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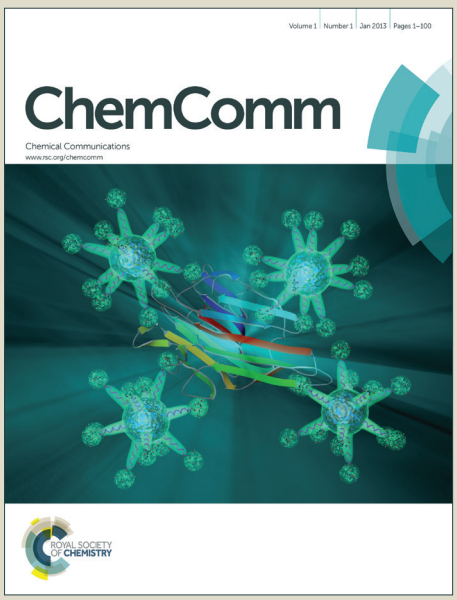

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Copper catalysed amidation of aryl halides through chelation assistance

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Subban Kathiravan,[a] Shishir Ghosh,[b] Graeme Hogarth,[b] and Ian A. Nicholls[a,c*]

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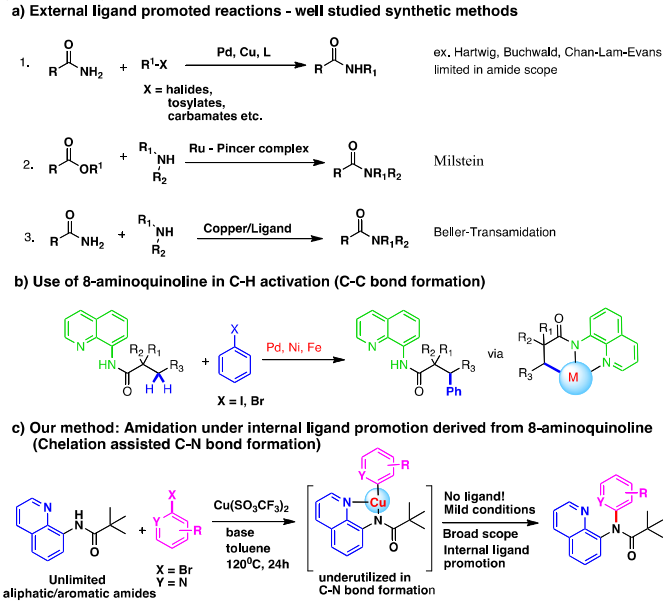
A copper mediated C-N bond formation for the amidation of aryl halides using 8-aminoquinoline has been developed. This strategy provides efficient access to amides bearing two contiguous heterocyclic moieties and does not require the presence of additional ligands.

The selective construction of C-N bonds continues to be an important goal in organic synthesis and is extensively utilized in medicinal chemistry and industrial processes.[1] Among the different types of C-N bond forming reactions, the synthesis of *N*-substituted amides is of crucial importance due to the prevalence of this structural motif in pharmaceuticals, agrochemicals and biologically active natural products as well as in biological and synthetic polymers, *i.e.* proteins and nylons.[2] Traditionally amides have been prepared by the reaction of amines with carboxylic acid derivatives,[3] alcohols,[4] or aldehydes,[5] hydroamination of alkynes,[6] and hydration of nitriles.[7] Further, a number of methodologies for the synthesis of amides and related compounds by the palladium-catalysed amidation of arylhalides have been presented in pioneering studies by the research groups of Buchwald and Hartwig.[8] Milstein and co-workers introduced the dearomatized Ru-pincer complex for the direct synthesis of amides from esters and amines.[9] Beller has explored the transamidation of non-activated primary carboxamides and ureas with amines in the presence of copper catalysts.[10] Fu *et. al.* described the photoinduced copper catalysed amidation of secondary alkyl halides under mild conditions.[11] Despite notable progress in this area, the establishment of a general intermolecular process with amides remains a challenge. The development of innovative chelating groups that enable transformations through C-N bond formation under mild and simple conditions is highly desirable.

The recent seminal work on the use of 8-aminoquinoline as a bidentate directing group in the transformation of C−H bonds by Daugulis[12] has led to a number of developments including the report by Kanai *et al.* of a copper catalysed intramolecular C(sp^2)-H and C(sp^3)-H amidations by oxidative cyclization.[13] We envisioned that the copper catalysed reaction of readily available amides derived from 8-aminoquinoline and various commercial aryl halides would constitute a new complementary route for the facile synthesis of substituted amides without any the use of either noble metal catalysts or ligands. To the best of our knowledge chelation-assisted copper catalysed amidation of aryl halides has not been yet reported (Scheme 1).

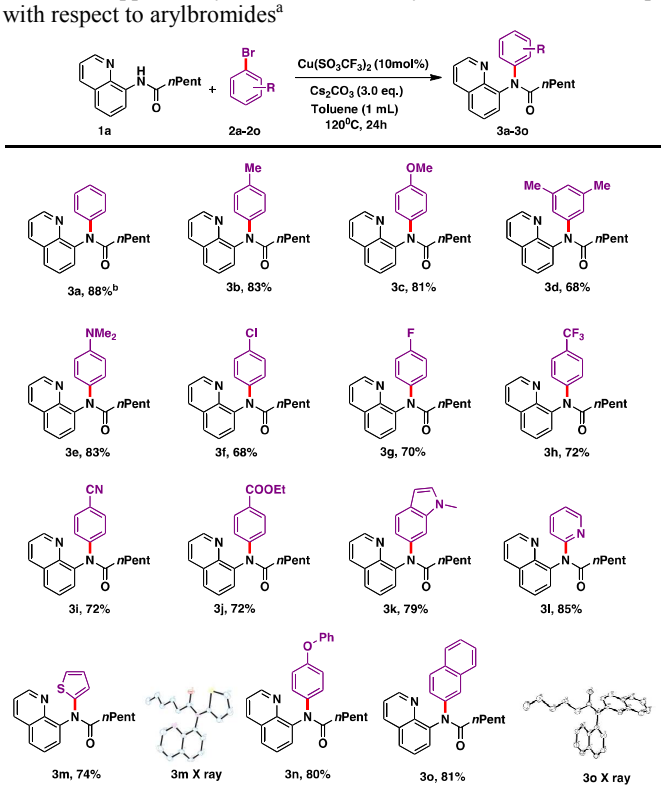


Scheme 1. Transition metal catalysed amidation reactions

Initial model reaction studies were conducted using carboxamide **1a**, phenyl bromide **2a** and 10 mol% of $Cu(SO_3CF_3)_2$, and different bases in toluene at 120^{0}C for 24h in the presence of different ligands (**L1-L14**) (For detailed optimization studies see supporting information). With the best reaction conditions in hand we next examined the scope of aryl bromides **2a-2o** amenable to reaction with **1a** to test the feasibility of preparing a variety of corresponding carboxamides **3a-3o** (Table 2). We established that this method could be applied to the amidation of an array of unactivated N-H bonds, generating the desired C−N bonds in good yield (Table 2).

The reactions were successful for both electron-rich (**3b-3e**) and electron-poor (**3f-3j**) arylbromides. Various functionalities, such as sterically hindered 3,5-dimethyl groups (**3d**), chloride (**3f**), fluoride (**3g**), and trifluoromethyl (**3h**) are tolerated. 5-bromo-*N*-methylindole (**3k**), 2-pyridine (**3l**), 2-thiophene (**3m**) bromides are reactive, thus showing the compatibility of reaction conditions with heterocycles. Interestingly, the catalytic reaction proceeded very well with 4-bromo diphenylether (**3n**), which afforded the amidation product (**3n**) in 80% yield. Moreover, we were pleased to find that 2-bromonaphthalene (**2o**) could also be used in this reaction with the corresponding N-H functionalized product (**3o**) being obtained in very good yield 86%. Further the structures of **3m** and **3o** were unambiguously confirmed through x-ray crystallographic analysis.[14]

Table 1. Copper catalysed amidation of aryl halides: Substrate scope with respect to arylbromides[a]

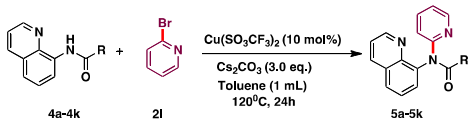


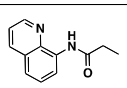
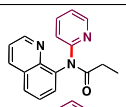
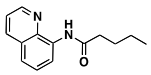
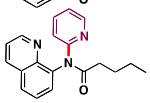
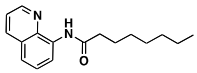
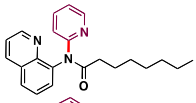
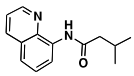
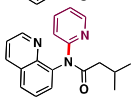
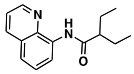
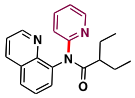
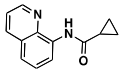
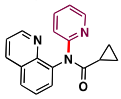
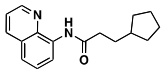
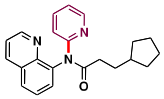
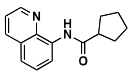
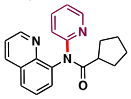
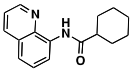
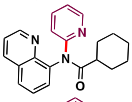
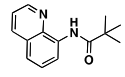
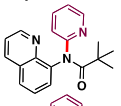
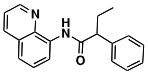
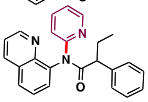
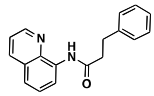
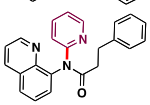
[a]Reaction conditions: **1a** (1.0 equiv.), **2a-2p** (2.0 equiv.), $Cu(SO_3CF_3)_2$ (10 mol%), CS_2CO_3 (3.0 equiv.) toluene 1 mL, at 120°C, 24h; [b]isolated yield.

The versatility of the copper catalyst was not limited to carboxamide **1a,** as seen in its catalysis of amidations with challenging carboxamides **4a-4k**, highlighting the scope of the reaction as presented in Table 3 (entry 1-11). Thus, propionoyl (**4a**), valeroyl (**4b**), and octanoyl (**4c**), 3-methyl butanoyl (**4d**) and 2-ethyl butanoyl (**4e**) carboxamides were efficiently arylated with 2-bromopyridine (**2l**) and furnished the products (**5a-5e**) in 80, 75, 85, and 68% yields, respectively (entry 1-5). Functionalization with cyclopropanyl moieties was then explored due to the utility of this structural motif in medicinal chemistry and as scaffolds for other chemical transformations; here using the arylation of aminoquinoline cyclopropylamide (**4f**) with 2-bromopyridine (**2l**) which resulted in **5f** in moderate yield (60%) (entry 6).[15] Aminoquinoline cyclopentyl actamide (**4g**) was also reacted with 2-bromopyridine (**2l**) under standard conditions to afford **5g** in 82% yield (entry 7). Cyclopentyl and cyclohexyl carboxamides (**4h** & **4i**) also proving to be effective coupling partners and furnishing their corresponding arylated derivatives **5h** and **5i** in good yields 80 and 69%, respectively (entry 8-9). Pivalimide (**4j**) also afforded the desired regioselective product **5j** in 69% yield (entry 10). In addition 2-phenylbutanamide (**4k**) gave the corresponding product **5k** in 60% yield (entry 11). A substrate containing the hydrocinnamoyl group was also readily employed, furnishing **5l** in 59% yield (entry 12).

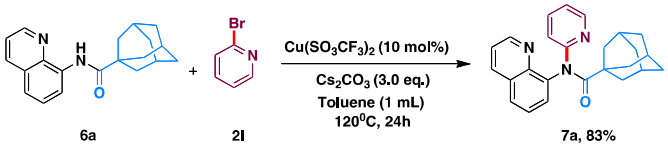
The value of this method was further emphasised through the preparation of arylated adamantanyl amides derived from (**6a**), a motif found in number of pharmaceuticals (scheme 2).[16]

Table 2. Copper catalysed amidation of aryl halides: Substrate scope with respect to amides



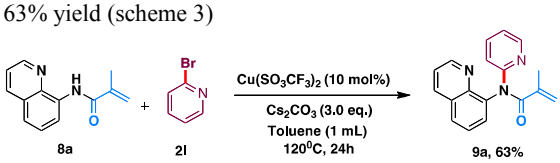
Entry	Carboxamide	Product		Yield(%)[b]
1			5a	80
2			5b	75
3			5c	85
4			5d	68
5			5e	68
6			5f	90
7			5g	82
8			5h	89
9			5i	80
10			5j	69
11			5k	60
12			5l	59

Reaction conditions[a]: 4a-4m (1.0 equiv.), 2l (2.0 equiv.) $Cu(SO_3CF_3)_2$ (10 mol%), CS_2CO_3 (3.0 equiv.) toluene 1 mL, at 120°C, 24h; [b]isolated yield.



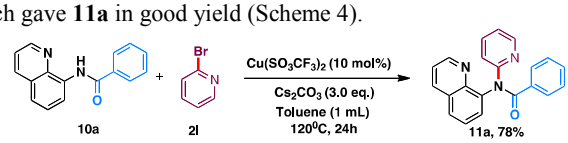
Scheme 2. Reaction with adamantanyl amides

We also explored the reactivity of more challenging aminoquinoline vinylamides (**8a**). These were also found to be reactive and provided **9a** in 63% yield (scheme 3)



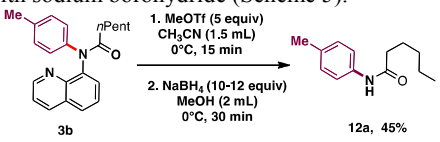
Scheme 3. Reaction with vinylamide

Finally, to further demonstrate the utility of our process, we performed amidation of 2-bromothiophene (**2l**) with benzamide **10a**, which gave **11a** in good yield (Scheme 4).



Scheme 4. Reaction with aminoquinoline benzamide

Importantly, the chelating group could be efficiently removed by treatment with methyl trifluoromethanesulfonate followed by reduction with sodium borohydride (Scheme 5).[17]



Scheme 5. Removal of chelating group

Conclusions

In conclusion, we have developed a general and straightforward chelation-assisted, copper-mediated amidation of weakly activated arylbromides with 8-aminoquinoline. This catalytic protocol facilitates the synthesis of variety of disubstituted amides (e.g. thiophenyl, pyridinyl, indolyl and adamantanyl) from available primary carboxamides in good to excellent yields. Interestingly, this amidation procedure is user friendly as it does not required external ligands to promote C-N bond formation. More detailed investigations of the mechanism are currently underway in our laboratory including exploring the use of alternative chelating amides. We believe that this novel procedure is and will be of significant value in the synthesis of substituted peptides and other bioactive molecules.

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Notes and references

[a]*Bioorganic & Biophysical Chemistry Laboratory, Linnaeus University Centre for Biomaterials Chemistry, Linnæus University, SE-391 82 Kalmar, Sweden, Fax: (+) 46 0480-446244, E-mail: ian.nicholls@lnu.se*
[b]*Department of Chemistry, King's College London, Britannia House, 7 Trinity Street, London SE1 1DB.*
[c]*Department of Chemistry, BMC, Uppsala University, SE-751 23 Uppsala, Sweden.*

Electronic Supplementary Information (ESI) available: [Detailed experimental procedures, crystallographic data, and spectroscopic data for all the new compounds]. See DOI: 10.1039/c000000x/

1 D. Ma, and Q. Cai, *Acc. Chem. Res.* 2008, ***41***, 1450; S. V. Ley, and A. W. Thomas, *Angew. Chem. Int. Ed*. 2003, ***42***, 5400; M. Wasa, and J.-Q. Yu, *J. Am. Chem. Soc*. 2008, ***130***, 14058; M. P. Huestis, L. Chan, D. R. Stuart, K. Fagnou, *Angew. Chem. Int. Ed.* 2011, ***50***, 1338; K. Shin, Y. Baek, and S. Chang, *Angew. Chem. Int. Ed*. 2013, ***52***, 8031; F. Monnier and M. Taillefer, *Angew. Chem. Int. Ed*. 2009, ***48***, 6954; J. E. R. Sadig, and M. C. Willis, *Synthesis* 2011, ***43***, 1; T. Liu, and H. Fu, *Synthesis* 2012, ***44***, 2805. S. Kathiravan, and I. A. Nicholls, *Chem. Commun.* 2014, ***50***, 14964.

2. N. Sewald, H. D. Jakubke, *Peptides*: Chemistry and Biology; Wiley-VCH: Weinheim, 2002; A. Greenberg, C. M. Breneman, J. F. Liebman, *Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry, and Materials Science;* Wiley-Interscience: New York, 2000; J. S. Carey, D. Laffan, C. Thomson, and M. T. Williams, *Org. Biomol. Chem*. 2006, ***4***, 2337.
3. K. Arnold, B. Davies, D. Herault, and A. Whiting, *Angew. Chem., Int. Ed.* 2008, ***47***, 2673; H. Charville, D. Jackson, G. Hodges, and A. Whiting, *Chem. Commun*. 2010, ***46***, 1813; S. D. Roughley, and A. M. Jordan, *J. Med. Chem*. 2011, ***54***, 3451; C. L. Allen, R. A. Chhatwal, and J. M. J. Williams, *Chem. Commun*. 2012, ***48***, 666.
4. J. F. Soule, H. Miyamura, and S. Kobayashi, *J. Am. Chem. Soc*. 2011, ***133***, 18550; C. Gunanathan, Y. Ben-David, and D. Milstein, *Science* 2007, ***317***, 790; L. U. Nordstrøm, H. Vogt, and R. Madsen, *J. Am. Chem. Soc*. 2008, ***130***, 17672; T. Zweifel, J. –V. Naubron, and H. Grutzmacher, H. *Angew. Chem. Int. Ed*. 2009, ***48***, 559; A. J. A. Watson, A. C. Maxwell, and J. M. J. Williams, *Org. Lett*. 2009, ***11***, 2667; K. Yamaguchi, H. Kobayashi, T. Oishi, and N. Mizuno, *Angew. Chem.Int. Ed*. 2012, ***51***, 544.
5. W. J. Yoo, and C. J. Li, *J. Am. Chem. Soc*. 2006, ***128***, 13064; J. W. Bode, and S. S. Sohn, *J. Am. Chem. Soc*. 2007, ***129***, 13798; A. Sakakura, T. Ohkubo, R. Yamashita, M. Akakura, and K. Ishihara, *Org. Lett*. 2011, ***13***, 892; S. C. Ghosh, J. S. Y. Ngiam, A. M. Seayad, D. H. Tuan, C: L. L. Chai, and A. Chen, *J. Org. Chem*. 2012, ***77***, 8007.
6. S. Cho, E. Yoo, I. Bae, and S. Chang, *J. Am. Chem. Soc*. 2005, ***127***, 16046; Z.-W. Chen, H. –F. Jiang, X. –Y. Pan, and Z. –J. He, *Tetrahedron* 2011, ***67***, 5920.
7. K. Yamaguchi, M. Matsushita, and N. Mizuno, *Angew. Chem., Int. Ed.* 2004, ***43***, 1576; R. S. Ramon, N. Marion, and S. P. Nolan, *Chem. Eur. J.* 2009, ***15***, 8695; T. Mitsu-dome, Y. Mikami, H. Mori, S. Arita, T. Mizugaki, K. Jitsukawa, and K. Kaneda, *Chem. Commun*. 2009, 3258.
8. D. S. Surry, and S. L. Buchwald, *Chem. Sci*. 2011, ***2***, 27; A. R. Muci, and S. L. Buchwald, *Top. Curr. Chem*. 2002, ***219***, 131; J. F. Hartwig, *Angew. Chem. Int. Ed*. 1998, ***37***, 2047.
9. B. Gnanaprakasam, and D. Milstein, *J. Am. Chem. Soc*. 2011, ***133***, 1682.
10. M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann, and M. Beller, *Angew. Chem. Int. Ed.* 2012, ***51***, 3905; S. N. Rao, D. C. Mohan, and S. Adimurthy, *Org. Lett*. 2013, ***15***, 1496.
11. H. -Q. Do, S. Bachman, A. C. Bissember, J. C. Peters, and G.C. Fu, *J. Am. Chem. Soc*. 2014, ***136***, 2162.
12. L. D. Tran, J. Roane, and O. Daugulis, *Angew. Chem. Int. Ed.* 2013, ***52*** 6043; G. Rouquet, and N. Chatani, *Angew. Chem. Int. Ed.* 2013, ***52***, 11726; G. Shan, X. yang, Y. Zong, and Y. Rao, *Angew. Chem. Int. Ed*. 2013, ***52***, 13606; R. Shang, L. Ilies, S. Asako, and E. Nakamura, *J. Am. Chem. Soc*. 2014, ***136***, 14349.
13. Z. Wang, J. Ni, Y. Kuninobu, and M. Kanai, *Angew. Chem. Int. Ed.* 2014, ***53***, 3496.
14. The X-ray crystallographic data was deposited at the Cambridge

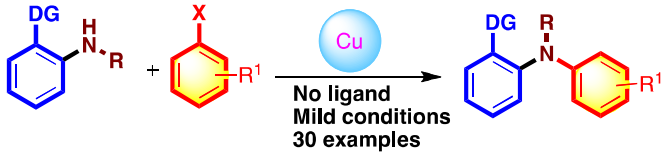
Crystallographic Data Centre. For compounds **3m** and **3o** the data have been assigned as CCDC-1038093 and CCDC 1038092, respectively.

15. H. Lebel, J. F. Marcoux, C. Molinaro, and A. B. Charette, *Chem. Rev.* 2003, ***103***, 977.
16. G. Lamoureux, and G. Artavia, *Curr. Med. Chem*. 2010, ***17***, 2967.
17. V. Smout, A. Peschiulli, S. Verbeeck, E. A. Mitchell, W. Herrebout, P. Bultinck, C. M. L. Vande Velde, D. Berthelot, L. Meerpoel, B. U. W. Maes, *J. Org. Chem*. 2013, ***78***, 9803.

Graphical Abstract

Copper catalysed amidation of aryl halides through chelation assistance

Subban Kathiravan, Shishir Ghosh, Graeme Hogarth, and Ian A. Nicholls*



Using 8-aminoquinoline-based alkyl and aryl carboxamides, the direct N-arylation was achieved in good yields in the presence of a copper catalyst via chelation-assisted reaction.