RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2016, **6**, 29638

Combined experimental/theoretical study of D-glucosamine promoted Ullmann-type C–N coupling catalyzed by copper(I): does amino really count?†

Xin Ge,[ab] Xinzhi Chen,[b] Chao Qian*[b] and Shaodong Zhou*[c]

Received 1st February 2016
Accepted 14th March 2016

DOI: 10.1039/c6ra03015g

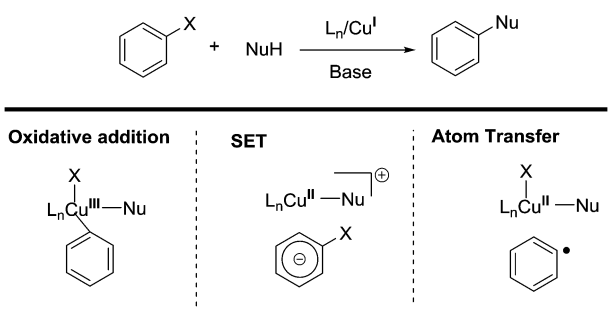
www.rsc.org/advances

Ullmann type C–N coupling reaction catalyzed by copper(I) with D-glucosamine derivatives as promoters was studied by means of combined experimental/theoretical investigation. The catalytic role of D-glucosamine was addressed. In contrast with previous speculations, the amino group may not count in the catalytic cycle in which the oxidative addition/reductive elimination mechanism works. Experimental results are in good agreement with theoretical findings. Extensive work indicates the wide applicability of the C–N coupling strategy exploited in this work.

Introduction

The copper-catalyzed Ullmann coupling reaction is an important strategy for C–N coupling, which plays a fundamental role in pharmaceutical and agrochemical industry.[1] Application of the traditional copper-catalyzed Ullmann coupling reaction was limited by the high temperature (about 200 °C), stoichiometric usage of catalyst and fastidiousness about the substrate. These imperfections have inspired development of the prevalent palladium-catalyzed cross-coupling reaction.[2] In 2001, great progress reported by Buchwald indicated that ligand diamines could efficiently improve the copper-catalyzed cross-coupling of N–H heterocycles with aryl halides;[3] the afterward work done by Cristau and Taillefer also provided such C–N coupling strategies with high efficiencies alternatively by using Schiff bases and oximes as ligand.[4] The prospect of Ullmann coupling reaction catalyzed by copper catalysts is to perform such processes in more economic way. Up till now, while various ligands such as diamines,[3,5] glycol,[6] Schiff base,[4,7] amino acids,[8] diketones,[9] phenanthroline,[10] 2,2′-bipyridine,[11] carbohydrates,[12] oxalamic acid,[13] diamide,[14] have already been proved efficient for promoting the targeted coupling reactions, it is always challenging and interesting to develop eco-friendly and more efficient ligand,[15] as well as to unravel the associated mechanistic aspects.

Due to the high density of chiral information on the backbone and environmental benignity, carbohydrates have been widely used in organic synthesis, especially as efficient ligands. Several reports has proved the effectiveness of carbohydrates in promoting copper-catalyzed Ullmann coupling reaction. For example, Cheng *et al.* found that D-glucosamine could efficiently promote CuI catalyzed C–N coupling reaction;[12a] per-6-amino-β-cyclodextrin was prepared as a supramolecular ligand for CuI catalyzed *N*-arylation of imidazole with aryl bromide;[12c] Zhang *et al.* also reported Ullmann type reaction by using D-glucosamine as ligand.[12b] In spite of the abundant findings described above, the associated catalytic mechanisms deduced at a molecular level remain unclear. So far as reported, most mechanistic investigations focused on the reactions catalyzed by β-diketone-, 1,10-phenanthroline- and diamine-ligated copper complexes.[16] Compared with the single-electron-transfer (SET) and atom-transfer mechanisms, the oxidative addition/reductive elimination mechanism was more widely accepted,[16b,17] the corresponding intermediates are shown in Scheme 1. As indicated by the oxidative addition/reductive mechanism, the intermediate of Cu^{III} was formed by the

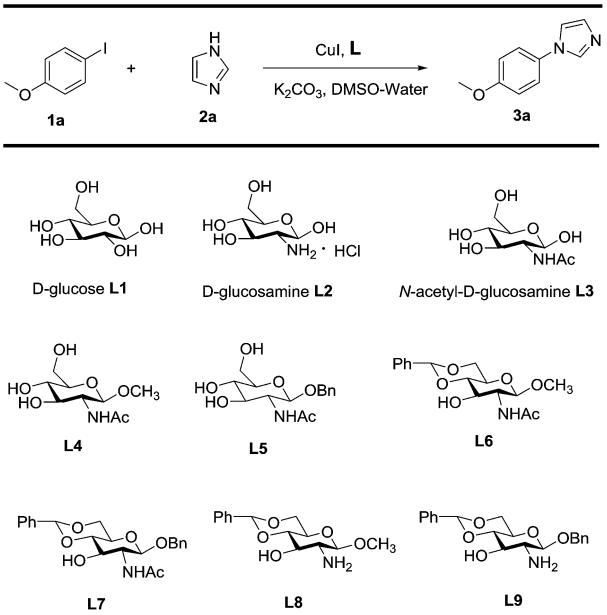


Scheme 1 The intermediates reported in previous studies.

[a]School of Chemical and Material Engineering, Jiangnan University, Wuxi, P. R. China
[b]Key Laboratory of Biomass Chemical Engineering of Ministry of Education, College of Chemical and Biological Engineering, Zhejiang University, Hangzhou, P. R. China. E-mail: qianchao@zju.edu.cn
[c]Institut für Chemie, Technische Universität Berlin, Straße des 17. Juni 135, 10623 Berlin, Germany. E-mail: shaodong.zhou@campus.tu-berlin.de

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c6ra03015g

Table 1 Ligand effect on CuI-catalyzed coupling of 4-iodoanisole and imidazole[a]



Ligand	L1	L2	L3	L4	L5	L6	L7	L8	L9
Yield[b]/%	73	85	84	76	73	0	0	0	0

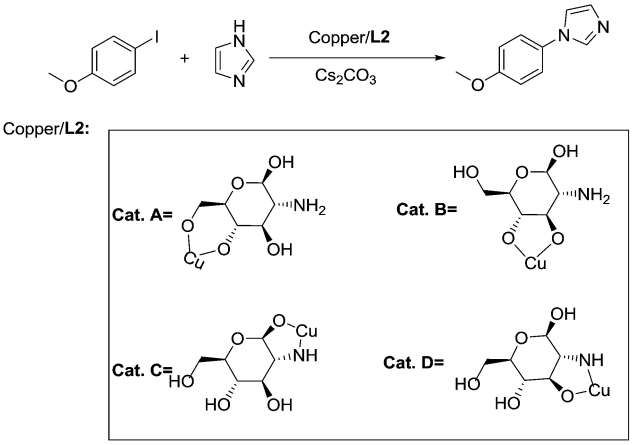
[a] Reaction conditions: 4-iodoanisole **1a** (1.0 mmol), imidazole **2a** (1.2 mmol), K_2CO_3 (2.0 mmol), CuI (0.1 mmol) and ligand (0.1 mmol) in the DMSO–water (5 mL, 1 : 1/v/v) at 110 °C for 24 h. [b] Isolated yield.

oxidative addition of a ligand (L_n)–Cu^I–nucleophile (Nu) complex with the aryl halide.[16e,18] Moreover, it was also concluded that the rate-limiting step was oxidative addition of ligand (L_n)–Cu^I–nucleophile (Nu) complex with the aryl halide.[16b,17,19]

Our recently interest focuses on the ligand- and catalytic effect of carbohydrates,[20] we herein present mechanistic study on D-glucosamine promoted C–N coupling reactions catalyzed by copper catalyst. The experimental study on fine-tuning and design of D-glucosamine-derived ligand was complemented by theoretical investigation using DFT calculation.

Result and discussion

To rationally obtain some mechanistic information experimentally, the D-glucosamine-derived ligand were finely tuned and designed. The coupling of 4-iodoanisole (1.0 equiv.) and imidazole (1.2 equiv.) was adopted as the model reaction, and detailed results are shown in Table 1. First, when D-glucose (**L1**) and D-glucosaminium chloride (**L2**) were used as ligands, the coupling product **3a** was obtained with yields of 73% and 85%, respectively, which is consistent with previous reports.[12a,b] Pitchumani speculated the catalytic mechanism of CuI/per-6-amino-β-cyclodextrin that the ligand–Cu^I complex was obtained by interaction between the amino groups of per-6-amino-β-cyclodextrin and CuI.[12c] Zhang *et al.* elaborated the similar viewpoint in D-glucosamine/CuI catalyzed the Ullmann type C–S coupling reaction.[21] However, considering the very activity of **L1**, possibly, rather than the amino it is the hydroxyls that work in the present C–N coupling processes. To verify this speculation, we protected the hydroxyl and exposed the amino groups of **L2**, respectively. Thus, **L6**, **L7**, **L8** and **L9** were obtained by protecting the hydroxyl groups in the position C-4 and C-6. However, copper complexes prepared with these ligands are completely inactive in promoting the coupling reaction, no matter if the amino group is acylated (**L6**, **L7**) or not (**L8**, **L9**). Alternatively, by just protecting the amino group and exposing some hydroxyl groups, **L3**, **L4**, and **L5** were obtained, which turned out to be very active for the model coupling reaction. Moreover, only protecting the hydroxyl group in the position C-1 of **L3** (*i.e.* **L4** and **L5**) does not affect the activities of ligands obviously. Compared with **L1**–**L5**, while **L6**–**L9** are much more conformationally rigid, and sterically hindered, the sharp contrast in Table 1 clearly indicates that the amino or imino group maybe not count in the catalytic process. Thus, as the most effective promoter, the prototype of **L2** and **L3**, *i.e.* D-glucosamine, was selected for theoretical investigation presented later.



Scheme 2 Possible active complexes that are directly involved in the C–N coupling processes.

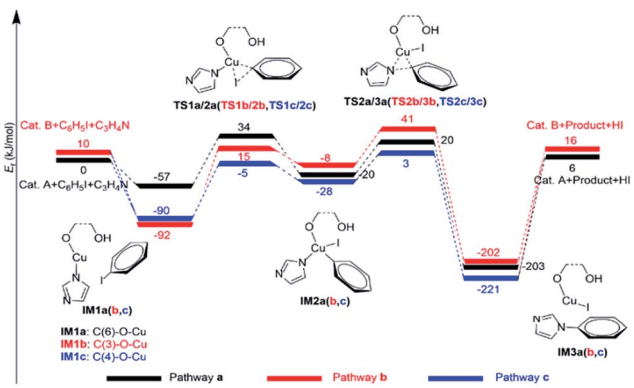


Fig. 1 PES and relevant structural sketches of the most favorable reaction pathways for D-glucosamine promoted C–N(1) coupling reaction; charges are omitted for the sake of clarity.

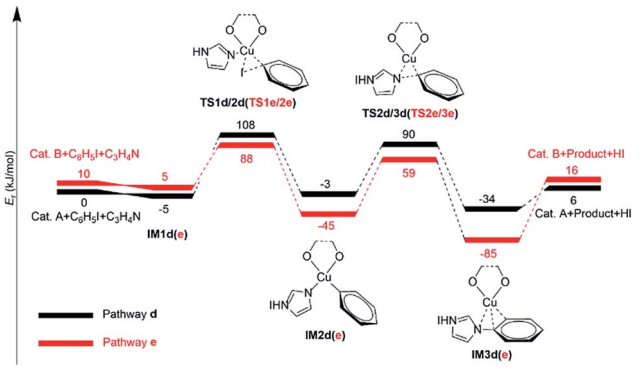


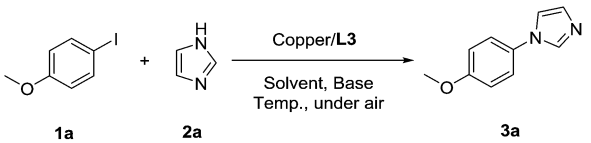
Fig. 2 PES and relevant structural sketches of the most favorable reaction pathways for D-glucosamine promoted C–N(3) coupling reaction; charges are omitted for the sake of clarity.

The reaction mechanisms were interrogated with DFT calculations. As found in the experiments, the amino maybe not count in the catalytic process. We attempted to clarify the active ligand–Cu^{I} complex structure by DFT first. As concluded above, other than the amine, hydroxyls on the C3, C4 and C6 positions are crucial for the CuI catalyzed Ullmann reaction promoted by glucosamine derivatives. Thus, two oxo-ligated Cu complexes, *i.e.* Cat. A and B and two N–O ligated Cu complexes, *i.e.* Cat. C and D (as shown in Scheme 2), are considered as the possible active species that directly catalyze the reaction. However, the structure of Cat. C and D can't converge by DFT. It tallies with the experiment results. In addition, C–N couplings involving either N atom of 1*H*-imidazole are taken account. The potential energy surfaces (PES) and relevant structural sketches of the most favorable reaction pathways are shown in Fig. 1–3; more detailed structural information is given in the ESI.†

For C–N(1) coupling, as shown in Fig. 1, the reactions promoted by Cat. A and B proceed *via* the same mechanisms, and three most probable pathways were located. Being found as the thermodynamically most favorable one, pathway **c** is selected for more detailed elucidation. From an encounter complex **IM1c**, in which the N–H bond has already been activated barrierlessly and the N(1) atom coordinates with the metal center, an initial insertion of the Cu atom into the C–I bond of iodobenzene takes place *via* **TS1c/2c**, forming the Cu–C and Cu–I bonds, respectively. Subsequent step corresponds to formation of the C–N bond with concomitant cleavage of the Cu–C and Cu–N bonds, generating **IM3c**. Finally, dissociation of **IM3c** liberates the coupling product 1-phenyl-1*H*-imidazole and regenerates Cat. A or B. For this stepwise C–N coupling process, insertion of the Cu atom into the C–I bond serves as the rate limiting step. In addition, both Cat. A and B are capable of bringing about a coupling process proceeding *via* pathway **c**.

For C–N(3) coupling, once again, the same mechanisms for reactions promoted by Cat. A and B were addressed, and two energetically most favorable pathways were found. Likewise, elucidation of only the more preferable pathway, **e** is to be presented. As shown in Fig. 2, the transformations starts from an encounter complex **IM1e** in which the N(3) atom coordinates with the metal center, and the initial step involves insertion of the Cu atom into the C–I bond of iodobenzene *via* **TS1e/2e**. Next, the C–N(3) coupling is achieved *via* **TS2e/3e**, forming the

Table 2 The coupling reaction of 4-iodoanisole and imidazole catalyzed by copper/**L3**[a]



Entry	Copper salt	Base	Solvent	Temp/°C	Yield[b]/%
1	CuI	K_2CO_3	DMSO–water (1 : 1)	110	84
2	CuCl	K_2CO_3	DMSO–water (1 : 1)	110	37
3	$CuCl_2$	K_2CO_3	DMSO–water (1 : 1)	110	24
4	$CuSO_4$	K_2CO_3	DMSO–water (1 : 1)	110	71
5	$Cu(OAc)_2$	K_2CO_3	DMSO–water (1 : 1)	110	76
6	CuI	K_2CO_3	DMF	110	32
7	CuI	K_2CO_3	DMSO	110	61
8	CuI	K_2CO_3	Methanol	110	21
9	CuI	K_2CO_3	Water	110	Trace
10	CuI	K_2CO_3	DMF–water (1 : 1)	110	69
11	CuI	Cs_2CO_3	DMSO–water (1 : 1)	110	91
12	CuI	KOH	DMSO–water (1 : 1)	110	57
13	CuI	NaOH	DMSO–water (1 : 1)	110	65
14	CuI	Na_2CO_3	DMSO–water (1 : 1)	110	60
15	CuI	Cs_2CO_3	DMSO–water (1 : 1)	80	40
16	CuI	Cs_2CO_3	DMSO–water (1 : 1)	100	68
17	CuI	Cs_2CO_3	DMSO–water (1 : 1)	120	75

[a] Reaction conditions: 4-iodoanisole **1a** (1.0 mmol), imidazole **2a** (1.2 mmol), base (2.0 mmol), copper salt (0.1 mmol) and **L3** (0.1 mmol) in the solvent (5 mL) for 24 h. [b] Isolated yield.

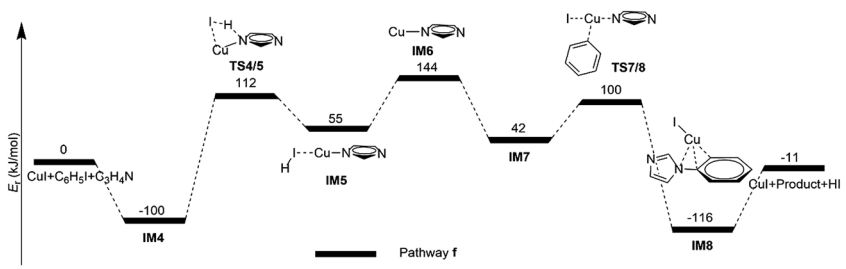
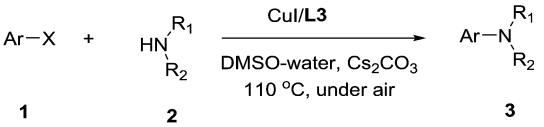


Fig. 3 PES and relevant structural sketches of the most favorable reaction pathways for bare CuI catalyzed reaction; charges are omitted for the sake of clarity.

Table 3 CuI/**L3** catalyzed C–N coupling reaction[a]



1 **2** **3**

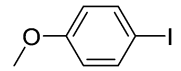
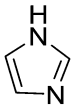
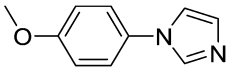
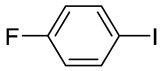
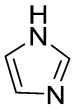
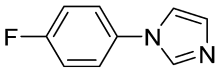
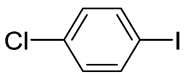
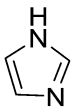
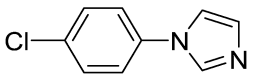
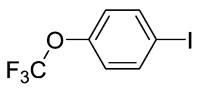
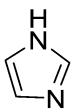
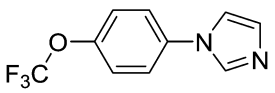
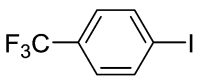
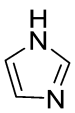
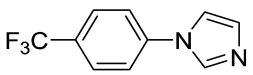
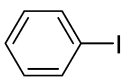
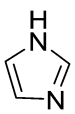
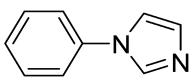
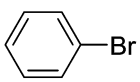
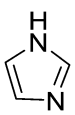
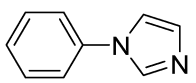
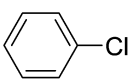
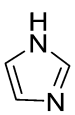
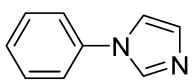
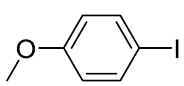
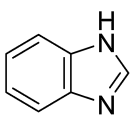
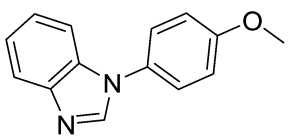
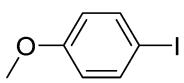
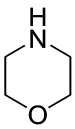
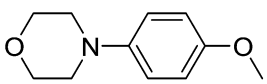
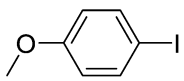
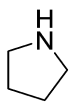
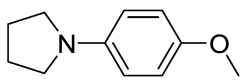
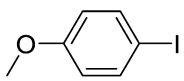
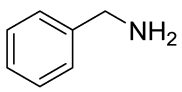
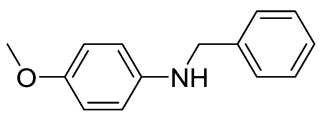
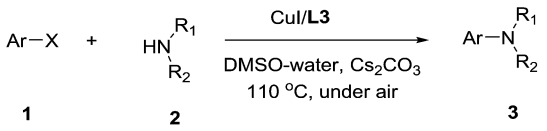
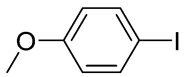
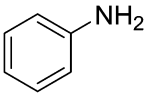
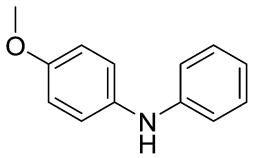
Entry	Aryl halides **1**	Nitrogen compound	Product	Yield[b]/%
1				91 (**3a**)
2				94 (**3b**)
3				95 (**3c**)
4				87 (**3d**)
5				89 (**3e**)
6				86 (**3f**)
7				81 (**3f**)
8				Trace
9				76 (**3g**)
10				69 (**3h**)
11				57 (**3i**)
12				99 (**3j**)

Table 3 (*Contd.*)



1 2 3

Entry	Aryl halides **1**	Nitrogen compound	Product	Yield[b]/%
13				71 (**3k**)

[a] Reaction conditions: aryl halides **1** (1.0 mmol), nitrogen nucleophiles **2** (1.2 mmol), Cs_2CO_3 (2.0 mmol) and CuI (0.1 mmol) in the DMSO–water (5 mL, 1 : 1/v/v) at 110 °C for 24 h. [b] Isolated yield.

product complex **IM3e**. Finally, release of 1-phenyl-1*H*-imidazol-3-ium iodide regenerates Cat. A. Although energy barrier of the rate limiting step of pathway **e**, *i.e.* **IM1e** → **IM2e**, is comparable with that of pathway **c**, the much lower stability of encounter complex **IM1e** as compared to **IM1c** makes formation of the former much less efficient, so that pathway **e** is bypassed. Thus, only C–N(1) coupling is available according to our calculation.

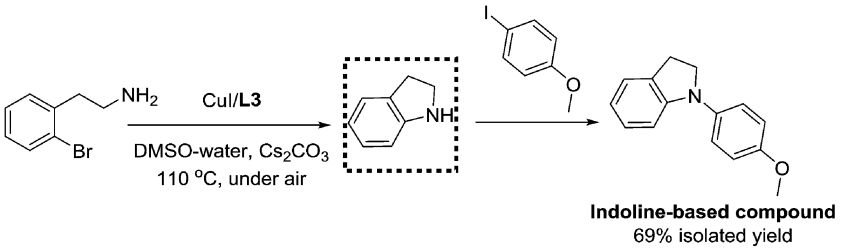
To make it clear if the effect of ligands is just to increase the solubility of Cu or more than that, the reaction of bare CuI catalyzed C–N coupling process was also calculated; PES and relevant structural sketches of the most favorable pathway (**f**) are shown in Fig. 3, and more detailed structural information is given in the ESI.† Alternative mechanisms were addressed for bare CuI catalyzed reaction. Initially, a σ-bond metathesis process takes place *via* cleavage of the Cu–I and N–H bonds to form **IM5**, with concomitant formation of the Cu–N and I–H bonds. Next, another σ-bond metathesis process is involved in subsequent reaction of intermediate **IM6** with iodobenzene to generate **IM8**, that is, formation of C–N and the new Cu–I bonds is accomplished under cleavage of the Cu–N and C–I bonds. Finally, liberation of 1-phenyl-1*H*-imidazole regenerates the bare CuI. The initial activation of the Cu–I and N–H bonds corresponds to the rate limiting step; here, the energy barrier (212 kJ mol^{-1}) is much higher as compared to pathway **c** (85 kJ mol^{-1}).

To be concluded from the computational results, D-glucosamine has considerably promotive effect on the C–N coupling reaction in that, alternative pathways are available such that much lower activation energy is needed; the oxidative addition/reductive elimination mechanisms are addressed; only C–N(1) coupling is available; both Cat. A and B can serve as the active complex that directly promotes a catalytic cycle.

For C–N coupling reaction, **L1** and **L2** have been reported, but **L3** was not involved in this reaction. Thus, **L3** selected for further examination, and detailed results can be found in Table 2. Comparison of different copper sources, *i.e.* CuI, CuCl, $CuCl_2$, $CuSO_4$ and $Cu(OAc)_2$, showed that CuI was the best copper source (Table 2, Entry 1–5). Next, a series of solvents were tested and it was found that polar aprotic solvent favors this coupling reaction (Table 1, Entry 6–9). While water is not an ideal solvent, it serves to increase the solubility of ligand in the mixed solvents, DMSO–water (1 : 1) and DMF–water (1 : 1), so as to increase the reaction efficiencies (Table 2, Entry 1 and 10). Further, Cs_2CO_3 outperforms all the other bases employed (Table 1, Entry 11–14). With regard to the reaction temperature, the reactions at 110 °C proceeds most efficiently (Table 1, Entry 15–17). Thus, the optimum conditions are obtained: Cs_2CO_3 as the acid-binding reagent, DMSO–water (1 : 1) as solvent, 110 °C. In addition, CuI and DMSO were selected as catalyst precursor and solvent, respectively for subsequent theoretical investigation.

Further extensive study focused on expanding the substrate scope for CuI/**L3** catalyzed Ullmann coupling reaction; more details are shown in Table 3. To our delight, both electron-withdrawing and electron-donating aryl iodides react efficiently with imidazole and the targeted products were obtained with good to excellent yields (Table 3, Entry 1–6). In addition, neither electron withdrawing nor donating groups substituted on the phenyl ring has obvious influence on the yields. Next, we examined the influences of different halides(Table 3, Entry 6–8), and the corresponding reactivities with imidazole decrease in the order PhI > PhBr > PhCl. Considering the increasing BDE(C_6H_5–X):[22] BDE(C_6H_5–I) = 272.0 kJ mol^{-1} < BDE(C_6H_5–Br) = 336.4 kJ mol^{-1} < BDE(C_6H_5–Cl) = 397.9 kJ mol^{-1}, the experimental result is in line with our theoretical conclusion that insertion of the C–X bond serves as the rate limiting step. Further, experiments with the different nitrogen nucleophiles were performed, and several N–H heterocycles including 1*H*-benzimidazole, morpholine, pyrrolidine give the corresponding products in moderate to excellent yields.

As the final part of this work, we present a tricky application of the C–N coupling strategy in the synthesis of 1-(4-methoxyphenyl)indoline, which is abundant in nature and widely employed in biological and pharmaceutical chemistry.[23] As shown in Scheme 3, 1-(4-methoxyphenyl)indoline was obtained from 2-bromo-phenethylamine stepwisely *via* intramolecular



Scheme 3 Application of the Cu/L3-catalyzed C–N coupling reaction in the one-pot synthesis of 1-(4-methoxyphenyl)indoline.

cyclization and subsequent coupling with 4-iodoanisole in one pot; the yield amounts to 69%. All the above extensive reactions indicate the wide applicability of the C–N coupling strategy exploited in this work.

Conclusions

In summary, we have presented the combined experimental/theoretical investigation on the D-glucosamine derivatives promoted Ullmann type C–N coupling reactions catalyzed by copper. In the first part, by finely tuning and designing the ligands, it was found that the hydroxyls on the C-3, C-4 and C-6 position may have significant influence on the catalysis process, while the hydroxyl on C-1 and the amino do not count. Subsequently, by using DFT calculation, not only the catalytic role of D-glucosamine was addressed, but also the inactiveness of bare CuI was explained. Here, the oxidative addition/reductive elimination mechanism works, and experimental results are in good agreement with theoretical findings. Next, extensive work was performed by employing various phenyl halide and amines as substrates, and moderate to excellent yields of corresponding coupling products were obtained. Finally, the wide applicability of the coupling strategy was further proved by a tricky application in the efficient preparation of 1-(4-methoxyphenyl)indoline starting from 2-bromo-phenethylamine.

General methods

Melting points were determined on an X4-Data microscopic melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were measured at 400 MHz (^{1}H) or at 100 MHz (^{13}C) on a Bruker Avance DRX-400 spectrometer. All reactions were monitored by analytical thin-layer chromatography (TLC) from Merck with detection by spraying with 5% (w/v) phosphomolybdic acid in ethanol and subsequent heating or UV. The products were purified by column chromatography through silica gel (300–400 mesh). D-Glucose, D-glucosamine and *N*-acetyl-D-glucosamine were purchased in Aladdin Industrial Corporation. All reagents and solvents were general reagent grade unless otherwise stated.

General procedure of CuI@ligand catalyzed coupling reaction of N–H heterocycles and aryl halides

To a stirred solution of DMSO–water (1 : 1, 5 mL) were added aryl halide (1.0 mmol), N–H heterocycle (1.2 mmol), CuI (0.1 mmol, 19 mg), ligand (0.1 mmol) and Cs_2CO_3 (2 mmol) at room temperature. Then the reaction mixture was heated to 110 °C under air and stirred for 24 h. After cooling to room temperature, the reaction mixture was partitioned by adding the ethyl acetate (20 mL) and water (20 mL). Subsequently, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic phases were washed with saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. Then the crude product was purified by column chromatography through silica gel, eluting with ethyl acetate/petroleum ether solvent mixture, to give the pure **3**.

General procedure for one-pot synthesize of 1-(4-methoxyphenyl)indoline

To a stirred solution of DMSO–water (1 : 1, 5 mL) were added 2-bromo-phenethylamine (1.0 mmol), CuI (0.1 mmol, 19 mg), **L3** (0.1 mmol) and Cs_2CO_3 (4 mmol) at room temperature. Then the reaction mixture was heated to 110 °C under air and stirred for 24 h. Subsequently, 4-iodoanisole (1.0 mmol) was added to this solution and continued to stir for 24 h. After cooling to room temperature, the reaction mixture was partitioned by adding the ethyl acetate (20 mL) and water (20 mL). Subsequently, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (20 mL) twice. The combined organic phases were washed with saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. Then the crude product was purified by column chromatography through silica gel, eluting with ethyl acetate/petroleum ether solvent mixture, to give the pure product.

Computational details

The theoretical work was performed using the Gaussian 09 program.[24] The def2-TZVP basis set[25] with the ECP-28 pseudopotential[26] were used for the I atom, and the def2-TZVP all-electron basis set[25] was chosen for the Cu atoms; for all the other atoms, the def2-SVP all-electron basis set[25] was used for optimization and frequency analysis (BSI), and the def2-TZVP all-electron basis set[25] (BSII) for calculating the single-point energies. The Polarizable Continuum Model using the integral equation formalism variant (IEFPCM)[27] was employed to evaluate the solvation energies. The B97-1 functional[28] was employed for geometry optimizations and frequency analysis, which has previously been proven to be reliable for calculating Cu complexes.[29] Stationary points were optimized without

symmetry constraint, and their nature confirmed by vibrational frequency analysis. Intrinsic reaction coordinate[30] calculations were performed to link transition structures with the respective intermediates. Unscaled vibrational frequencies were used to correct the relative energies for zero-point energy (ZPE) contributions.

Acknowledgements

The authors are grateful for the financial support from the Natural Science Foundation of China (21376213, 21476194), Zhejiang Provincial Public Technology Research of China (2014C31123, 2015C31038) and the Fundamental Research Funds for the Central Universities (JUSRP115A05).

Notes and references

1 (*a*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954; (*b*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (*c*) R. B. Bambal and R. P. Hanzlik, *Chem. Res. Toxicol.*, 1995, **8**, 729; (*d*) V. Nair, S. Bindu and V. Sreekumar, *Angew. Chem., Int. Ed.*, 2005, **44**, 1907; (*e*) T. Wiglenda, I. Ott, B. Kircher, P. Schumacher, D. Schuster, T. Langer and R. Gust, *J. Med. Chem.*, 2005, **48**, 6516; (*f*) M. Voets, I. Antes, C. Scherer, U. Muller-Vieira, K. Biemel, S. Marchais-Oberwinkler and R. W. Hartmann, *J. Med. Chem.*, 2006, **49**, 2222; (*g*) I. P. Beletskaya and V. P. Ananikov, *Chem. Rev.*, 2011, **111**, 1596; (*h*) J. Bariwal and E. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 9283; (*i*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337.

2 (*a*) A. S. Guram, R. A. Rennels and S. L. Buchwald, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1348; (*b*) J. Louie and J. F. Hartwig, *Tetrahedron Lett.*, 1995, **36**, 3609; (*c*) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046; (*d*) E. A. B. Kantchev, C. J. O'Brien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2007, **46**, 2768.

3 (*a*) A. Klapars, J. C. Antilla, X. H. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727; (*b*) A. Klapars, X. H. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2002, **124**, 7421; (*c*) J. C. Antilla, J. M. Baskin, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578.

4 H. J. Cristau, P. P. Cellier, J. F. Spindler and M. Taillefer, *Chem.–Eur. J.*, 2004, **10**, 5607.

5 D. S. Surry and S. L. Buchwald, *Chem. Sci.*, 2010, **1**, 13.

6 (*a*) F. Y. Kwong, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 581; (*b*) B. Yang, Z. X. Mao, X. H. Zhu and Y. Q. Wan, *Catal. Commun.*, 2015, **60**, 92.

7 Y. Wang, J. Y. Gao, M. D. Zhao and J. M. Li, *Chem. Res. Chin. Univ.*, 2015, **31**, 549.

8 (*a*) D. W. Ma and Q. Cai, *Synlett*, 2004, 128; (*b*) J. M. Tang, B. Q. Xu, X. Mao, H. Y. Yang, X. X. Wang and X. Lv, *J. Org. Chem.*, 2015, **80**, 11108.

9 (*a*) A. Shafir and S. L. Buchwald, *J. Am. Chem. Soc.*, 2006, **128**, 8742; (*b*) B. de Lange, M. H. Lambers-Verstappen, L. S. van de Vondervoort, N. Sereinig, R. de Rijk, A. H. M. de Vries and J. G. de Vries, *Synlett*, 2006, 3105.

10 R. A. Altman and S. L. Buchwald, *Org. Lett.*, 2006, **8**, 2779.

11 C. Zhang, B. Huang, A. Q. Bao, X. Li, S. Guo, J. Q. Zhang, J. Z. Xu, R. Zhang and D. M. Cui, *Org. Biomol. Chem.*, 2015, **13**, 11432.

12 (*a*) D. P. Cheng, F. F. Gan, W. X. Qian and W. L. Bao, *Green Chem.*, 2008, **10**, 171; (*b*) M. Wen, C. Shen, L. F. Wang, P. F. Zhang and J. Z. Jin, *RSC Adv.*, 2015, **5**, 1522; (*c*) P. Suresh and K. Pitchumani, *J. Org. Chem.*, 2008, **73**, 9121.

13 (*a*) Y. Zhang, X. Y. Yang, Q. Z. Yao and D. W. Ma, *Org. Lett.*, 2012, **14**, 3056; (*b*) Y. B. Wang, Y. Zhang, B. B. Yang, A. Zhang and Q. Z. Yao, *Org. Biomol. Chem.*, 2015, **13**, 4101.

14 W. Zhou, M. G. Fan, J. L. Yin, Y. W. Jiang and D. W. Ma, *J. Am. Chem. Soc.*, 2015, **137**, 11942.

15 (*a*) L. Liang, Z. K. Li and X. G. Zhou, *Org. Lett.*, 2009, **11**, 3294; (*b*) F. T. Wu, N. N. Yan, P. Liu, J. W. Xie, Y. Liu and B. Dai, *Tetrahedron Lett.*, 2014, **55**, 3249; (*c*) J. W. Xie, X. H. Zhu, M. N. Huang, F. Meng, W. W. Chen and Y. Q. Wan, *Eur. J. Org. Chem.*, 2010, 3219; (*d*) X. F. Li, D. S. Yang, Y. Y. Jiang and H. Fu, *Green Chem.*, 2010, **12**, 1097; (*e*) D. P. Wang, F. X. Zhang, D. Z. Kuang, J. X. Yu and J. H. Li, *Green Chem.*, 2012, **14**, 1268.

16 (*a*) G. O. Jones, P. Liu, K. N. Houk and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 6205; (*b*) P. F. Larsson, C. J. Wallentin and P. O. Norrby, *ChemCatChem*, 2014, **6**, 1277; (*c*) E. R. Strieter, D. G. Blackmond and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4120; (*d*) J. W. Tye, Z. Weng, A. M. Johns, C. D. Incarvito and J. F. Hartwig, *J. Am. Chem. Soc.*, 2008, **130**, 9971; (*e*) E. R. Strieter, B. Bhayana and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 78; (*f*) R. Giri and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 15860.

17 S. L. Zhang and Y. Q. Ding, *Organometallics*, 2011, **30**, 633.

18 (*a*) S. L. Zhang, L. Liu, Y. Fu and Q. X. Guo, *Organometallics*, 2007, **26**, 4546; (*b*) H. Z. Yu, Y. Y. Jiang, Y. Fu and L. Liu, *J. Am. Chem. Soc.*, 2010, **132**, 18078.

19 G. Lefevre, G. Franc, C. Adamo, A. Jutand and I. Ciofini, *Organometallics*, 2012, **31**, 914.

20 (*a*) C. Shen, P. F. Zhang and X. Z. Chen, *Helv. Chim. Acta*, 2010, **93**, 2433; (*b*) C. Shen, H. J. Xia, H. Zheng, P. F. Zhang and X. Z. Chen, *Tetrahedron: Asymmetry*, 2010, **21**, 1936; (*c*) C. Shen, F. Y. Shen, H. J. Xia, P. F. Zhang and X. Z. Chen, *Tetrahedron: Asymmetry*, 2011, **22**, 708; (*d*) C. Shen, F. Shen, G. Zhou, H. Xia, X. Chen, X. Liu and P. Zhang, *Catal. Commun.*, 2012, **26**, 6; (*e*) C. Shen, H. J. Xia, H. Yan, X. Z. Chen, S. Ranjit, X. J. Xie, D. Tan, R. Lee, Y. M. Yang, B. G. Xing, K. W. Huang, P. F. Zhang and X. G. Liu, *Chem. Sci.*, 2012, **3**, 2388; (*f*) X. Ge, C. Qian and X. Z. Chen, *Tetrahedron: Asymmetry*, 2014, **25**, 1450; (*g*) X. Ge, C. Qian, Y. B. Chen and X. Z. Chen, *Tetrahedron: Asymmetry*, 2014, **25**, 596.

21 M. Yang, H. Y. Shen, Y. Y. Li, C. Shen and P. F. Zhang, *RSC Adv.*, 2014, **4**, 26295.

22 Y. R. Luo, *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, London, New York, Washington, D.C., 2002.

23 (*a*) L. Basolo, A. Bernasconi, E. Borsini, G. Broggini and E. M. Beccalli, *ChemSusChem*, 2011, **4**, 1637; (*b*) J. Q. Liu, C. Qian and X. Z. Chen, *Synthesis*, 2010, 403.

24 M. J. Frisch; G. W. Trucks; H. B. Schlegel; G. E. Scuseria; M. A. Robb; J. R. Cheeseman; G. Scalmani; V. Barone; B. Mennucci; G. A. Petersson; H. Nakatsuji; M. Caricato; X. Li; H. P. Hratchian; A. F. Izmaylov; J. Bloino; G. Zheng; J. L. Sonnenberg; M. Hada; M. Ehara; K. Toyota; R. Fukuda; J. Hasegawa; M. Ishida; T. Nakajima; Y. Honda; O. Kitao; H. Nakai; T. Vreven; J. A. Montgomery Jr; J. E. Peralta; F. Ogliaro; M. Bearpark; J. J. Heyd; E. Brothers; K. N. Kudin; V. N. Staroverov; R. Kobayashi; J. Normand; K. Raghavachari; A. Rendell; J. C. Burant; S. S. Iyengar; J. Tomasi; M. Cossi; N. Rega; J. M. Millam; M. Klene; J. E. Knox; J. B. Cross; V. Bakken; C. Adamo; J. Jaramillo; R. Gomperts; R. E. Stratmann; O. Yazyev; A. J. Austin; R. Cammi; C. Pomelli; J. W. Ochterski; R. L. Martin; K. Morokuma; V. G. Zakrzewski; G. A. Voth; P. Salvador; J. J. Dannenberg; S. Dapprich; A. D. Daniels; O. Farkas; J. B. Foresman; J. V. Ortiz; J. Cioslowski and D. J. Fox, *Gaussian 09*.

25 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297.

26 B. Metz, H. Stoll and M. Dolg, *J. Chem. Phys.*, 2000, **113**, 2563.

27 G. Scalmani and M. J. Frisch, *J. Chem. Phys.*, 2010, **132**, 114110.

28 F. A. Hamprecht, A. J. Cohen, D. J. Tozer and N. C. Handy, *J. Chem. Phys.*, 1998, **109**, 6264.

29 (*a*) S. M. Tekarli, M. L. Drummond, T. G. Williams, T. R. Cundari and A. K. Wilson, *J. Phys. Chem. A*, 2009, **113**, 8607; (*b*) W. Y. Jiang, M. L. Laury, M. Powell and A. K. Wilson, *J. Chem. Theory Comput.*, 2012, **8**, 4102; (*c*) W. J. Zhang, D. G. Truhlar and M. S. Tang, *J. Chem. Theory Comput.*, 2013, **9**, 3965; (*d*) S. J. Luo, B. Averkiev, K. R. Yang, X. F. Xu and D. G. Truhlar, *J. Chem. Theory Comput.*, 2014, **10**, 102.

30 (*a*) H. P. Hratchian and H. B. Schlegel, *J. Chem. Theory Comput.*, 2005, **1**, 61; (*b*) D. G. Truhlar, N. J. Kilpatrick and B. C. Garrett, *J. Chem. Phys.*, 1983, **78**, 2438; (*c*) K. Fukui, *Acc. Chem. Res.*, 1981, **14**, 363.