



Cite this: *Org. Biomol. Chem.*, 2018, **16**, 8984

N,O-Bidentate ligand-tunable copper(II) complexes as a catalyst for Chan–Lam coupling reactions of arylboronic acids with 1*H*-imidazole derivatives†

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An efficient procedure for Chan–Lam coupling reactions of arylboronic acids with 1*H*-imidazole derivatives using *N,O*-bidentate ligand-tunable copper(II) complexes as a catalyst under base-free conditions has been developed. This protocol features mild reaction conditions, high yields and compatibility with different functional groups, providing a direct and facile strategy for the construction of C–N bonds and synthesis of heterocyclic compounds.

Received 12th September 2018,
Accepted 5th November 2018

DOI: 10.1039/c8ob02254b

rsc.li/obc

Introduction

Since 1998, copper-promoted coupling reactions of arylboronic acids with nucleophiles containing N–H or O–H bonds reported by Chan, Evans and Lam have become a powerful and valuable synthetic strategy for the construction of carbon–heteroatom bonds.¹ Many versions of the Chan–Lam reactions under various conditions have been described and extensively applied in the construction of C–N, C–O and C–S bonds due to their unique advantages such as mild reaction conditions, wide scope of substrates, and the use of weak bases and cheap metal catalysts.² Until now, various organic boron reagents including arylboronic acid,³ vinylboronic acid,⁴ alkylboronic acid,⁵ cyclopropylboronic acid,⁶ arylboronic esters⁷ and alkylboranes⁸ have been employed in these coupling reactions. However, the use of stoichiometric amounts of Cu(OAc)₂, base and ligands was always involved in the coupling process. Therefore the development of new catalytic systems in “green” fashion and the exploration of new substrates still represent a major area of research.

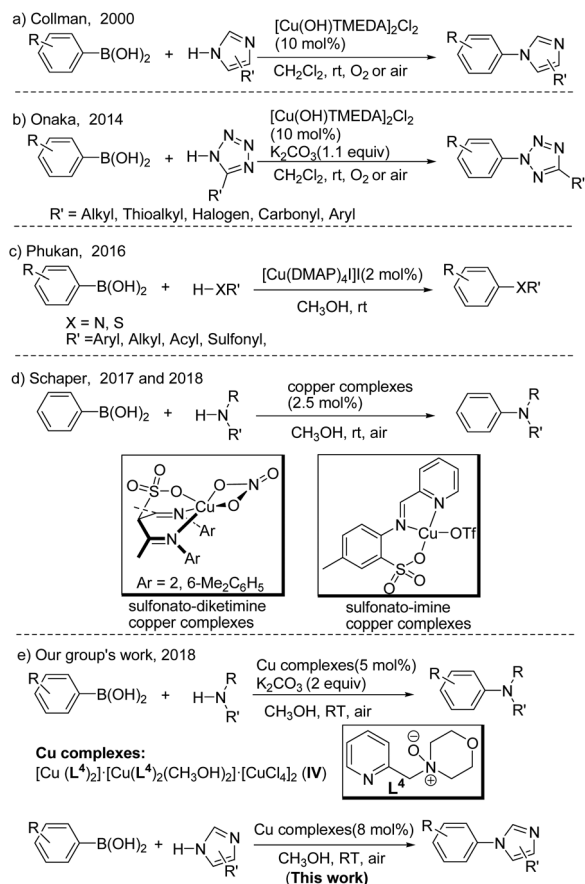
In 2014, sulfonyl azides were used as new coupling partners to react with arylboronic acids for the synthesis of *N*-arylsulfonamides using 10 mol% of CuCl as the catalyst.⁹ These reactions proceeded at room temperature under base-free, ligand-free and additive-free conditions. In the same year, copper-catalyzed sequential coupling reactions for

N-arylation of *C*-amino-*NH*-azoles without a base or ligands were reported by Das's group, providing facile access to diarylaminoazole derivatives in high yields.¹⁰ In 2015, D. J. Gorin documented copper-catalyzed aerobic methylation of carboxylic acids with methylboronic acid in the presence of 10 mol% [CuCO₃·Cu(OH)₂], which offered an efficient strategy for the synthesis of a variety of methyl esters.¹¹ Recently M. R. Harris developed potassium tertiary trifluoroborates as new organic boron reagents to couple with substituted pyrazoles for the construction of 1-heteroaryl-3-azabicyclo[3.1.0]hexanes.¹² The cyclopropylation of phenols and azaheterocycles with potassium cyclopropyl trifluoroborate was also achieved in toluene/H₂O in the presence of Cu(OAc)₂ (10–25 mol%), 1,10-phenanthroline (10–12.5 mol%) and 1 atm of O₂ as the terminal oxidant.¹³ In addition, some new synthetic technologies such as solid phase synthesis,¹⁴ microwave irradiation^{14,15} and the use of ionic liquids¹⁶ as reaction solvents have been applied in Chan–Lam coupling to improve the efficiency of reactions. S. Kobayashi disclosed the copper-catalyzed aerobic oxidative coupling of arylboronic acids and aniline derivatives assisted by *fac*-[Ir(ppy)₃] as a visible-light photoredox catalyst, expanding the substrate scope of Chan–Lam reactions to electron-deficient arylboronic acids.¹⁷ Following Kim's procedure,⁹ the CuCl-catalyzed heterogeneous Chan–Lam reaction of sulfonyl azides with arylboronic acids was achieved by M. Cai and coworkers using MCM-41-*l*-proline-CuCl as the recyclable and reused catalyst.¹⁸

Despite these advances, the study on the Chan–Lam reaction catalyzed by copper complexes¹⁹ or other metal salts²⁰ is rather rare. In recent years, the Chan–Lam couplings catalyzed by copper complexes with novel ligands have attracted special attention. After Collman's pioneering work (Scheme 1a),^{19a}

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† Electronic supplementary information (ESI) available: General experimental information, NMR data and spectral copies of Chan–Lam coupling product 3. See DOI: 10.1039/c8ob02254b



Scheme 1 The Chan–Lam coupling reaction catalyzed by different copper complexes.

T. Onaka reported the first example of regioselective 2-arylation of 5-substituted tetrazoles with arylboronic acids catalyzed by $[\text{Cu}(\text{OH})(\text{TMEDA})_2]\text{Cl}_2$ under an O_2 atmosphere in 2014 (Scheme 1b).²¹ A new copper complex $[\text{Cu}(\text{DMAP})_4]\text{I}$ was also synthesized by Phukan's group and successfully used as an excellent catalyst for coupling reactions of N-nucleophiles or thiol with arylboronic acid at a lower loading level (Scheme 1c).²² F. Schaper and coworkers continuously investigated the synthesis of sulfonato-diketimine or sulfonato-imine copper complexes and their catalytic application in Chan–Evans–Lam couplings of amines with phenylboronic acid in detail, including the scope of substrates and reaction mechanism (Scheme 1d).²³ Considering the potential properties of copper complexes with different ligands, our group has recently described the synthesis of four new *N,O*-bidentate ligands and their copper(II) complexes, which were further used as highly active catalysts for the Chan–Lam reaction between amines and arylboronic acids under mild conditions (Scheme 1e).²⁴ Encouraged by these contributions, we herein further disclosed the Chan–Lam couplings of arylboronic acids with 1*H*-imidazole derivatives catalyzed by *N,O*-bidentate-chelated copper complexes under base-free conditions (Scheme 1e).

Results and discussion

According to our reported methods,²⁴ *N,O*-bidentate ligand-tunable copper(II) complexes $\{[\text{Cu}(\text{L}^1)_2]\text{Cl}_2$ (I), $[\text{Cu}(\text{L}^2)_2][\text{CuCl}_4]$ (II), $[\text{Cu}(\text{L}^3)_2\text{Cl}]\text{Cl}_2 \cdot [\text{CuCl}_2 \cdot (\text{H}_2\text{O})_2]\text{Cl}_2 \cdot 10\text{H}_2\text{O}$ (III) and $[\text{Cu}(\text{L}^4)_2] \cdot [\text{Cu}(\text{L}^4)_2(\text{CH}_3\text{OH})_2][\text{CuCl}_4]_2$ (IV) $\}$ were easily prepared by the treatment of anhydrous CuCl_2 with *N,O*-bidentate ligands (L^1 – L^4) in ethanol at room temperature, respectively. The structures of *N,O*-bidentate ligands (L^1 – L^4) and their copper complexes (I–IV) are shown in Fig. 1 and 2. Then we selected 1*H*-benzimidazole (1a) and phenylboronic acid (2a) as model substrates to evaluate catalytic activities of four *N,O*-bidentate-chelated copper(II) complexes in Chan–Lam coupling reactions. Firstly, the reactions were performed in methanol at room temperature for 22 h using 8 mol% copper complexes (I–IV) as the catalyst and K_2CO_3 as the base. We found that the desired products (3aa) were obtained in 39%, 75%, 77% and 90% yields, respectively. However, when no K_2CO_3 was used, the yields of 3aa had different changes (Table 1, entries 1–4), which indicated that the base had a slight effect on the reactivity of the model reaction. Importantly, the coupling product (3aa) was isolated in 92% yield using IV as the catalyst in the absence of K_2CO_3 . Thus, from the point of view of environmentally friendly and green synthesis, the copper complex (IV) was selected as the catalyst to further screen the other conditions under base-free conditions. The impact of catalyst loading on Chan–Lam coupling was examined. Actually, the yield of 3aa was improved to 97% using 10 mol% IV as the catalyst (entry

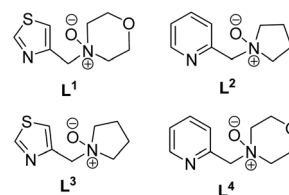


Fig. 1 The structure of *N,O*-bidentate ligands (L^1 – L^4).

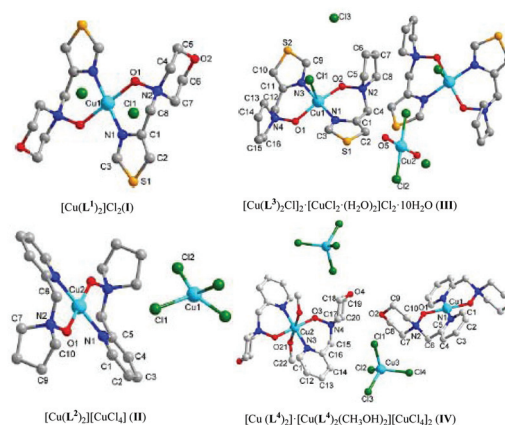
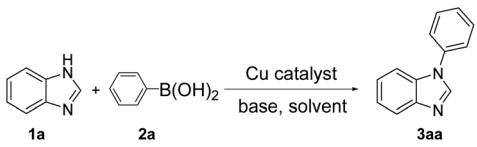


Fig. 2 Crystal structure of copper complexes (I–IV).

Table 1 Screening for optimal reaction conditions


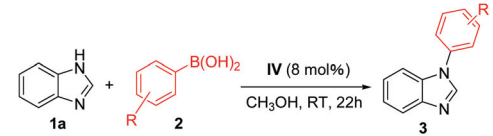
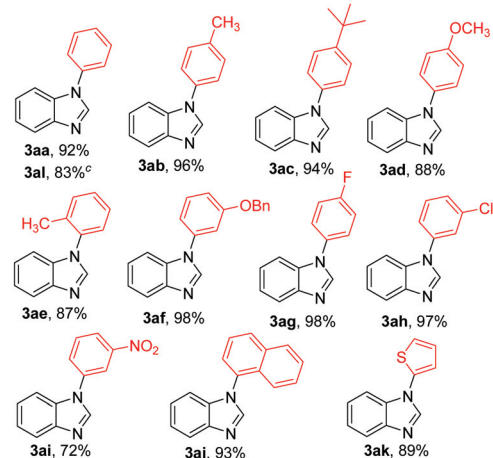
Entry ^a	Catalyst (mol%)	Solvent	T (°C)	Yield ^b (%)
1	I (8)	CH ₃ OH	RT	56(39) ^c
2	II (8)	CH ₃ OH	RT	61(75) ^c
3	III (8)	CH ₃ OH	RT	37(77) ^c
4	IV (8)	CH ₃ OH	RT	92(90) ^c
5	IV (10)	CH ₃ OH	RT	97
6	IV (5)	CH ₃ OH	RT	79
7	IV (3)	CH ₃ OH	RT	72
8	IV (1)	CH ₃ OH	RT	70
9	IV (8)	CH ₃ OH : H ₂ O = 1 : 1	RT	75
10	IV (8)	1,4-Dioxane	RT	77
11	IV (8)	DMA	RT	50
12	IV (8)	DMSO	RT	27
13	IV (8)	DMF	RT	0
14	IV (8)	CH ₃ CN	RT	0
15	IV (8)	CH ₃ OH	80	73
16	IV (8)	CH ₃ OH	100	61

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.) and Cu catalyst in solvents (1 mL) at the indicated temperature for 22 h. ^b Isolated yield. ^c K₂CO₃ was used.

5). But the yields of **3aa** were obviously decreased when the model reaction was carried out at lower catalyst loading (5 mol%, 3 mol% and 1 mol%) (entries 6–8). With respect to the cost of the catalyst, 8 mol% **IV** is the good choice of catalyst.

Subsequently, we investigated the effect of solvents and temperature on the model reaction using 8 mol% **IV** as the catalyst. When the coupling of **1a** with **2a** was performed in other different solvents (such as CH₃OH : H₂O, 1,4-dioxane, DMA, DMSO), the yields of the product (**3aa**) sharply reduced from 75% to 27% (entries 9–12). Using DMF or CH₃CN as reaction solvents, no coupling product was detected (entries 13–14). On increasing the reaction temperature (80 or 100 °C), the model reaction could take place and the lower yields were obtained (entries 15–16). As a result, the optimized conditions for copper complex-catalyzed Chan–Lam coupling reactions were identified as follows: **1a/2a** = 1 : 2, 8 mol% **IV** as the catalyst, and CH₃OH (1 mL) as the solvent at room temperature for 22 h.

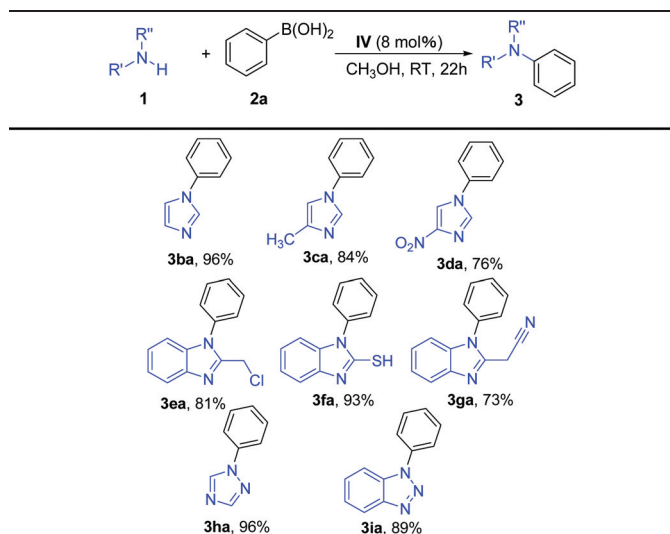
With the optimal conditions in hand, we began to explore the generality of copper-catalyzed Chan–Lam coupling of 1*H*-benzimidazole (**1a**) with different arylboronic acids. In general, all reactions smoothly took place and gave the corresponding products in excellent yields. The steric and electronic effects of substituents on the coupling reaction were observed. As shown in Table 2, arylboronic acids bearing electron-donating groups (–Me, –*t*-Bu, –OMe) at the *para* position led to the desired products in 88–96% yields. The lower yield of the product (87% for **3ae**) was obtained when *ortho*-methyl-substituted phenylboronic acid was used as the substrate. To our delight, the

Table 2 The Chan–Lam coupling reactions of 1*H*-benzimidazole (**1a**) with different arylboronic acids^{a,b}



^a Reaction condition: **1a** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), +**IV** (8 mol%), CH₃OH (1 mL), RT, 22 h. ^b Isolated yield. ^c Phenylboronic acid pinacolester (**2l**) was used as the coupling partner.

coupling reaction of 1*H*-benzimidazole (**1a**) with phenylboronic acid containing 3-benzyloxy, 4-fluoro and 3-chloro groups proceeded well, providing the desired products in almost quantitative yields (98% for **3af**, 98% for **3ag** and 97% for **3ah**; respectively). But 3-nitrophenylboronic acid (**2i**) furnished the corresponding product (**3ai**) in 72% yield. 1-Naphthylboronic acid (**2j**), 2-thiopheneboronic acid (**2k**) and phenylboronic acid pinacolester (**2l**) were proved to be good coupling partners, affording the products in good to excellent yields (93% for **3aj**; 89% for **3ak**; 83% for **3al**).

With a wide range of arylboronic acids established, we further investigated the scope of 1*H*-imidazole derivatives using phenylboronic acids (**2a**) as the coupling partner under optimal conditions. The reaction results are listed in Table 3. The coupling of 1*H*-imidazole (**1b**) with phenylboronic acids (**2a**) gave the *N*-arylated product (**3ba**) in 96% yield. When 4-methyl-1*H*-imidazole (**1c**) and 4-nitro-1*H*-imidazole (**1d**) were employed as reaction substrates, the yields of the products were slightly decreased (84% for **3ca**; 76% for **3da**), indicating that the substrate with electron-donating groups had higher activity than those with electron-withdrawing groups. We also found that the reaction regioselectively took place and provided the sole *N*1-arylated product (**3ca**, **3da**), which may be due to the steric effects of substituents (–Me, –NO₂). Next, we further studied the effect of substituents on the 1*H*-benzimidazole ring on the reactivity. 2-Chloromethyl-1*H*-benzimidazole (**1e**), 2-mercapto-1*H*-benzimidazole (**1f**) and (2-benzimidazolyl) acetonitrile (**1g**) could react with **2a** to provide the corresponding products in 73–93% yields. Importantly, 1*H*-1,2,4-tri-

Table 3 The Chan–Lam coupling reactions of phenylboronic acid (**2a**) with 1*H*-imidazole derivatives^{a,b}

^a Reaction condition: **1** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), **IV** (8 mol%), CH₃OH (1 mL), RT, and 22 h. ^b Isolated yield.

azole (**1h**) and 1*H*-benzotriazole (**1i**) also participated well in the coupling process, leading to the products **3ha** and **3ia** in excellent yields (96% and 89%, respectively). These experimental data demonstrated that this Chan–Lam coupling could tolerate different substrates with many functional groups, which may be favourable to the synthetic application of this reaction in organic synthesis.

On the basis of the related studies^{23,25} and above results, the reaction mechanism of this Chan–Lam coupling seems to follow the catalytic cycle proposed by our group.²⁴ In this process, the interaction of *N,O*-bidentate-chelated copper complexes with arylboronic acid produces aryl Cu(II) species followed by the aryl Cu(III) intermediate. Then 1*H*-imidazole derivatives as nucleophiles in place of amines react with the aryl Cu(III) intermediate to furnish the desired coupling products and copper(I) intermediate *via* reductive elimination. The catalytic cycle is completed by oxidation of the copper(I) intermediate in air and regeneration of copper(II) complexes.

Conclusions

In summary, we have described a general and efficient procedure for the well-known Chan–Lam coupling reaction of arylboronic acids with 1*H*-imidazole derivatives using *N,O*-bidentate-chelated copper(II) complexes as the catalyst under room temperature and base-free conditions. This new protocol exhibits good functional group tolerance, high yields and mild reaction conditions, which further enriches the application of the Chan–Lam coupling reaction in organic synthesis.

Experimental section

General procedure for the Chan–Lam coupling reaction of 1*H*-imidazole derivatives with arylboronic acids catalyzed by copper complexes

To a mixture of 1*H*-imidazole derivatives **1** (0.2 mmol), arylboronic acid **2** (0.4 mmol, 2.0 equiv.) and CH₃OH (1.0 mL) in a 25 mL Schlenk reaction tube was added copper complex **IV** (8 mol%). Then the reaction mixture was stirred on a parallel synthetic reactor at room temperature for 22 hours. After completion, the mixture was quenched with water (3 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic phase was concentrated. Purification of the residue were performed on GF-254 silica gel by preparative thin layer chromatography (petroleum ether/ethyl acetate = 15 : 1) to give the coupling product **3**.

Conflicts of interest

There are no conflicts of financial interest to declare.

Acknowledgements

We gratefully acknowledge financial support from Scientific and Technological Innovation Programs of Higher Education Institutions in Shanxi (2015157) and the “1331” project in Shanxi province.

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