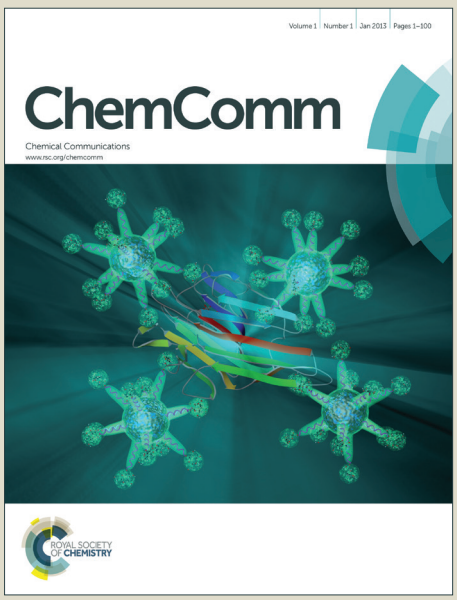
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. Kathiravan and I. A. Nicholls, *Chem. Commun.*, 2014, DOI: 10.1039/C4CC06020B.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C4CC06020B

Chemical Communications

RSCPublishing

COMMUNICATION

Rhodium(III)-catalysed aerobic synthesis of highly functionalized indoles from *N*-arylurea under mild conditions through C-H activation

Cite this: DOI: 10.1039/xoxxoooooox

Subban Kathiravan,[a] and Ian A. Nicholls[a,b*]

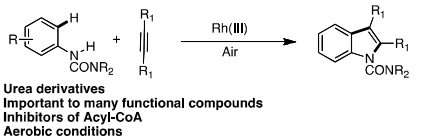
Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

A Rh(III) catalysed amino arylation of alkynes using copper as the terminal oxidant for regeneration of the catalytically active species under aerobic conditions is described. This novel C-H activation reaction was applied to the synthesis of a wide range of substituted indoles from *N*-arylureas.

Nitrogen-containing heterocycles are ubiquitous in both natural products and pharmaceuticals, therefore the development of new selective and user friendly methods for their preparation is of importance.[1] The indole moiety is one of the more common nitrogen containing structural motifs present in drugs, natural products, and other functional molecules.[2] The Fischer indole synthesis has remained one of the most widely accepted techniques among the synthetic community due to its operational simplicity and general functional group tolerance. However, the development of alternative synthesis strategies starting from less expensive and more readily available reagents is of interest, *e.g.* the Larock procedure which makes use of modified aniline derivatives, such as *ortho*-haloanilines, in the presence of palladium catalysts.[3] More recently, Glorius and co-workers developed a divergent method based upon a palladium-catalysed oxidative cyclization of aniline and ketone derived *N*-aryl enamines to afford the corresponding indoles,[4] and Yoshikai has explored the use of palladium catalysed aerobic oxidative cyclization of *N*-arylimines for improving substrate scope.[5] In another example, Ackermann demonstrated that indole synthesis could take place via a selective copper catalyzed amination of dihaloarenes followed by a palladium catalysed C-H activation reaction.[6]

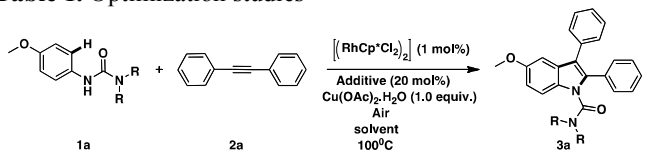


Scheme 1.

Generally, Rh(III) catalysed C-H activation directed by heteroatom containing groups has rapidly emerged as a fruitful field for developing a diverse range of catalytic carbon-carbon and carbon-heteroatom bond forming reactions.[7] A number of initial attempts to use rhodium catalysed chelation assisted metalation approaches for indole synthesis have been described. Fagnou and co-workers have presented a rhodium (III) catalysed oxidative coupling of *N*-acetyl anilines and alkynes through a chelation assisted metalation pathway with high regioselectivity.[8] Glorius developed a hydrazine directed traceless redox neutral N-N bond cleavage strategy involving oxidizing directing groups coupling with alkynes,[9] while Huang developed triazene directing groups for alkyne annulation to access unprotected indoles, in which the N=N bond of the triazene is cleaved in the reaction.[10] Recently the use of hydrazones, azines, and *N*-oxides in combination with additives for C-H activation has been reported.[11]

We envisaged that the development of an operationally simple catalytic system, where copper is used as the terminal oxidant in air, would simplify the practical use of Rh-catalysed C-H activation reactions. Herein, we report a mild protocol for the Rh(III) catalysed aminoarylation of internal alkynes with *N*-arylurea that uses readily available catalysts. We propose that this development is based upon the combination of a urea auxiliary for promoting C-H activation and copper as oxidant for closing the catalytic cycle under aerobic conditions.

Table 1. Optimization studies[a]



Entry	Solvent	Catalyst	Additive	Yield (%)
1	1,2-DCE	Rh(III)	$AgBF_4$	trace
2	1,2-DCE	Rh(III)	KPF_6	38
3	1,2-DCE	Rh(III)	AgOTf	45
4	1,2-DCE	Rh(III)	$AgCO_3$	12
5	1,2-DCE	Rh(III)	$AgNO_3$	trace
6	1,2-DCE	Rh(III)	$AgSbF_6$	92[b]
7	1,2-DCE	Ru(II)	$AgSbF_6$	55
8	*t*-AmylOH	Ir(III)	$AgSbF_6$	NR
9	THF	Rh(III)	$AgSbF_6$	19

[a]All reactions were carried out under the following conditions: **1a** (1.5 mmol), **2a** (1 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), additive (20 mol%) and $Cu(OAc).H_2O$ (1.0 equiv.), in solvent (2 mL) at 100^0C for 12 h under air; R=Me, [b] Yields were determined by

View Article Online
DOI: 10.1039/C4CC06020B Journal Name

integration of ^{1}H NMR spectra, by using mesitylene as an internal standard. Rh(III) = $[Cp^*RhCl_2]_2$, Ru(II) = $[(p\text{-Cymene})RuCl_2]_2$, Ir(III) = $[IrCp^*Cl_2]_2$, (NR=No reaction).

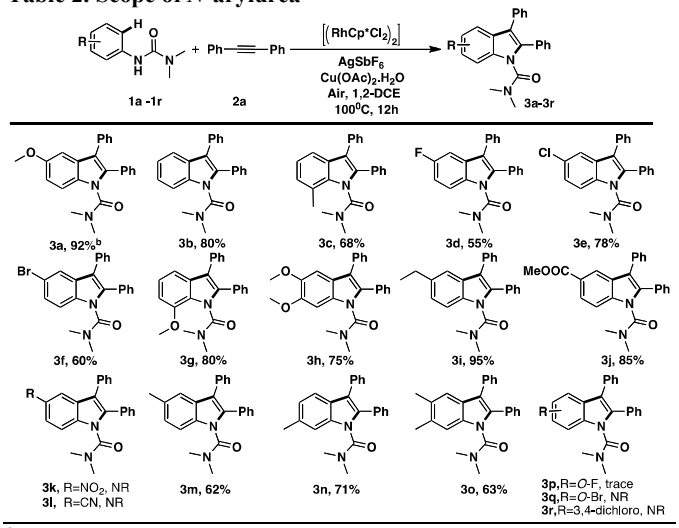
Our study was initiated using the 4-methoxy phenyl substituted *N*-aryl urea **1a** and diphenylacetylene **2a** in the presence of $[Cp^*RhCl_2]_2$ as catalyst precursor. The C-H activation reaction of **1a** and **2a** was tested with a series of solvents, such as *tert*-amylOH, 2-methyl-1-butanol, *tert*-BuOH, THF, DMF, DMSO, dichloromethane, 1,2-dichloroethane (1,2-DCE), 1,4-dioxane, toluene, methanol, ethanol, AcOH, and CF_3COOH. Among them, 1,2-DCE was effective, providing **3a** in 70 % yield. Next, various additives (20 mol%; $AgBF_4$, KPF_6, AgOTf, $AgCO_3$, $AgNO_3$ and $AgSbF_6$) in the presence of Rh(III) catalyst in 1,2-DCE as solvent at 100^0C for 12 h under air was screened (Table 1, entries 1-5). While, $AgBF_4$ was not effective for the reaction (entry 1), KPF_6 and AgOTf demonstrated some affectivity, yielding **3a** in 38 and 45% yield, respectively (entries 2 and 3). $AgCO_3$ and $AgNO_3$ were also completely not effective (entries 4 and 5). $AgSbF_6$ was found to be very effective for this reaction affording the product **3a** in 85 % NMR spectroscopic yield (entry 6). Next, the indole synthesis was examined with various oxidants, including $K_2S_2O_8$, $Na_2S_2O_8$, $(NH_4)_2S_2O_8$, Ag_2O, AgOAc, PhI(OAc), and $Cu(OAc)_2.2H_2O$. Of these, only $Cu(OAc)_2.H_2O$ was demonstrated to be very effective, affording the product **3a** in 92 % yield (entry 7).

The reaction was then tested with two alternative catalysts [(*p*-cymene)$RuCl_2]_2$[12] and $[IrCp^*Cl_2]_2$. Although the Ru(II) catalyst demonstrated some efficiency, furnishing **3a** in 55 % yield (entry 7), the Ir(III) catalyst was totally ineffective (entry 8). Based on these optimization studies, we have concluded that $AgSbF_6$, $Cu(OAc)_2.2H_2O$, and 1,2-DCE in the presence of $[RhCp^*Cl_2]_2$ at 100^0C for 12 h under air offers the best conditions for this C-H activation reaction.

With the optimized reaction conditions in hand, the scope of this reaction was examined with various *ortho*, *para*, and *meta*-substituted *N*-arylureas, **1a-1r**, with diphenylacetylene **2a** (Table 2). The C-H activation reaction is compatible with electron donating, halogen, and electron-withdrawing functional groups such as Me, H, I, Br, Cl, and F substituted *N*-aryl urea **1a-1r**. Thus, 4-methoxy **1a** and unsubstituted **1b** *N*-arylurea reacted with **2a** gave indole **3a** and **3b** in 92 and 80% yield respectively. Substrates containing a methyl group at the *ortho* position, **1c**, halogen groups such as F (**1d**), Cl (**1e**), and Br (**1f**) substituted arylureas were effectively involved in the reaction, providing indole derivatives **3c-3f** in 68, 55, 78 and 60% yields, respectively. Ureas bearing electron donating groups such as methoxy **1g**, 3,4-dimethoxy **1h**, and 4-ethyl **1i** afforded the corresponding products **3g-3i** in 80, 75, 95% yield respectively. In the case of electron deficient ureas, *e.g.* ester **1j**, nitro **1k**, and cyano **1l**, were also screened under optimized reaction conditions. While the ester substituted urea afforded **3j** in 85%, the more strongly electron withdrawing nitro and cyano (**3k** and **3l**) substituents did not yield corresponding products. Next, the indole synthesis was tested with the *para*- **1m**, *meta*- **1n**, and *m,p*- **1o** methyl substituted ureas provided the corresponding indoles **3m-3o** in moderate yields (62, 71 and 63%). The sterically hindered *ortho*-F **1p**, and *ortho*-Br **1q**, substituted ureas offered the corresponding indole **3p-3q** in trace quantities.

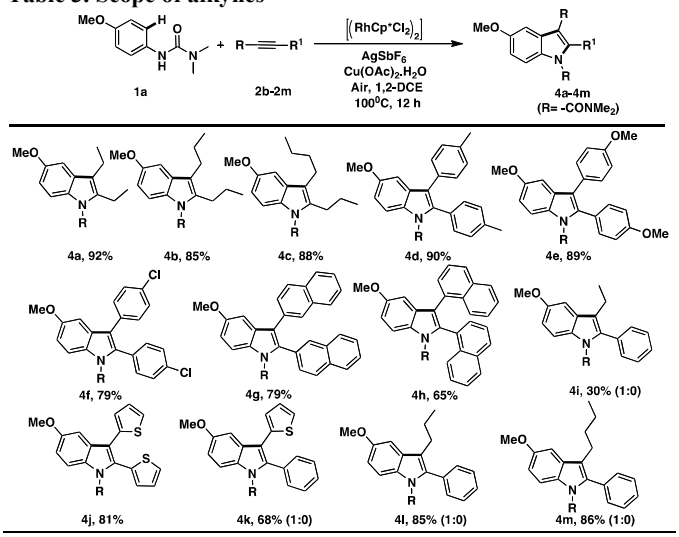
We then turned our attention to the substituent on the alkyne (Table 3). When the aromatic group was replaced with an alkyl chain the reactivity of the substrate was greatly enhanced, and gave 2,3-ethyl, propyl, and butyl substituted indoles (**4a-4c**) in 92%, 85%, and 88% respectively. This reaction was not restricted to aromatic substituents, as *para* substituted methyl, methoxy and chloro diphenylacetylene derivatives (**2d** & **2f**) could also be used in this protocol, although moderate yields were obtained. Next, this reaction was extended with 1, and 2-bromonaphthalenes (**2g**&**2h**) with *N*-arylurea **1a** and found that the corresponding sterically crowded polyphenyl substituted indoles (**4g**&**4h**) in reasonable yields (79% and 65%). That the coupling of a heterocyclic thiophene motif could be performed in excellent yield was pleasing. When asymmetrical alkynes **2j**, and **2k-2m** were employed a 1:0 regioselectivity was observed.

Table 2. Scope of *N*-arylurea[a,b]



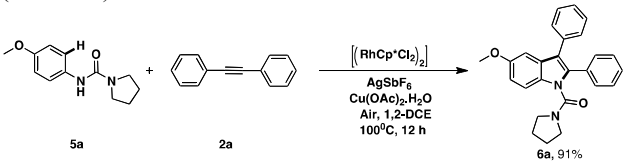
[a]All reactions were carried out under the following conditions: **1a** (1.5 mmol), **2a** (1 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), additive (20 mol%) and $Cu(OAc).H_2O$ (1.0 equiv.), in solvent (2 mL) at 100^0C for 12 h under air. [b] Yields were determined by integration of ^{1}H NMR spectra, by using mesitylene as an internal standard., (NR= no reaction).

Table 3. Scope of alkynes [a,b]



[a]All reactions were carried out under the following conditions: **1a** (1.5 mmol), **2a** (1 mmol), $[RhCp^*Cl_2]_2$ (1 mol%), additive (20 mol%) and $Cu(OAc).H_2O$ (1.0 equiv.), in solvent (2 mL) at 100^0C for 12 h under air; [b] Yields were determined by integration of ^{1}H NMR spectra, by using mesitylene as an internal standard.

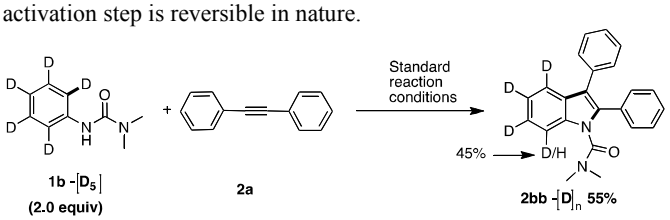
To further explore the scope of this method the reaction was tested with urea derivatives such as *N*-(4-methoxyphenyl)-1-pyrrolidinecarboxamide **5a**, which under similar reaction conditions provided the corresponding indole **6a** in very good yield (91%) (Scheme 3).



Scheme 3.

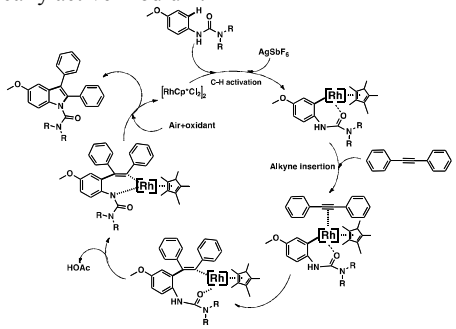
View Article Online
DOI: 10.1039/C4CC06020D COMMUNICATION

To gain insights into the mechanism for the intermolecular C-H aminoarylation of alkynes with *N*-arylureas, we performed a kinetic isotopic exchange study using the pentadeuterated substrate 1b-[D_5] (Scheme 4). The observed H/D scrambling indicated that the C-H activation step is reversible in nature.



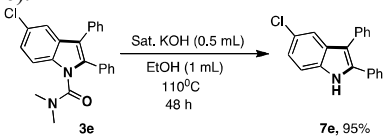
Scheme 4. KIE experiment

Based on these experimental findings and literature precedent, we proposed a catalytic cycle relying on an initial reversible cyclometallation with the Rh(III) complex (Scheme 5), where a six membered rhodacycle is formed as the important intermediate. Subsequently, this complex undergoes coordination and migratory insertion with the alkyne to furnish the rhodacycle. Finally, reductive elimination delivers the desired product and reoxidation generates the catalytically active rhodium.



Scheme 5. Proposed mechanism

Finally, efficient removal of the carbamoyl moiety was demonstrated by heating compound **3e** in ethanol and saturated aqueous potassium hydroxide (3:1) in a sealed vessel, delivered the indole **7e** in 95% yield (Scheme 6).



Scheme 6. Removal of directing group

Conclusions

In summary, we have developed a mild and efficient operationally simple rhodium(III) catalysed C-H activation-aminoarylation of *N*-arylureas with alkynes to prepare *N*-carbamoyl indoles under aerobic reaction conditions. Conveniently, this reaction can be carried out under aerobic conditions, and efficient removal of the *N*-carbamoyl moiety from the indole can be achieved. In addition this reaction is highly regioselective with respect to unsymmetrical alkynes. This reaction also demonstrates broad substrate scope, providing access to a wide range of indoles, and even highly sterically crowded indole derivatives. The demonstration of the use of air enabled C-H activation provides guidance for further development of mild and more effective approaches to the catalysis of C-C bind formation.

This research was supported by the generous financial support provided by Linnaeus University and the KK foundation (Sweden).

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, BMC, Uppsala University, SE-751 23 Uppsala, Sweden*

† Electronic Supplementary Information (ESI) available: [Experimental procedures, full spectroscopic data for all new compounds]. See DOI: 10.1039/c000000x/

1 T. Eicher, S. Hauptmann, and A. Speicher, *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*, 3rd ed.; Wiley-VCH: Weinheim, Germany, 2012; J. A. Bull, J. J. Mousseau, P. Guillaume, and A. B. Charrette, *Chem. Rev*. **2012**, *112*, 2642; G. Zeni, and R. C. Larock, *Chem. Rev*. **2006**, *106*, 4644; A. Deiters, and S. F: Martin, *Chem. Rev*. **2004**, *104*, 2199.

2. B. Robinson, *Chem. Rev*. **1963**, *63*, 373; B. Robinson, *The Fischer Indole Synthesis*, Wiley-Interscience, New York, **1982**; "*Heterocyclic Scaffolds II: Reactions and Applications of Indoles*": *Topics in Heterocyclic Chemistry, Vol. 26* (Ed.: G. W. Gribble), Springer, Berlin, 2010; R. J. Sundberg, *Indoles*, Academic Press, London, 1996.

3. R. C. Larock, and E. K. Yume, *J. Am. Chem. Soc*. **1991**, *113*, 6689.

4. S. Wurtz, S. Rakshit, J. J. Neumann, T. Droge, and F. Glorius, *Angew. Chem. Int. Ed*. **2008**, *47*, 7230.

5. Y. Wei, I. Deb, and N. Yoshikai, *J. Am. Chem. Soc*. **2012**, *134*, 9098.

6. L. Ackermann, *Org. Lett*. **2005**, *7*, 439.

7. L. Zhou, and W. Lu, *Chem. Eur. J*. **2014**, *20*, 634; T. K. Hyster, K. E. Ruhl, and T. Rovis, *J. Am. Chem. Soc*, **2013**, *135*, 5364; F. W. Patureau, J. Wencel-Delord, and F. Glorius, *Aldrichimica Acta*, **2012**, *45*, 31; D. A. Colby, A. S. Tsai, R. G. Bergman, and J. A. Ellman, *Acc. Chem. Res*. **2012**, *45*, 814; G. Song, F. Wang, and X. Li, *Chem. Soc. Rev*. **2012**, *41*, 3651; C. Zhu, R. Wang, and J. R. Falck, *Chem. Asian J*. **2012**, *7*, 1502; A. Korotvicka, D. Nacas, and M. Kotora, *Curr. Org. Chem*. **2012**, *16*, 1170; T. Satoh, and M. Miura, *Chem. Eur. J*. **2010**, *16*, 11212; K. Ueura, T. Satoh, and M. Miura, *Org. Lett*. **2007**, *9*, 1407; V. Ritleng, C. Sirlin, and M. Pfeffer, *Chem. Rev*. **2002**, *102*, 1731; G. Dyker, *Angew. Chem. Int. Ed*. **1999**, *38*, 1699; For reactions under air: see B. Zhou, J. Du, Y. Yang, H. Feng, and Y. Li, *Org. Lett*. **2014**, *16*, 592; K. Morimoto, K. Hirano, T. Satoh, and M. Miura, *Org. Lett*. **2010**, *12*, 2068; J. Seo, Y. Park, I. Jeon, T. Ryu, S. Park, and P. H. Lee, *Org. Lett*. **2013**, *15*, 3358; A. Seoane, N. Casanova, N. Quinones, J. L. Mascarenas, and M. Gulias, *J. Am. Chem. Soc*. **2014**, *136*, 834; A. Seoane, N. Casanova, N. Quinones, J. L. Mascarenas, and M. Gulias, *J. Am. Chem. Soc*. **2014**, *136*, 834.

8. D. R. Stuart, M. B. Laperle, K. M. N. Burgass, and K. Fagnou, *J. Am. Chem. Soc*. **2008**, *130*, 16474; D. R. Stuart, P. Alsabeh, M. Kuhn, and K. Fagnou, *J. Am. Chem. Soc*. **2010**, *132*, 18326.

9. D. Zhao, Z. Shi, and F. Glorius, *Angew. Chem. Int. Ed*. **2013**, *52*, 12426.

10. C. Wang, H. Sun, Y. Fang, and Y. Huang, *Angew. Chem. Int. Ed.* **2013**, *52*, 5795.

11. L. Zheng, and R. Hua, *Chem. Eur. J*. **2014**, *20*, 2352; C. Wang, and Y. Huang, *Org. Lett.* **2013**, *15*, 5294; B. Liu, C. Song, C. Sun, S. G. Zhou, and J. Zhu, *J. Am. Chem. Soc*. **2013**, *135*, 16625.

12. L. Ackermann, *Acc. Chem. Res*, **2014**, *47*, 281; M. Ramu Yadav, R. K. Rit, and A. K. Sahoo, *Org. Lett*. **2013**, *15*, 1638; K. Parthasarathy, N. Senthilkumar, J. Jayakumar, and C.-H. Cheng, *Org. Lett*. **2012**, *14*, 3478; P. B. Arockiam, C. Fischmeister, C. Bruneau, and P. H. Dixneuf, *Angew. Chem. Int. Ed*. **2010**, *49*, 7833; T.-J. Gong, W.-M. Cheng, W. Su, B. Xiao, and Y. Fu, *Tetrahedron Lett*. **2014**, *55*, 1859.

View Article Online
DOI: 10.1039/C4CC06020B Journal Name

Graphical Abstract

Rhodium(III)-catalysed aerobic synthesis of highly functionalized indoles from *N*-arylurea under mild conditions through C-H activation

Subban Kathiravan,[a] and Ian A. Nicholls[a,b*]