RESEARCH ARTICLE

# Merging Cu-catalysed C-H functionalisation and intramolecular annulations: computational and experimental studies on an expedient construction of complex fused heterocycles

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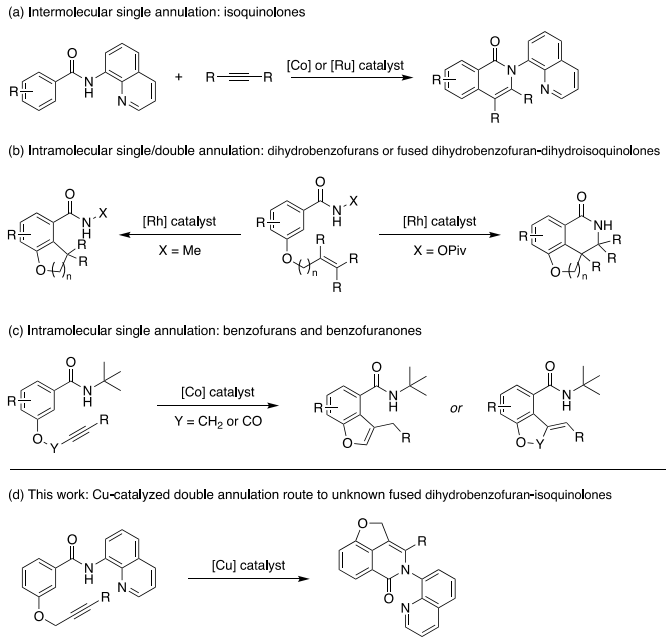
Intramolecular annulation reactions provide a powerful opportunity to access complex heterocyclic compounds with higher complexity than intermolecular conversions. This report details how, previously unknown fused dihydrobenzofuran-isoquinolone compounds, exhibiting an unusually strained shared aromatic unit, can be readily obtained from simply prepared benzamide derivatives bearing a tethered alkyne moiety, using copper C-H bond functionalisation catalysis. The mechanism has been proposed based on detailed DFT and topological analysis studies, and shows that the two key heterocycles are formed during distinct mechanistic steps; the dihydrobenzofuran arises from a migratory insertion and the isoquinolone from the following reductive elimination, resulting in an efficient Double Annulation Reaction (DAR). Actually, the results present an unprecedented migratory insertion of alkynes with benzamides when using copper as catalyst with the 8-aminoquinoline directing group and also study why the intermolecular variant is not operative.

## Introduction

Over recent years there has been a surge of interest in the development of new synthetic protocols based on direct C-H bond functionalisation, either as a late or early stage synthetic tool.[1,2] Of these approaches, the field of metal-mediated C-H bond functionalisation has drawn significant attention, with recent major breakthroughs being highly prized using abundant 3d transition metals in place of more expensive and less abundant 4d and 5d analogues.[3] In general, these protocols fall into two distinct categories; (a) linear additions where a C-H bond is simply elaborated with a new functional group and (b) Single Annulation Reactions (SARs) which result in the formation of useful single heterocyclic compounds which are often otherwise challenging to synthesise.[4] One particular substrate which has attracted significant attention is the benzamide bearing a bidentate 8-aminoquinoline directing group (Scheme 1a),[5] which was originally introduced by Daugulis in the mid-2000's.[6] In terms of annulation reactions with this aforementioned substrate, one of the most common coupling partners reported to date are alkynes, which have been used to efficiently synthesise highly prized isoquinolone and isoindolinone derivatives with a range of 3d and 4d catalysts.[7-10] Isoquinolone and its derivatives are considered to be privileged scaffolds in medicinal chemistry and as a result, new methods for their preparation as well as the development of novel derivatives has potential to make significant impact.[11]




**Scheme 1** Intermolecular annulation of alkynes to benzamides bearing the 8-aminoquinoliine directing group and in intramolecular variants using alkenes an alkynes.

Current research in our group focuses on the development of protocols for rapid access to heterocyclic compounds through the use of cheap and readily available benzamide starting compounds, using C-H functionalisation as the key

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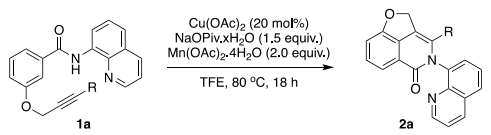
*† Electronic Supplementary Information (ESI) available: Experimental procedures, analytical data for new compounds, original $^{1}H$, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$ and 2D COSY NMR spectra and DFT study details. See DOI: 10.1039/x0xx00000x.*

**Table 1** Optimisation studies.[a]




| Entry | Deviation from standard conditions | Yield of **2a** (%)[b] |
|---|---|---|
| **1** | **none** | **77** |
| 2 | nitrogen atmosphere | 6 |
| 3 | $Mn(OAc)_3.2H_2O$ instead of $Mn(OAc)_2.4H_2O$ | trace |
| 4 | AgOAc instead of $Mn(OAc)_2.4H_2O$ | trace |
| 5 | NaOAc instead of $NaOPiv.xH_2O$ | 37 |
| 6 | $CsOPiv.H_2O$ instead of $NaOPiv.xH_2O$ | 41 |
| 7 | $KOPiv.H_2O$ instead of $NaOPiv.xH_2O$ | 57 |
| 8 | 60 °C instead of 80 °C | trace |
| 9 | 100 °C instead of 80 °C | 61 |
| 10 | $Co(acac)_3$ instead of $Cu(OAc)_2$ | n.d. |
| 11 | $Co(OAc)_2$ instead of $Cu(OAc)_2$ | n.d. |
| 12 | 1,2-DCE instead of TFE | n.d. |
| 13 | no $Cu(OAc)_2$ | n.d. |
| 14 | no $Mn(OAc)_2.4H_2O$ | 30 |
| 15 | 2.0 mmol scale reaction | 68[c] |
| 16 | intermolecular reaction: *N*-(quinolin-8-yl)benzamide and 1-phenyl-1-propyne | n.d. |

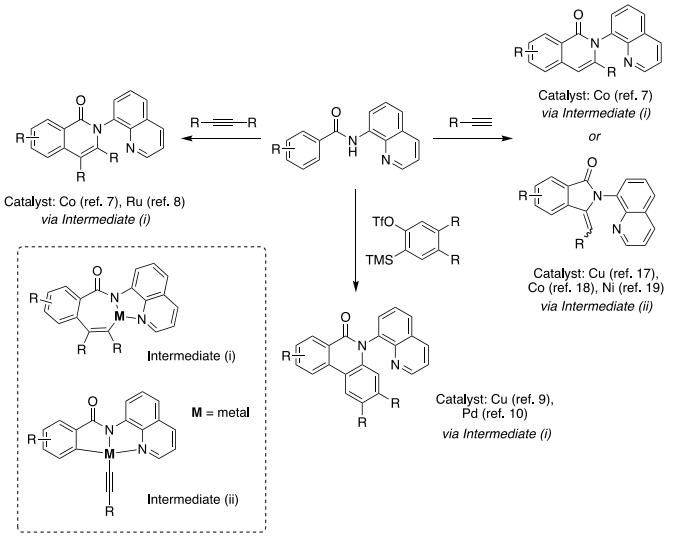
[a]Conditions: benzamide (0.10 mmol), $Cu(OAc)_2$ (20 mol%, 0.02 mmol), $NaOPiv.xH_2O$ (1.5 equiv., 0.15 mmol), $Mn(OAc)_2.4H_2O$ (2.0 equiv., 0.20 mmol) in TFE (1.0 mL) at 80 °C under air for 18 h. [b]Yields of **2a** calculated from $^1H$ NMR of crude reaction mixture using mesitylene as internal standard. [c]Isolated yield. n. d. = not detected.

tool,[12,13] a field which is attracting a lot of attention.[14] One method to potentially and easily achieve even higher molecular complexity is to include the coupling partner as part of the substrate, thus operating through an intramolecular approach and providing the opportunity for Double Annulation Reactions (DAR's). In this context, a novel route towards fused dihydrobenzofuran-dihydroisoquinolone compounds from benzamides with tethered olefins, operating through a DAR approach, was reported independently by the groups of Rovis and Glorius in late 2013/early 2014 utilising relatively expensive rhodium catalysts (Scheme 1b).[15] Surprisingly, in both of these reports no efforts were made to convert benzamides with tethered alkynes, thus realising the corresponding analogous fused dihydrobenzofuran-isoquinolones.

To this end, the recent report by Maji, applying cobalt C-H functionalisation catalysis for an intramolecular SAR approach to the synthesis of benzofurans and benzofuranones was of significant interest (Scheme 1c).[16] In this work, for the first time, benzamides with tethered alkynes were used as substrate in combination with a 3d transition metal, although the products with a DAR, as with the previous work from Rovis and Glorius, were not achieved. As a result, we surmised that through use of the stronger bidentate 8-aminoquinoline directing group, pioneered by Daugulis, in combination with cobalt catalysis, it would be possible to extend the work of Maji and provide a route towards previously unreported fused dihydrobenzofuran-isoquinolone compounds, thus expanding chemical space. As will be described herein, an unexpected copper-catalysed C-H functionalisation DAR approach has actually been developed for the synthesis of the target fused dihydrobenzofuran-isoquinolone compounds (Scheme 1d), which is complimented with a full study of the unique mechanistic complexities through a DFT investigation.

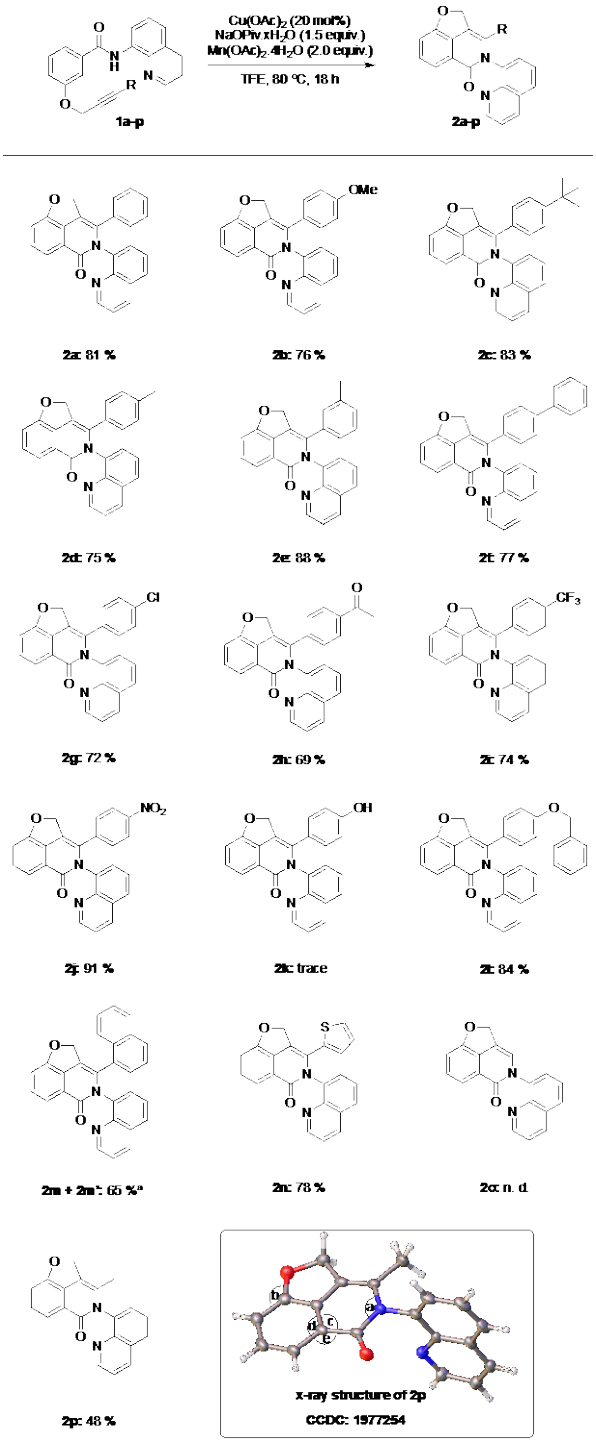
## Results and discussion

With substrate **1a** in hand (which can be readily prepared in high yield), our initial approach was to transfer the cobalt-catalysed conditions from the intermolecular SAR of benzamides bearing the 8-aminoquinoline substrate and alkynes reported by Daugulis.[7a] However, to our dismay, these initial reactions failed to provide any of the desired fused heterocyclic product (**2a**). When $Co(OAc)_2$ was replaced with $Cu(OAc)_2$, to our surprise a 77 % yield of target compound **2a** could be obtained (Table 1, entry 1). This result was unexpected as migratory insertion reactions of internal alkynes with the intermolecular variant of this reaction are currently unknown, except with highly reactive arynes in copper-catalysis (Scheme 2). Indeed, previously, only isoindolinones and not isoquinolines have been prepared using copper catalysis and terminal alkynes (Scheme 2).[17] It should also be noted that the reaction takes place in the presence of air, making this a very appealing and easily applied protocol. However, in the absence of oxygen (nitrogen atmosphere; Table 1, entry 2), the reaction is significantly retarded, indicating that oxygen form air acts as the terminal oxidant as has been previously observed by Daugulis for the intermolecular Co(II) catalysed variant of this reaction.[7a] Upon further changing the reaction conditions, in order to attempt further optimization, no further improvement in the yield could be made (Table 1). Notably, it was still possible to obtain 30 % yield in the absence of the $Mn(OAc)_2.4H_2O$ additive, although when $Mn(OAc)_3.2H_2O$ was used instead of $Mn(OAc)_2.4H_2O$, only trace product was observed (Table 1, entry 2), which is in line with the cobalt-catalysed intermolecular work reported previously by Daugulis.[7a] The procedure was also attempted on a 2.0 mmol scale, where it was found to be amenable to larger scale and a




**Scheme 2** Reported intermolecular annulations of benzamides with 8-aminoquinoline substrates with alkynes.




**Scheme 3** Scope and isolated yields of the copper-catalysed intramolecular annulation reaction. Conditions: benzamide (0.50 mmol), $Cu(OAc)_2$ (20 mol%, 0.10 mmol), NaOPiv.x$H_2O$ (1.5 equiv., 0.75 mmol), $Mn(OAc)_2.4H_2O$ (2.0 equiv., 1.00 mmol) in TFE (5.0 mL) at 80 °C under air for 18 h. [a]Obtained as a mixture of two inseparable isomers, **2m** and **2m'** (see Supporting Information). n. d. = not detected.

68 % isolated yield was achieved (Table 1, entry 14). The intermolecular variant using 1-phenyl-1-propyne was tested for completeness and found not to work with this new copper-catalysed protocol, whilst operating successfully when cobalt catalysis is employed (Scheme 2 and Table 1, entry 15). This final result indicates the complementarity and importance of the newly developed procedure to the already reported intermolecular cobalt work.

The following step was to study the wider applicability of the developed protocol. As the target of our research programme is to provide access to increased molecular complexity thorough the use of readily available reagents, the logical substrate scope was to make derivatives based on variation at the aromatic moiety of the tethered alkyne. These modifications can be easily affected through a Sonogashira coupling to the terminal alkyne (see supporting information for details). Pleasingly, it was possible to convert a variety of different substrates with both electron-withdrawing and electron-donating substituents being tolerated (Scheme 3). However, there are a several exceptions; the phenolic substrate (**1k**) could not be converted, although protection of this compound as the benzyl ester (**1l**) provided a route towards the derivative product (**2l**) in good yield. In the case of conversion of naphthyl substituted substrate (**1m**), an inseparable mixture of the two possible optical isomers was obtained (see supporting information for full information). Finally, the terminal alkyne (**1o**) could not be converted. This latter observation is not surprising as with the intermolecular variants of this reaction with cobalt, the alkyne preferentially inserts to give the substituted end of the terminal alkyne next to the amide,[7] which is not accessible with the intramolecular tethered example described here. To further confirm the structural motif of the fused heterocyclic compounds, a crystal structure of the methyl substituted product (**2p**) was obtained (Scheme 3). Interestingly, the 3 fused rings result in some significant distortions from idealised geometries. Studies with

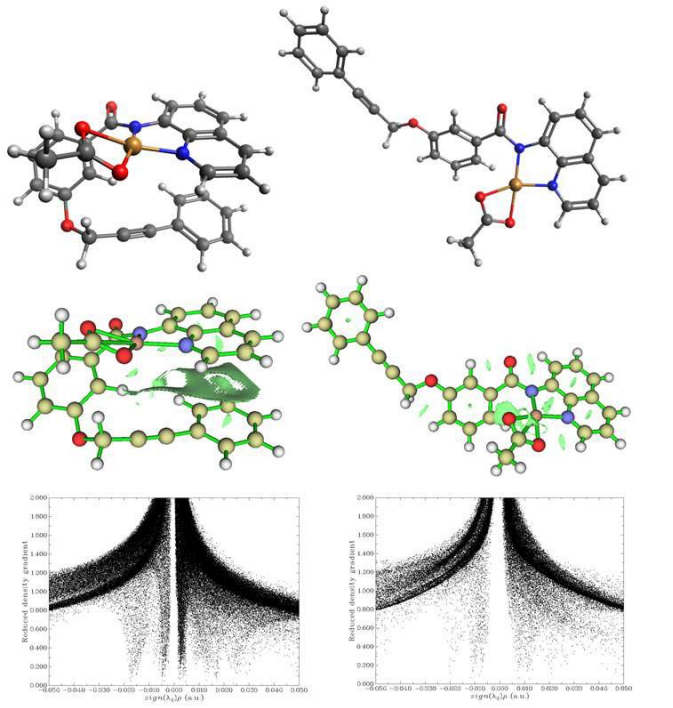
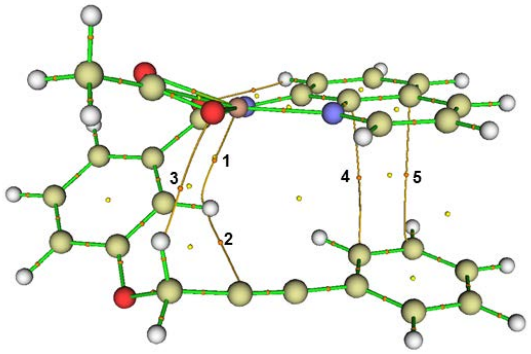


**Figure 1** Top: Calculated structure (PBE0-D3BJ/def2-tzvp) for complex A and complex Ai. Middle: The Reduced Density Gradient (RDG) isosurface plot (value of 0.5). Bottom: Plot of the RDG versus sign($\lambda_2$)ρ, highlighting Non-Covalent Interactions (NCI) for each structure.

**Table 2** QTAIM topological analysis and tabulated parameters highlighting line critical points for the stabilizing non-covalent interactions in A. No comparative interactions were located for Ai.




| | Line critical points (lcp) | | | | |
|---|---|---|---|---|---|
| QTAIM | 1 | 2 | 3 | 4 | 5 |
| ρ | 0.017 | 0.015 | 0.006 | 0.005 | 0.005 |
| $\nabla^2\rho$ | 0.051 | 0.049 | 0.021 | 0.015 | 0.015 |
| V(r) | -0.012 | -0.009 | -0.003 | -0.002 | -0.002 |
| G(r) | 0.013 | 0.011 | 0.004 | 0.003 | 0.003 |
| H(r) | 0.0002 | 0.002 | 0.001 | 0.001 | 0.001 |

Mogul[20] suggested that eight of the angles were unusual (see Figure S106, Supporting Information). Of particular note is the internal angle of the nitrogen (angle "a") of 126.42(12)°, that is more obtuse than any of the known suggested similar structures (121.85-125.40°). Similarly, the external angle to the 5-member ring (angle "b") of 135.42(12)° *vs* 126.21-130.62° is unexpected. Further, looking at the 3 angles around C2 (angles "c-e"; ideally should all be 120°) of 116.59(11), 116.91(13) and 126.48(12)°. These type of distortions of the benzene rings have been previously well studied by Taddei.[21] Pleasingly, these distorted angles are also present in the calculated structures arising from the following DFT study (see coordinates in the Supporting Information).

Next, in order to fully understand the experimental observations and elucidate the unusual mechanism, we turned to DFT calculations (see supporting information for computational details). Recent work by Duan and Zhang[9b] on a related copper-catalysed C-H activation of acrylamides using in-situ formed arynes as coupling partners, calculated the initial acetate assisted N-H deprotonation to form the resulting bidentate complex (equivalent to complex **A**, Figures 1 and 2), with a barrier of only 7.2 kcal mol$^{-1}$. Based on this low barrier of

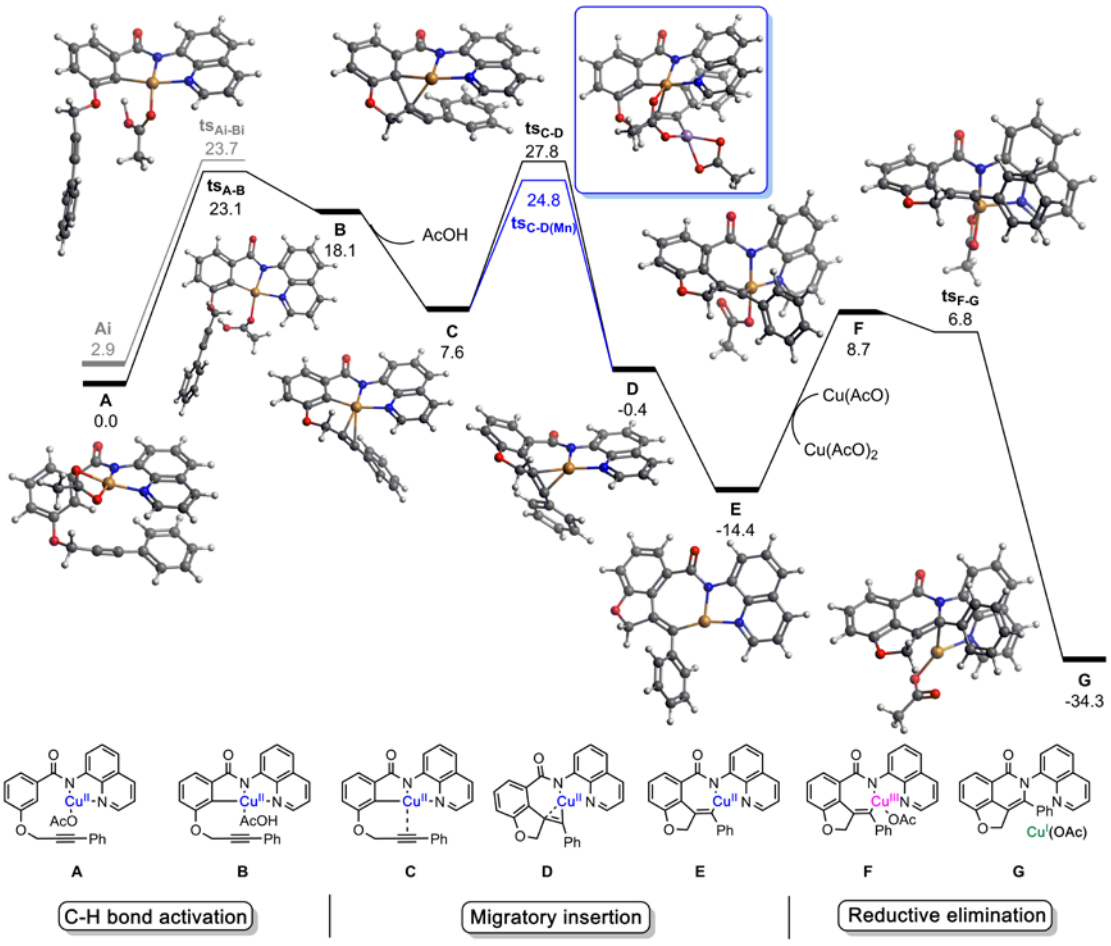
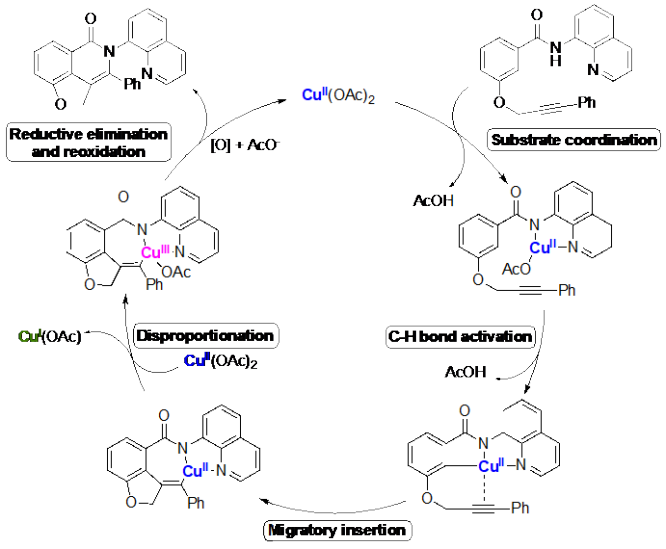



**Figure 2** Calculated free energy surface ($\Delta G_{298K}$), PBE0-D3BJ/def2-tzvp, for the mechanism of the copper-catalysed intramolecular annulation reaction. Note: Structure of the transitions state for the Mn(II) assisted migratory insertion step is highlighted in the blue box.

activation we choose to start our mechanistic investigation from this resulting complexed species. Complex **A** is the regio-determining intermediate, with the potential for C-H activation at either of the distinct ortho-positions. Calculation of complexes **A** and **Ai** (Figure 1) sheds light on an interaction which enhances the regioselectivity for the C-H activation step, with complex **A** being 2.9 kcal mol$^{-1}$ more stable. This increase in stability, and reactivity in what would be considered the more sterically congested and thus less-favoured position, is due to the increased non-covalent interactions between the directing group quinoline ring and phenyl of the intramolecular coupling partner. Additionally and significantly, which sheds light on why this intramolecular reactions occurs, the conformation of the alkyne group leads to a closer Cu···H interaction for **A** (2.39Å compared to 2.67 Å in **Ai**) and a long-range hydrogen bonding (2.7Å) interaction between the $CH_2$ of the tethered alkyne moiety and the copper bound acetate oxygen (line critical points 1 and 3 in Figure 2). The Reduced Density Gradient (RDG) isosurface and NCI plots (Figure 1) as well as Quantum Theory of Atoms in Molecules (QTAIM) topological analysis, using the Multiwfn software,[22] highlights and quantifies these stabilizing interactions (Table 1). The low-density low gradient spikes in the plot of the RDG versus sign($\lambda_2$)$\rho$ for complex **A**, in Figure 1, show a significant increase in stabilising non-covalent interactions, in the range of ±0.005 (π···π interactions) and -0.02 (hydrogen bonding), compared to complex **Ai**.[23] Analysis of the line critical points in Table 2 highlights the strength and characteristics of the non-covalent interactions, with lcp 1, 2 and 3 (hydrogen bonding) being the dominant interactions compared the weaker π···π interactions (lcp 4 and 5).

With an inspection of the regioselectivity in hand, we turned our attention to full elucidation of the reaction mechanism (Figure 2). From complex **A** an acetate assisted Concerted Metallation Deprotonation (CMD) step produces the five-membered metallocycle intermediate, complex **B**, *via* $\mathbf{ts_{A-B}}$, with a free energy ($\Delta G_{298K}$) barrier of 23.1 kcal mol$^{-1}$. The observed regioselectivity is also again accounted for by the higher barrier for $\mathbf{ts_{Ai-Bi}}$ of $\Delta\Delta G^{\ddagger}_{298K}$ of 0.6 kcal mol$^{-1}$. Direct oxidation of complex **A** to the Cu(III) variant was found to be energetically unfeasible *via* both a SET mechanism (37.2 kcal mol$^{-1}$) and addition of $AcO^-$ (63.5 kcal mol$^{-1}$). The exergonic and entropically favourable loss of AcOH from complex **B** leads to intermediate complex **C**, which has the intramolecular tethered alkyne occupying the already vacant coordination site of the copper centre. Migratory insertion of the tethered alkyne, passing via $\mathbf{ts_{C-D}}$, forms the 5-membered dihydrobenzofuran part of the heterocycle, related to the intermediate resulting in the work of Maji,[16] to form complex **D**. From the calculated surface, this step is the rate determining step of the mechanism, with a barrier of 27.8 kcal mol$^{-1}$. This differs from the intermolecular study of Duan and Zhang using arynes[9b] where it was implicated that C-H activation was the rate determining step. This difference can be accounted for due to the increased reactivity of aryne species compared to the more common and less reactive internal alkynes. The addition of the $Mn(OAc)_2$ additive was studied and the results indicate that it has an important effect on the turnover determining step ($\mathbf{ts_{C-D}}$), reducing the barrier height by approximately 3.0 kcal mol$^{-1}$ (Figure 2). This improved reactivity with the inclusion of $Mn(OAc)_2$ is observed experimentally (Table 1; entries 1 and 14), with an increase in yield upon inclusion of $Mn(OAc)_2.4H_2O$. Furthermore, for completeness, the analogous intermolecular alkyne insertion for the copper-catalysed system described in this work has a barrier height of 41.6 and 42.6 kcal mol$^{-1}$ for 1-phenyl-1-propyne and 3-phenyl-2-propyn-1-ol respectively (see Figure S1), suggesting the intramolecular migratory insertion for the newly developed protocol is energetically less demanding. The increase in energy requirements for the intermolecular reaction is due to the unfavourable entropic contributions from the incoming external coupling partner. Isomerization of complex **D** to the more stable complex **E**, prior to disproportionation with $Cu(OAc)_2$, leads to the Cu(III) intermediate complex **F**. A barrierless reductive elimination step then occurs, through $\mathbf{ts_{F-G}}$, resulting in complex **G**, which then produces the fused heterocyclic product and the catalyst can then also regenerate via another disproportionation reaction. Cu(III) barrierless reductive elimination pathways have previously been reported by Roithová and Ribas.[24] Finally, direct reductive elimination from complex **E**, a Cu(II) to Cu(0) process, was explored with and without explicit TFE solvent coordination. Both reaction barriers, $\mathbf{ts_{E-H}}$, were calculated to be approximately 8.0 kcal mol$^{-1}$ higher in energy than the discussed Cu(III) to Cu(I) reductive elimination step (see Figure S2). Cu(I)/Cu(II)/Cu(III) catalytic cycles have previously been proposed by Zeng and Zhao, albeit operating through a radical process, but encompassing the key Cu(II)/Cu(III) step confirmed in this study.[25]

Overall, based on the DFT study, the mechanism depicted in Scheme 4 is proposed to be operative. Initially, the copper coordinates to the substrate, which is followed by C-H bond activation through a CMD step. This organometallic complex results in the alkyne being in close proximity to the Cu(II) centre,




**Scheme 4** Proposed mechanism for the copper-catalysed intramolecular annulation reaction producing the fused heterocyclic compounds. Note: the migratory insertion step is enhanced by the presence of Mn(II).

which leads to weak coordination to the vacant coordination site. Thereafter, the alkyne reacts with the organometallic complex through a migratory insertion, resulting in the formation of the dihydrobenzofuran heterocycle. Disproportionation of the Cu(II) species to a Cu(III) species provides an unstable organometallic complex which thereafter undergoes a facile reductive elimination forming the isoquinolone heterocycle and thus the target novel fused heterocyclic product.

## Conclusions

In conclusion, we have developed a novel and easily applied copper-catalysed protocol for the preparation of previously undescribed complex fused heterocyclic compounds, where oxygen from air appears to be the terminal oxidant. This work demonstrates the power of C-H functionalisation technologies for realising new previously unexplored/inaccessible chemical space. The equivalent intramolecular protocol is not operative under cobalt catalysis, in contrast to the previously reported intermolecular variant of this reaction. Full mechanistic understanding from DFT calculations gives an insight into the intriguing copper-catalysed reaction and also why the intermolecular reaction does not proceed with copper. Interestingly, the observed selectivity for the C-H activation step is directed *via* unusual non-covalent interactions, which have been further explored by topological analysis. The reaction described here is, to the best of our knowledge, the first example of a copper-catalysed migratory insertion of an alkyne to a benzamide with an 8-aminoquinoline directing group, likely possible due to the intramolecular interactions disclosed in the DFT study.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## Notes and references

CCDC 1977254 contains supplementary X-ray crystallographic data for **2p**. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html, or from the Cambridge Crystallographic Data Centre, Union Road, Cambridge, CB2 1EZ; fax(+44) 1223-336-033 or email: deposit@ccdc.cam.ac.uk.

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