coupling of a carboxylic acid (by using coupling reagents such as carbodiimide)[3] with an amine; this procedure produces a stoichiometric amount of waste products and thus innately faces serious environmental problems.[4] The rearrangement of ketoximes in the presence of acid, known as the Beckmann rearrangement,[5] often offers a straightforward method for the formation of *N*-substituted amides ($R_2C{=}NOH \rightarrow RCONHR$). Nevertheless, the necessity of high reaction temperatures and the use of large amounts of strong Brønsted acids and dehydrating media with the production of large amounts of byproducts[6] are the inevitable drawbacks of this reaction. Notably, the acid-catalyzed Beckmann rearrangement of aldoximes, in general, leads to nitriles,[7] whereas the same substrate in the presence of transition-metal catalysts leads to primary amides.[8] It has been hypothesized that the transition-metal-catalyzed reactions proceed through a dehydration/hydration sequence via the formation of a discrete nitrile intermediate.[9,10] Evidently, a number of precious transition metal (i.e., Rh,[11] Ru,[12] Ir,[13] Pd,[14] and Au/Ag[15]) catalysts were successfully employed for the atom-efficient synthesis of primary amides from aldoximes. Owing to their economic attractiveness, the use of copper catalysts for such transformations has drawn significant attention. For instance, Williams and Ramón independently used a low concentration of a cheap Cu^{II} catalyst for the effective transformation of aldoximes into primary amides.[16] $CuSO_4{\cdot}5H_2O$-mediated transformation of aldehydes into primary amides in one-pot through an aldoxime intermediate was revealed by Ganguly and his co-workers.[10] However, the copper-catalyzed direct transformation of oximes into *N*-substituted amides does not yet have precedent. Rather, a few methods including the rearrangement of ketoximes into *N*-aryl amides in the presence of some other transition metals such as Rh and Hg have been reported. For example, Yamaguchi and Arisawa described a Rh-catalyzed protocol for the transformation of ketoximes into *N*-substituted amides.[17] Acetonitrile-mediated $HgCl_2$-catalyzed conversion of ketoximes into secondary amides/lactams was reported by Ramalingan and Park.[18] Although, these results are promising, the use of toxic and precious catalysts impedes the practicality of these approaches. Moreover, if oximes of unsymmetrical ketones are used, the formation of regioisomeric mixtures limits the scope of these reactions. Hence, the development of efficient and less-expensive catalytic systems (preferably by using low-costing Fe and/or Cu catalysts) for the regioselective synthesis of amides from oximes is deemed to be important.

Over the past decades, the ligand-assisted copper-catalyzed *N*-arylation of amides with aryl halides has emerged as a potential method for the construction of C–N bonds[19] (Scheme 1, a). Furthermore, the reacting primary amides can be obtained in an atom-economic fashion from the copper-catalyzed dehydration/hydration of aldoximes (Scheme 1, b).[9,10] Stimulated by these facts, we anticipated that copper-catalyzed rearrangement of aldoximes in the presence of an aryl halide might lead directly to *N*-aryl amides with alleviation of the regioselectivity problem that is frequently associated with the Beckmann rearrangement. For the first time, we report herein a ligand-assisted, copper-catalyzed, regioselective, practical synthesis of *N*-aryl amides from the reaction of aldoximes with aryl halides (Scheme 1, c).

[a] Department of Chemistry, National Institute of Technology, Rourkela, Odisha 769008, India
E-mail: npanda@nitrkl.ac.in
https://sites.google.com/site/nitrklcynpanda/
[‡] These authors contributed equally to this work.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301868.

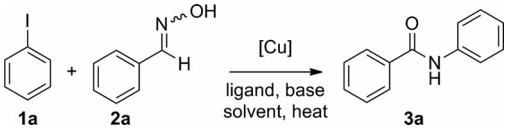


Scheme 1. Approaches to *N*-aryl amides from aldoximes.

Results and Discussion

We began our study with the reaction of iodobenzene (**1a**) and benzaldoxime (**2a**) as the model reaction. Upon heating **1a** and **2a** at reflux in toluene in the presence of CuI and Cs_2CO_3, in line with the earlier report of Maitra and co-workers[20] on the copper-catalyzed *O*-arylation of aldoximes with aryl iodides, the deoximation occurred with the formation of contaminating benzaldehyde, and no trace of benzanilide (**3a**) or the *O*-aryl oxime ether was obtained (Table 1). However, upon the addition of 1,10-phenanthroline (1,10-phen, 30 mol-%) to the reaction mixture, **3a** was isolated in 20% yield with the decomposition of the remaining aldoxime. This observation persuaded us to optimize the reaction conditions by identifying the best catalyst, ligand, base, solvent, and reaction temperature. Among the various ligands examined, the use of *N*,*N*′-dimethylethylenediamine (DMEDA) was the most effective to produce **3a** (Table 1, entry 8). The choice of base as well as its concentration was found to be crucial for this reaction. Among the tested bases [Cs_2CO_3, *t*BuOK, K_3PO_4, KOH, NaOAc, K_2CO_3, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine] K_2CO_3 (5 equiv.) furnished the best result (82% yield; Table 1, entries 8–13), whereas a lower amount of K_2CO_3 (2 equiv.) gave **3a** in 47% yield over a period of 12 h. NaOAc, DBU, and pyridine did not furnish **3a**. Likewise, different copper catalysts were screened (Table 1, entries 8, 14–19), and $CuSO_4{\cdot}5H_2O$ (10 mol-%) and DMEDA (30 mol-%) in the presence K_2CO_3 (5 equiv.) afforded the optimum yield of **3a**. Other catalysts such as $CuCl_2$, CuCl, CuBr, $Cu(OAc)_2$, and CuO were less effective. The use of CuI/DMEDA (Table 1, entry 18) gave a comparable result (70%), which demonstrates that both Cu^{I} and Cu^{II} catalyst precursors are able to facilitate this transformation. Furthermore, it is possible that conversion between the Cu^{II} and Cu^{I} species might occur during this reaction process. Upon performing the reaction at 130 °C in *o*-xylene, the optimum yield of **3a** was obtained. However, lowering the temperature to 110 °C (at reflux in toluene) and increasing the temperature to 140 °C (at reflux in *o*-xylene) furnished **3a** in 47 and 58% yield, respectively. If a similar reaction was performed in DMSO, the *O*-aryl oxime ether[20] resulted without the formation of any trace of **3a** (from TLC). Control experiments demonstrated that in the absence of catalyst, base, or ligand, the amidation of iodobenzene did not occur; rather, the starting material was recovered. Reaction of **1a** with **2a** (4 equiv.) in the presence of $CuSO_4{\cdot}5H_2O$ (10 mol-%), DMEDA (30 mol-%), and K_2CO_3 (5 equiv.) at 130 °C in the absence of any solvent also delivered **3a** in appreciable yield (62%) with decomposition of the remaining starting materials.

Table 1. Optimization of the reaction conditions.[a]



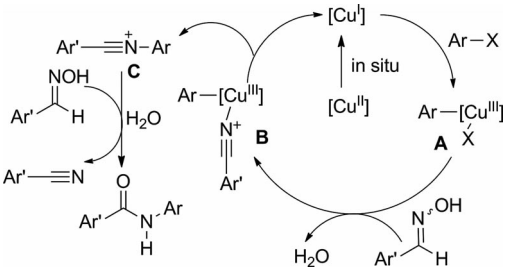
1a 2a 3a

Entry	Catalyst	Ligand[b]	Base	Solvent	Yield[c][%]
1	CuI	–	Cs_2CO_3	toluene	0
2	CuI	1,10-phen	Cs_2CO_3	*o*-xylene	20
3	$CuSO_4{\cdot}5H_2O$	1,10-phen	K_2CO_3	*o*-xylene	30
4	$CuSO_4{\cdot}5H_2O$	bipy	K_2CO_3	*o*-xylene	21
5	$CuSO_4{\cdot}5H_2O$	TMEDA	K_2CO_3	*o*-xylene	27
6	$CuSO_4{\cdot}5H_2O$	acac	K_2CO_3	*o*-xylene	17
7	$CuSO_4{\cdot}5H_2O$	EDA	K_2CO_3	*o*-xylene	n.r.
8	$CuSO_4{\cdot}5H_2O$	DMEDA	K_2CO_3	*o*-xylene	82
9	$CuSO_4{\cdot}5H_2O$	DMEDA	DBU	*o*-xylene	n.r.
10	$CuSO_4{\cdot}5H_2O$	DMEDA	Cs_2CO_3	*o*-xylene	49
11	$CuSO_4{\cdot}5H_2O$	DMEDA	NaOAc	*o*-xylene	n.r.
12	$CuSO_4{\cdot}5H_2O$	DMEDA	KOH	*o*-xylene	28
13	$CuSO_4{\cdot}5H_2O$	DMEDA	K_3PO_4	*o*-xylene	37
14	$Cu(OAc)_2$	DMEDA	K_2CO_3	*o*-xylene	21
15	$CuCl_2$	DMEDA	K_2CO_3	DMF	52
16	CuO	DMEDA	K_2CO_3	DMF	61
17	CuBr	DMEDA	K_2CO_3	*o*-xylene	32
18	CuI	DMEDA	K_2CO_3	*o*-xylene	70
19	CuCl	DMEDA	K_2CO_3	DMF	48
20	$CuSO_4{\cdot}5H_2O$	DMEDA	K_2CO_3	DMSO	0
21	$CuSO_4{\cdot}5H_2O$	DMEDA	K_2CO_3	toluene	53
22	$CuSO_4{\cdot}5H_2O$	DMEDA	K_2CO_3	1,4-dioxane	n.r.
23	–	DMEDA	K_2CO_3	*o*-xylene	n.r.
24	$CuSO_4{\cdot}5H_2O$	–	K_2CO_3	*o*-xylene	n.r.
25	$CuSO_4{\cdot}5H_2O$	DMEDA	–	*o*-xylene	n.r.
26	$CuSO_4{\cdot}5H_2O$	DMEDA	K_2CO_3	H_2O	n.r.

[a] Reaction conditions: A mixture of iodobenzene (100 mg), benzaldoxime (4 equiv.), copper catalyst (10 mol-%), ligand (30 mol-%), and base (5 equiv.) in solvent (1 mL) was heated at 130 °C for 12 h. [b] bipy = 2,2′-bipyridyl, TMEDA = *N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine, acac = acetylacetonate, EDA = ethylenediamine. [c] n.r.: no reaction.

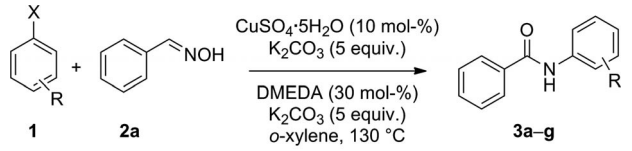
Treatment of the aldoxime under the optimum reaction conditions in the absence of iodobenzene afforded both benzonitrile and benzamide (from TLC and GC). Notably, under similar reaction conditions, if benzamide was taken instead of oxime **2**, the *N*-aryl amide (e.g., **3a**) was produced in excellent yield (see the Supporting Information for details), whereas a similar experiment with benznitrile did not furnish any anilide (from TLC). However, the addition of water (1 equiv.) to the benznitrile produced *N*-aryl amide **3a**, albeit in poor yield (20%). Reaction of benznitrile with iodobenzene[21] under similar reaction conditions in the presence of 4-methoxybenzaldoxime (**2b**) afforded **3a** along with a small amount of **4**. It was also observed that increasing the oxime concentration from 1 to 4 equiv. gave the best yield of anilide, which indicated that the OH group of the oxime was utilized in the hydrolysis. On the basis of these observations and in line with earlier reports, it may be expected that the oxime initially transforms into the primary amide,[10,16] which is subsequently *N*-arylated in one pot in

the presence of $CuSO_4 \cdot 5H_2O$ and a ligand (Scheme 1, a,b).[22] Moreover, considering the catalytic behavior of the CuI/DMEDA complex to produce reasonable amounts of **3a** (Table 1, entry 18), an alternate plausible pathway may be proposed. We speculate that in the presence of a diamine ligand, Cu^{II} quickly forms a complex, L_2Cu^{II}, that is subsequently reduced in situ by the OH group of the oxime to produce L_2Cu^{I}.[19b,23] Oxidative addition of the aryl halide to L_2Cu^{I} leads to complex **A** (Scheme 2). In the presence of a nucleophile, the halide on the Cu center is exchanged to furnish **B**.[9a,23b] Then, reductive elimination produces intermediate **C**, which undergoes hydrolysis by the oxime or the in situ generated H_2O to produce the *N*-aryl amide.[10]



Scheme 2. Alternative pathway for the synthesis of *N*-aryl amides.

Having the optimal reaction conditions, we explored the scope of the reaction with a variety of aryl halides. The reaction of benzaldoxime (**2a**) with aryl iodides produced *N*-aryl amides in good yields, whereas a similar reaction with aryl bromides furnished **3a**–**g** in moderate yields (Scheme 3). This reaction protocol was found to be compatible with electron-donating and electron-withdrawing substituents on the aryl bromides and iodides to produce the corresponding *N*-aryl amides in moderate to good yields (Scheme 3). Unfortunately, less-reactive aryl chlorides did not couple with **2a** under the optimum reaction conditions; rather, the benzamide resulted instead.

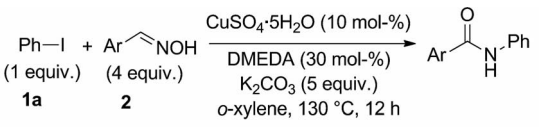


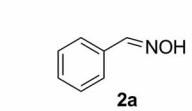
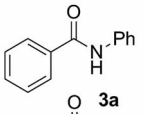
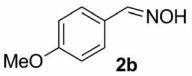
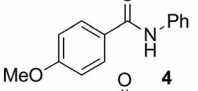
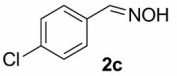
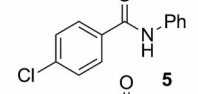
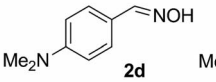
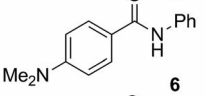
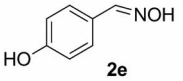
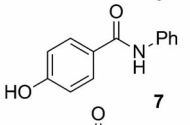
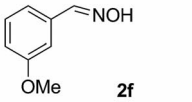
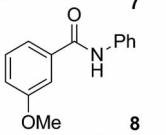
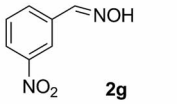
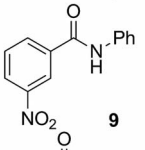
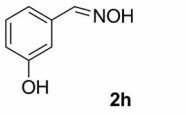
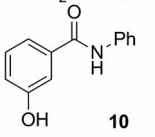
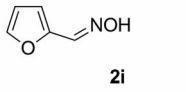
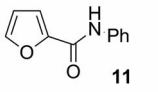
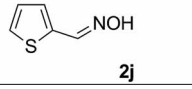
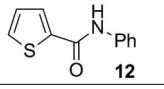
3a: X = I, R = H (82 %); X = Br, R = H (73 %)
3b: X = I, R = 4-NO_2 (75 %); X = Br, R = 4-NO_2 (56 %)
3c: X = I, R= 4-OMe (64 %); X = Br, R= 4-OMe (30 %)
3d: X = I, R = 2-CO_2Me (77 %); X = Br, R = 2-CO_2Me (61 %)
3e: X = I, R = 4-Cl (84 %); **3f**: X = Br, R = 4-$COCH_3$ (62 %)
3g: X = I, R = 3-Cl,4-Cl (80 %)

Scheme 3. Reaction of aryl halides with benzaldoximes.

Next, the optimized protocol was applied to the coupling of substituted aryl aldoximes with iodobenzene (Table 2). Pleasingly, the reaction furnished good results if aromatic aldoximes were used independent of the presence of electron-withdrawing or electron-donating groups with the alleviation of the regioselectivity problem. Surprisingly, 4-hydroxybenzaldoxime did not react with iodobenzene to produce the corresponding anilide (Table 2, entry 5). Heteroaryl amides were also produced under the optimum reaction conditions in appreciable yields (Table 2, entries 9 and 10).

Table 2. Reaction of aryl halides with aldoximes.



Entry	Aldoxime	Amide	Yield [%]
1	 **2a**	 **3a**	82
2	 **2b**	 **4**	71
3	 **2c**	 **5**	66
4	 **2d**	 **6**	61
5	 **2e**	 **7**	0
6	 **2f**	 **8**	61
7	 **2g**	 **9**	62
8	 **2h**	 **10**	51
9	 **2i**	 **11**	70
10	 **2j**	 **12**	51

Conclusions

In conclusion, we have developed a one-step protocol for the direct transformation of aldoximes into *N*-arylated amides in the presence of a copper catalyst. This reaction procedure is very simple and does not require any inert atmosphere to afford good yields of the amides with complete alleviation of the regioselectivity problem that is frequently associated with the Beckmann rearrangement. Further investigations on the application of this strategy for the syn-

thesis of C2-arylated benzoxazoles and benzthiazoles from the reaction of aldoximes with 2-halophenols and 2-halothiophenols are in progress.

Experimental Section

Typical Procedure for the Synthesis of 3a: To a reaction mixture of iodobenzene (**1a**) (100 mg, 0.49 mmol) and benzaldoxime (**2a**, 4 equiv.) in *o*-xylene (1 mL) was added $CuSO_4 \cdot 5H_2O$ (10 mol-%), K_2CO_3 (5 equiv.), and DMEDA (30 mol-%), and the reaction mixture was heated in an oil bath at 130 °C for 12 h. Then, the reaction mixture was cooled to room temperature and diluted with ethyl acetate and water. Then, the organic layer was separated, dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude reaction mixture was subjected to column chromatography on silica gel [ethyl acetate/petroleum ether (60–80 °C), 10%] to afford pure **3a** (79 mg) in 82% yield.

Supporting Information (see footnote on the first page of this article): Experimental procedures, analytical data, and copies of the ^{1}H NMR and ^{13}C NMR spectra of the synthesized compounds.

Acknowledgments

The authors thank the Department of Science and Technology (DST), New Delhi for funding of the project SR-S1/OC-60/2011. The Board of Research in Nuclear Sciences (BRNS), the Department of Atomic Energy (DAE) and the Government of India are also acknowledged for funding of the project 2012/37C/3/BRNS.

[1] a) J. B. Buckingham, *Dictionary of Natural Products*, Chapman and Hall, London, UK, **1994**, vol. 1; b) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* **1997**, *97*, 2243–2266; c) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337–2347; d) T. Cupido, J. Tulla-Puche, J. Spengler, F. Albericio, *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768–783; e) M. A. Mintzer, E. E. Simanek, *Chem. Rev.* **2009**, *109*, 259–302; f) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606–631; g) P. Anastas, N. Eghbali, *Chem. Soc. Rev.* **2010**, *39*, 301–312; h) C. L. Allen, J. M. J. Williams, *Chem. Soc. Rev.* **2011**, *40*, 3405–3415.

[2] J. M. García, F. C. García, F. Serna, J. L. de La Peña, *Prog. Polym. Sci.* **2010**, *35*, 623–686.

[3] C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827.

[4] D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaks, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411–420.

[5] E. Beckmann, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 988–993.

[6] a) L. D. S. Yadav, Garima, V. P. Srivastava, *Tetrahedron Lett.* **2010**, *51*, 739–743; b) N. Kaur, P. Sharma, D. Kishore, *J. Chem. Pharm. Res.* **2012**, *4*, 1938–1946, and references cited there in.

[7] M. B. Smith, J. March, *March's Advanced Organic Chemistry*, Wiley, New York, **2007**, vol. 6.

[8] For reviews, see: a) J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, 1st ed., Oxford University Press, Oxford, UK, UK, **2001**, p. 997–1000; b) R. E. Gawley, *Org. React.* **1988**, *35*, 1–420; c) K. Maruoka, H. Yamamoto, *Comprehensive Organic Synthesis* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, UK, **1991**, vol. 6, pp 763–765.

[9] a) R. García-Álvarez, A. E. Díaz-Álvarez, J. Borge, P. Crochet, V. Cadierno, *Organometallics* **2012**, *31*, 6482–6490; b) C. L. Allen, S. Davulcu, J. M. J. Williams, *Org. Lett.* **2010**, *12*, 5096–5099, and references cited therein.

[10] N. C. Ganguly, S. Roy, P. Mondal, *Tetrahedron Lett.* **2012**, *53*, 1413–1416.

[11] a) S. Park, Y. Choi, H. Han, S. H. Yang, S. Chang, *Chem. Commun.* **2003**, 1936–1937; b) H. Fujiwara, Y. Ogasawara, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2007**, *46*, 5202–5205; *Angew. Chem.* **2007**, *119*, 5294–5297; c) M. Kim, J. Lee, H.-Y. Lee, S. Chang, *Adv. Synth. Catal.* **2009**, *351*, 1807–1812; d) J. Lee, M. Kim, S. Chang, H.-Y. Lee, *Org. Lett.* **2009**, *11*, 5598–5601.

[12] a) N. A. Owston, A. J. Parker, J. M. J. Williams, *Org. Lett.* **2007**, *9*, 3599–3601; b) D. Gnanamgari, R. H. Crabtree, *Organometallics* **2009**, *28*, 922–924.

[13] N. A. Owston, A. J. Parker, J. M. J. Williams, *Org. Lett.* **2007**, *9*, 73–75.

[14] M. A. Ali, T. Punniyamurthy, *Adv. Synth. Catal.* **2010**, *352*, 288–292.

[15] R. S. Ramón, J. Bosson, S. Díez-González, N. Marion, S. P. Nolan, *J. Org. Chem.* **2010**, *75*, 1197–1202.

[16] a) S. K. Sharma, S. D. Bishopp, C. L. Allen, R. Lawrence, M. J. Bamford, A. A. Lapkin, P. Plucinski, R. J. Watson, J. M. J. Williams, *Tetrahedron Lett.* **2011**, *52*, 4252–4255; b) A. Martínez-Asencio, M. Yus, D. J. Ramón, *Tetrahedron* **2012**, *68*, 3948–3951.

[17] M. Arisawa, M. Yamaguchi, *Org. Lett.* **2001**, *3*, 311–312.

[18] C. Ramalingan, Y.-T. Park, *J. Org. Chem.* **2007**, *72*, 4536–4538.

[19] For recent reviews on the Cu-catalyzed *N*-arylation of amides, see: a) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; *Angew. Chem.* **2009**, *121*, 7088–7105; b) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; *Angew. Chem.* **2003**, *115*, 5558–5607; c) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131; d) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; e) C. Fischer, B. Koenig, *Beilstein J. Org. Chem.* **2011**, *7*, 59–74.

[20] P. De, Nonappa, K. Pandurangan, U. Maitra, S. Wailes, *Org. Lett.* **2007**, *9*, 2767–2770.

[21] S.-K. Xiang, D.-X. Zhang, H. Hu, J.-L. Shi, L.-G. Liao, C. Feng, B.-Q. Wang, K.-Q. Zhao, P. Hu, H. Yang, W.-H. Yu, *Adv. Synth. Catal.* **2013**, *355*, 1495–1499.

[22] a) Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151–1154; b) L. Liang, Z. Li, X. Zhou, *Org. Lett.* **2009**, *11*, 3294–3297; c) X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen, M. R. Tracey, *J. Org. Chem.* **2006**, *71*, 4170–4177.

[23] a) O. Das, T. K. Paine, *Dalton Trans.* **2012**, *41*, 11476–1148; b) E. Sperotto, G. P. M. van Klink, G. van Koten, J. G. de Vries, *Dalton Trans.* **2010**, *39*, 10338–10351.

Received: December 17, 2013
Published Online: February 7, 2014

