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A Simple Copper-Catalyzed Synthesis of Tertiary Acyclic Amides

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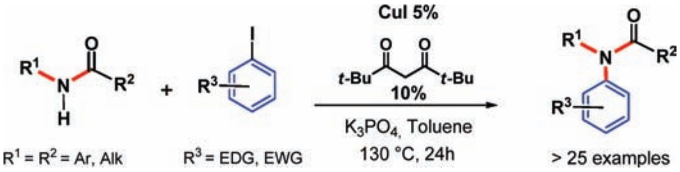
ABSTRACT



The *N*-arylation of aromatic and aliphatic secondary acyclic amides, known to be poor nucleophiles, has been accomplished using a simple and cheap copper catalytic system. The corresponding tertiary acyclic amides, which can be found in numerous biologically active compounds, have been obtained in good to excellent yields.

Copper-catalyzed *N*-arylation of amides has been known for over a century as the Goldberg reaction;[1] however, its development continues to be extensively investigated because improvements are still needed, particularly concerning the scope of the reaction.[2] Thus, the discovery of a general catalytic method allowing the intermolecular *N*-arylation of secondary acyclic amides,[3] which are known to be poor nucleophilic partners,[4] is still challenging. For this reaction, only few isolated examples involving either palladium or copper as catalysts have been described until recently.[4] This point was outlined in a very recent work based on an efficient catalytic system with palladium/monophosphine (JackiePhos) resulting in the synthesis of tertiary amides from aryl halides and secondary amides.[5] It is worth noting that the latter, classically obtained by acylation reactions, are found in numerous biologically active compounds and intermediates in total synthesis.[5]

We report herein a Cu-catalyzed general method for access to tertiary amides via intermolecular *N*-arylation of secondary amides avoiding the use of palladium and sophisticated phosphine ligands. This system allows the transformation, in an economical and ecological way, of already existing secondary amides in tertiary ones with an easy modulation of the aromatic component. It thus constitutes an interesting method facilitating structure–activity relationship studies of these important targets in life sciences.

First, a set of experiments was carried out using *N*-phenylbenzamide **1** (benzanilide) and iodobenzene **2** as model substrates. These two coupling partners were reacted in DMF at 130 °C in the presence of cesium carbonate as the base, a catalytic amount of Cu_2O (5%) as the copper

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(1) (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. (b) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 4541.

(2) For recent reviews, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.

(3) In this paper, we used the frequently encountered classification for amides RCONR′R″: $R' = R'' = H$ for primary amides, $R' = H$ and $R'' \neq H$ for secondary amides, R' and $R'' \neq H$ for tertiary amides. It is worth noting that following the IUPAC rules all these amides categories correspond in fact to primary amides differently *N*,*N*-substituted, $(RCO)_2NR'$ and $(RCO)_3N$ being respectively secondary and tertiary amides.

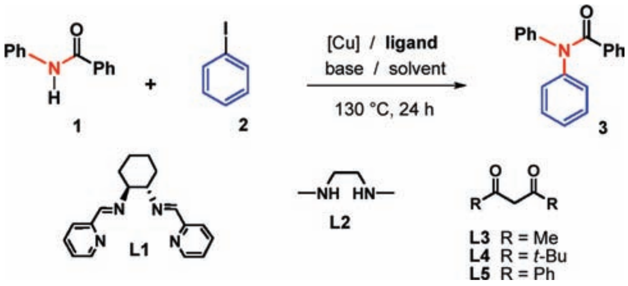
(4) (a) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101. (b) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (d) Lange, J. H. M.; Hofmeyer, L. J. F.; Hout, F. A. S.; Osnaburg, S. J. M.; Verveer, P. C.; Kruse, C. G.; Feenstra, R. W. *Tetrahedron Lett.* **2002**, *43*, 1101. (e) Deng, W.; Wang, Y. F.; Zou, Y.; Liu, L.; Guo, Q. X. *Tetrahedron Lett.* **2004**, *45*, 2311. (f) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001. (g) Mino, T.; Harada, Y.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 614. (h) Chen, W.; Li, J.; Fang, D.; Feng, C.; Zhang, C. *Org. Lett.* **2008**, *10*, 4565. (i) Wang, C.; Liu, L.; Wang, W.; Ma, D.-S.; Zhang, H. *Molecules* **2010**, *15*, 1154.

(5) Hick, J. D.; Hyde, A. M.; Martinez Cuezva, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720 and references cited therein.

10.1021/ol200750p

source, and chelating Schiff base **L1** (20%), a ligand known to be efficient for the *N*-arylation of secondary cyclic amides, primary amides, and benzenesulfonamides.[6]

Table 1. *N*-Arylation of *N*-Phenylbenzamide (Benzanilide) **1**[a]

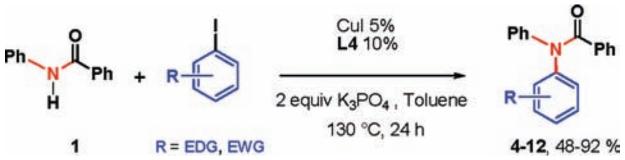


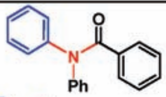
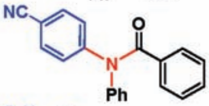
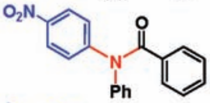
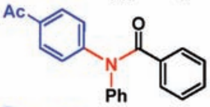
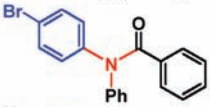
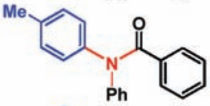
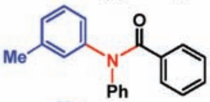
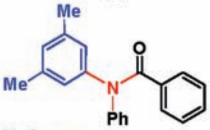
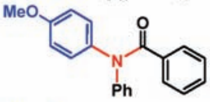
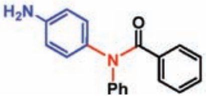
entry	[Cu](5 mol %)	ligand (mol %)	base	solvent[e]	**3** (%)[b]
1	Cu_2O	**L1** (20)	Cs_2CO_3	DMF	3
2	Cu_2O	**L1** (20)	Cs_2CO_3	toluene	4
3	Cu_2O	**L1** (20)	K_3PO_4	toluene	7
4	Cu_2O	**L2** (20)	K_3PO_4	toluene	30
5	Cu_2O	**L3** (20)	K_3PO_4	toluene	10
6	Cu_2O	**L4** (20)	K_3PO_4	toluene	52
7	Cu_2O	**L5** (20)	K_3PO_4	toluene	10
8	CuI	**L2** (20)	K_3PO_4	toluene	89
9	CuI	**L3** (20)	K_3PO_4	toluene	4
10	CuI	**L4** (20)	K_3PO_4	toluene	92
11	CuI	**L5** (20)	K_3PO_4	toluene	2
12	CuI	**L2** (10)	K_3PO_4	toluene	32
13	CuI	**L4** (10)	K_3PO_4	toluene	98 (95)[c]
14	CuI	**L4** (10)	K_3PO_4	toluene	traces[d,e]
15	Cu_2O	**L2** (10)	K_3PO_4	toluene	17
16	Cu_2O	**L4** (10)	K_3PO_4	toluene	30
17	$Cu(OAc)_2$	**L2** (10)	K_3PO_4	toluene	13
18	$Cu(OAc)_2$	**L4** (10)	K_3PO_4	toluene	24
19	CuI	**L4** (10)	K_2CO_3	toluene	3
20	CuI	**L4** (10)	Cs_2CO_3	toluene	6

[a] All reactions were performed with *N*-phenylbenzamide (0.24 mmol), PhI (0.2 mmol), base (0.4 mmol), and solvent (0.2 mL). Copper and ligand percentages are based on PhI. [b] HPLC yields (except otherwise noted) using 2,6-diisopropylaniline as internal standard. [c] Isolated yield. [d] Unreacted starting material is recovered when reactions are performed with 2% of CuI and 5 or 10% of **L4**. [e] Unreactive starting material was recovered when the reaction was carried out at 110 °C.

These reaction conditions only led to recovered starting materials and very low conversion to the corresponding tertiary aryl amide **3** (Table 1, entry 1). The same disappointing results were obtained by replacing DMF with toluene or using potassium phosphate, a base of greater interest to industry[7] (Table 1, entries 2 and 3). We next turned our attention to diamine and *β*-diketone ligands (Table 1, entries 4−7). With 20% of dimethylethylene diamine **L2**, a low yield in tertiary amide was obtained in the presence of toluene and K_3PO_4 (entry 4). Additionally, of the three *β*-diketones investigated, only the 2,2,6,6-tetramethyl-3,5-heptadione **L4** (TMHD) afforded acceptable but promising formation of tertiary amide (52%, Table 1, entry 6). Under similar conditions, we next tested copper iodide (CuI, 5%) as another source of catalyst. A very significant increase of the yield was immediately observed in the presence of **L2** and **L4** ligands, while **L3**

Table 2. *N*-Arylation of *N*-Phenylbenzamide **1** Using Various Aryl Iodides[a]



entry	R	product		yield (%)[b]
1	H		**3**	95
2	4-CN		**4**	87
3	$4-NO_2$		**5**	92
4	4-Ac		**6**	88
5	4-Br		**7**	82
6	4-Me		**8**	52 (92)[c]
7	3-Me		**9**	60 (86)[c]
8	3,5-diMe		**10**	51
9	4-OMe		**11**	48
10	$4-NH_2$		**12**	63

[a] Conditions of Table 1, entries 13 and 14. [b] Isolated yield. [c] 20% of **L2** was used instead of 10% of **L4**.

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(6) (a) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. **2001** Fr 16547 (WO 03053885). (b) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Ouali, A. **2002** Fr 06717(WO 031101966). (c) Taillefer, M.; Cristau, H.-J. ; Cellier, P. P.; Spindler, J.-F. **2002** US 10/159,506 (US 030171593). (d) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F. **2002** US 10/159,829 (US 030236413). (e) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607.

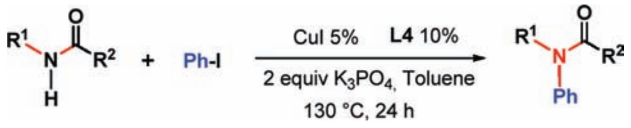
(7) Ouali, A.; Spindler, J.-F.; Cristau, H.-J.; Taillefer, M. *Adv. Synth. Catal.* **2006**, *348*, 499.

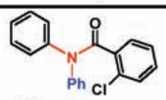
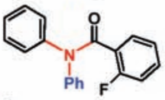
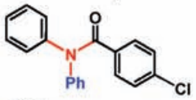
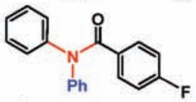
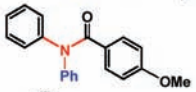
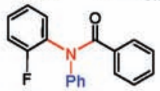
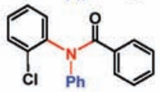
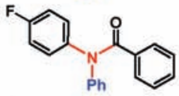
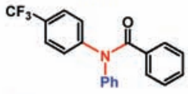
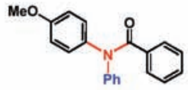
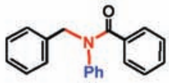
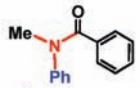
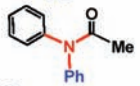
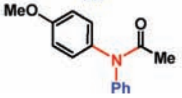
and **L5** remained totally inefficient (Table 1, entries 8–11). Finally, we were pleased to find that using only 10% of **L4** furnished an excellent isolated yield of coupling product **3** (Table 1, entries 13 and 14), **L2** being much less efficient in such proportions (entry 12). Under these optimized conditions, neither Cu_2O or $Cu(OAc)_2$ was able to afford any satisfying yields (Table 1, entries 15–18) and with potassium or cesium carbonate instead of potassium phosphate, only a small amount of coupling product was observed (Table 1, entries 19 and 20).

We next investigated the scope of the reaction, starting with the cross-coupling of *N*-phenylbenzamide **1** with various aryl iodides (Table 2). Electron-withdrawing groups on the electrophilic coupling partner were well tolerated leading to excellent isolated yields of coupling products **4–7** (Table 2, entries 2–5). Aryl iodides substituted with electron-donating groups also afforded the corresponding tertiary amides (**8–12**), however, in modest yields (Table 2, entries 6–10). On the other hand, it was found that the use of 20% of **L2** instead of 10% or 20% of **L4** afforded better yields in presence of a *p*- or *m*-methyl substituent (entries 6 and 7).[8] It is worth mentioning that these *N*,*N*-disubstituted benzamides **4–12**, often nondescribed in the literature, have never been prepared via a copper-catalyzed Goldberg-type reaction.

In another set of experiments, the methodology was tested for the preparation of other various tertiary amides (Table 3, **11**, **27–39**) by arylation of secondary amides such as *N*-aryl- (**13–22**) or *N*-alkylarylamides (**23**,**24**) and *N*-arylacetamide (**25**, **26**). Starting secondary amides were prepared by a classical condensation of anilines with aroyl chloride derivatives[9] and engaged in cross-coupling reactions with iodobenzene **2** under the optimized reaction conditions of Table 1 (entries 13). Thus, we were able to perform the coupling with *N*-arylarylamides substituted with electron-donating or electron-withdrawing groups on the aromatic rings (Table 3, entries 1–10). Good isolated yields were obtained, except with starting compounds derived from *o*-chloro and *p*-trifluoromethyl anilines (entries 7 and 9). In the former case, the use of DMEDA **L2** (20%) instead of **L4** (10%) allowed us to increase the isolated yield in tertiary amide **33** from 23% to 63%, whereas in the last case, a lower yield was obtained when **L2** was used (Table 3, entries 7,9). It is worth noting that the relationship between the ligand (nature and amount) and the formation of the expected product was difficult to understand or to predict. Indeed, in only three additional cases indicated in Table 3 (entries 2, 5, 6) was the presence of 20% of DMEDA beneficial for the catalytic system, while with the other secondary amines or with 10% catalyst loading the yields were disappointing.

Table 3. *N*-Arylation of *N*-Aryl- or *N*-Alkylarylamides and *N*-Arylacetamide[a]



entry	substrate	product		yield (%)[b,c]
1	**13**		**27**	60
2	**14**		**28**	58 (94)
3	**15**		**29**	66
4	**16**		**30**	65
5	**17**		**31**	72 (93)
6	**18**		**32**	62 (92)
7	**19**		**33**	23 (63)
8	**20**		**34**	76
9	**21**		**35**	35 (25)
10	**22**		**11**	78
11	**23**		**36**	71
12	**24**		**37**	87
13	**25**		**38**	93
14	**26**		**39**	91

[a] All reactions were performed with secondary amide (0.24 mmol), PhI (0.2 mmol), K_3PO_4 (0.4 mmol), and solvent (0.2 mL). [b] Isolated yield. [c] Values in parentheses: yields obtained with 20% of **L2** instead of 10% of **L4**.

Finally, other classes of starting secondary amides bearing both aliphatic and aromatic groups (**23–26**) were successfully functionalized using the standard

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(8) L2 has been used as ligand for copper in two cases for the preparation of tertiary acyclic amides, the *N*-methyl,*N*-phenylacetamide and the *N*-benzyl,*N*-(p-methylthio)phenyformamide (see ref 4c).

(9) For synthesis of these secondary acyclic amides, see the Supporting Information.

conditions (CuI and 10% of **L4**), the corresponding coupling products (**36**–**39**) being obtained in very good isolated yields.

In conclusion, we have discovered an efficient and versatile catalytic system allowing the intermolecular N-arylation of secondary acyclic amides, which are known to be poor nucleophilic partners. This challenge, overcome using a cheap and simple copper system, offers a general method for the preparation of acyclic tertiary amides. The structure–activity relationship studies of these important targets in life sciences is thus facilitated by this economical and ecological method, which interestingly complements the existing system based on more expensive palladium catalysts. Efforts to expand the versatility of this catalytic system, which should find applications very soon, are in progress in our laboratory, along with mechanistic studies.

Acknowledgment. We thank Bayer CropScience for funding and helpful discussions.

Supporting Information Available. Detailed experimental procedures and characterization data for starting secondary amides and corresponding coupling products. This material is available free of charge via the Internet at http://pubs.acs.org.