


 Cite this: *RSC Adv.*, 2021, **11**, 18080

# Copper-catalyzed aerobic oxidative radical alkoxylation of tryptamines to access 3-alkoxypyrroloindolines†

 Wei Wang,<sup>‡a</sup> Jun-Rong Song,<sup>‡b</sup> Zhi-Yao Li,<sup>‡a</sup> Ting Zhong,<sup>b</sup> Qin Chi,<sup>b</sup> Hai Ren<sup>‡\*b</sup> and Wei-Dong Pan<sup>\*ab</sup>

 Received 6th April 2021  
 Accepted 12th May 2021

DOI: 10.1039/d1ra02679h

[rsc.li/rsc-advances](http://rsc.li/rsc-advances)

We report a copper-catalyzed alkoxylation of tryptamine derivatives with O<sub>2</sub> as the sole oxidant, leading to a variety of C3a-alkoxypyrroloindolines in good yields with high diastereoselectivities. This reaction involves an interesting double catalytic cycle in which copper-catalyzed carboamination cyclization is favored to form the C-3 radical pyrrolidinoindoline intermediate, then a copper-catalytic radical alkoxylation reaction proceeds smoothly.

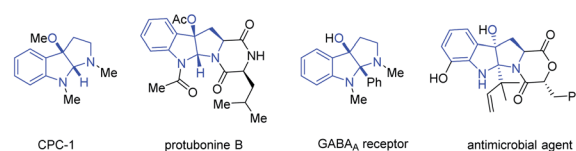
Pyrrolidino[2,3-*b*]indoline is an important heterocyclic core skeleton that exists in numerous biologically active natural products and pharmaceutical molecules.<sup>1</sup> Cyclotryptamine type molecules which are oxygenated at the C3a position are especially outstanding due to their prominent bioactivity profiles,<sup>2</sup> various applications in biological probes<sup>3</sup> and chiral catalysts.<sup>4</sup>

As direct access to these complex products, the development of C3a-oxygenation/cyclization reactions of tryptamine or tryptophan derivatives has attracted extensive interest from synthetic chemists. Recently, some remarkable efforts have contributed to the one-step assembly of 3-hydroxyl,<sup>5</sup> acetoxy,<sup>6</sup> peroxy<sup>7</sup> and other oxygenated<sup>8</sup> pyrroloindolines through oxidative cyclization of tryptophan substrates. However, by utilizing a similar strategy, the direct synthesis of 3-alkoxyl pyrroloindolines remains less developed. In 2020, Zhong *et al.*<sup>9</sup> reported the first example of alkoxylation of tryptamine derivatives using molecular iodine catalyst with *tert*-butyl hydroperoxide as the oxidant. None of the other studies, like using transition-metal catalysts, have been described yet.

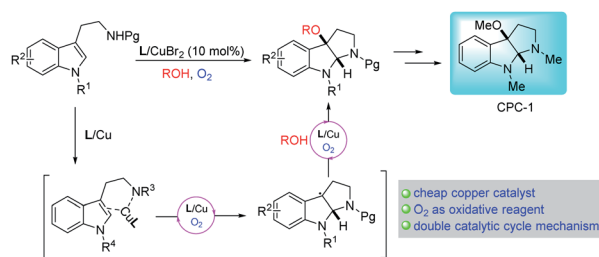
Copper salts, which are inexpensive and easily accessible, have been widely used in organic synthesis as catalysts. Copper(II)-promoted radical intramolecular carboamination of alkene has proven to be an effective means toward the synthesis of N-fused heterocycles.<sup>10</sup> Recent reports have utilized this strategy toward the cyclization and radical alkylation,

aromatization and aminoxygenation of alkene.<sup>10</sup> However, due to the difficulty in homolytic breakage of the oxygen–hydrogen bond in alcohols with a high bond dissociation energy (BDE is *ca.* 105 kcal mol<sup>-1</sup>),<sup>11</sup> the related direct cyclization and radical alkoxylation of carbon–carbon double bond with copper catalysts is still unknown. Inspired by the relevant research of copper-catalyzed radical alkoxylation reaction,<sup>12</sup> we assume that if the catalytic carboamination and radical alkoxylation tandem reaction could be realized by a single copper catalyst, which will represent as a new effective protocol for the direct construction of alkoxy-containing N-fused heterocycles. Herein, we report an oxazoline/copper-catalyzed cascade carboamination alkoxylation of substituted tryptamine under mild eco-friendly O<sub>2</sub> oxidation conditions, which facilitate the construction of the 3-

a) Selected C3-oxygenated pyrroloindolines natural products and bioactive molecules



b) This work: copper-catalyzed alkoxylation of tryptamines



**Scheme 1** Copper-catalyzed cyclization and alkoxylation of tryptamines.

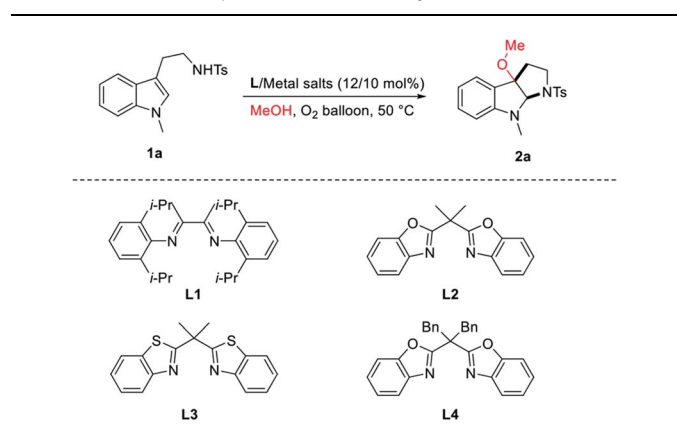
<sup>a</sup>School of Pharmaceutical Sciences, Guizhou University, Huaxi Avenue South, Guiyang 550025, P. R. China. E-mail: wdpan@163.com

<sup>b</sup>State Key Laboratory of Functions and Applications of Medicinal Plants, Guizhou Medical University, The Key Laboratory of Chemistry for Natural Products of Guizhou Province and Chinese Academy of Sciences, Guiyang 550014, China. E-mail: renh@gzcmu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra02679h

‡ These authors contributed equally to this work.



Table 1 Conditions optimization for alkoxylation<sup>a</sup>

Entry	Metal salts	Ligand	Yield <sup>b</sup> (%)	Dr <sup>c</sup>
1	CuBr <sub>2</sub>	—	38	14/1
2	CuBr <sub>2</sub>	L1	28	>20/1
3	CuBr <sub>2</sub>	L2	45	>20/1
4	CuBr <sub>2</sub>	L3	24	13/1
5	CuBr <sub>2</sub>	L4	35	8/1
6	Cu(OTf) <sub>2</sub>	L2	Trace	—
7	CuO	L2	nr	—
8	Cu(OAc) <sub>2</sub>	L2	nr	—
9	Cu(ClO <sub>4</sub> ) <sub>2</sub>	L2	nr	—
10	CuCl <sub>2</sub>	L2	15	8/1
11 <sup>d</sup>	CuBr <sub>2</sub>	L2	71	>20/1
12 <sup>d,e</sup>	CuBr <sub>2</sub>	L2	46	>20/1

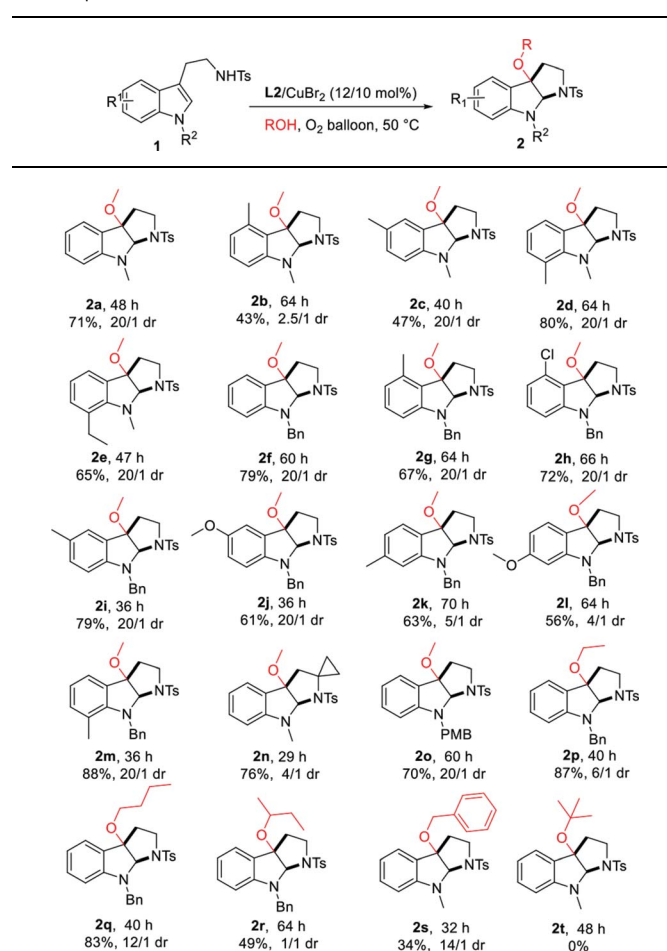
<sup>a</sup> Carried out under oxygen atmosphere: metal salt (0.02 mmol, 10 mol%), **1a** (0.2 mmol), 2 mL MeOH. <sup>b</sup> Isolated yields. <sup>c</sup> dr was determined by <sup>1</sup>H NMR. <sup>d</sup> 4 mL methanol was used. <sup>e</sup> Air atmosphere; nr: not reaction.

alkoxyl pyrroloindolines motif in good yield with good to excellent levels of diastereoselectivity (Scheme 1).

In our studies, the commercial easily available *N*-methyl tryptamine **1a** was chosen as model substrate. Initially, 10 mol% of metal salt CuBr<sub>2</sub> was used as catalyst, the 3-alkoxylation product **2a** was obtained as 38% yield with 14/1 dr (Table 1, entry 1). When the diimine ligand **L1** was added, only 28% yield of desired product was obtained (Table 1, entry 2). Interestingly, when the bisbenzoxazoline **L2**/CuBr<sub>2</sub> was used, the yield of the reaction was obtained in 45% with 20/1 dr (Table 1, entry 3). The bisbenzothiazoline **L3** and dibenzyl-modified bisbenzoxazoline **L4** failed to improve the reaction (Table 1, entries 4–5). Attempts to improve the yield by further screening of copper salts were not successful (Table 1, entries 6–10). A better result was obtained by increasing the solvent of methanol resulting in 71% yield with 20/1 dr (Table 1, entry 11). When the reaction was conducted at the air atmosphere, the yield decreased greatly (Table 1, entry 12). Therefore, the employment of **L2**/CuBr<sub>2</sub> (12/10 mol%) in 4 mL MeOH at 50 °C was selected as the optimal conditions for this reaction.

With the optimized reaction conditions in hand, we continued to investigate the substrate scope of the reaction (Table 2). Reactions of *N*-methyl substituted tryptamines that

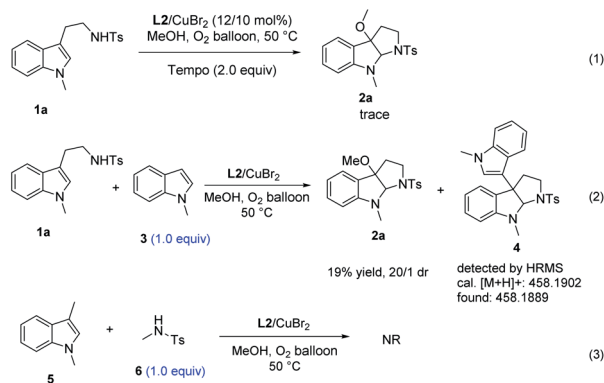
Table 2 Substrate scope of alkoxylation and concise synthesis of natural product CPC-1



#### Synthesis of natural product CPC-1



contain either a methyl or ethyl group at different positions of the indole ring proceeded smoothly to furnish the desired products **2a–e** in good to excellent yields with moderate to excellent diastereoselectivities. Notably, the *N*-Bn and *N*-PMB substituted tryptamines were also suitable substrates for this reaction, the corresponding products **2f**, **2o** were obtained in 70, 79% yields with >20/1 dr. *N*-Bn substituted substrates that contain different functional groups at different positions of the indole ring employed the reaction conditions well, affording the desired products **2g–m** in good to excellent yields with high diastereoselectivities. Furthermore, the use of other alcohols, for instance, ethanol, *n*-butanol, *sec*-butyl alcohol or benzyl alcohol allowed the cyclic alkoxylation reaction smoothly (**2p–s**). However, when the steric and bulky *tert*-butyl alcohol was employed under the optimal conditions, no trace amount of desired product was observed. The applicability of this protocol was further demonstrated by the short, rapid construction of

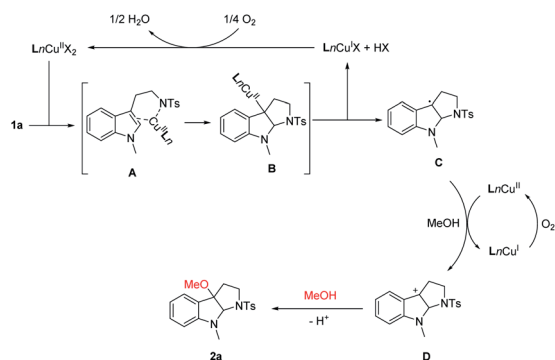


Scheme 2 Control experiments.

bio-active natural product **CPC-1** in a total yield of 54% with 4/1 dr from material **1u** (Table 2).

In order to gain insight into the mechanism of the methodology, several control experiments were carried out. As shown in Scheme 2, the radical scavenger, 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO), inhibited the alkoxy-cyclization process completely, suggesting that a radical process might be involved in this reaction (Scheme 2: eqn (1)).<sup>13</sup> When the nucleophilic substrate 1-methyl indole was involved in the standard conditions (Scheme 2: eqn (2)), trace amount of 3-indole pyrrolidinoindoline adduct **4** was detected by HRMS, suggesting that the exposed carbocation intermediate may be the precursor for the formation of the 3-alkoxylation product. Besides, the amidyl radical addition process has been ruled out by the substrate scope investigation of **1n** (Table 2) as the ring opening of cyclopropane moieties did not occur. When 1,3-dimethyl-indole (**5**) and *N*-4-dimethylbenzenesulfonamide (**6**) were involved in the standard conditions, the reaction did not take place (Scheme 2: eqn (3)), which indicated that this reaction proceeded *via* an intramolecular collaborative tandem process.

Combining with the previous reports about copper-catalyzed carboamination,<sup>10</sup> alkoxylation<sup>12</sup> of alkene, a possible reaction pathway is proposed in Scheme 3. Initially, a ligand-exchange reaction of Cu(II) species with substrate **1a** proceeds to form the chelation intermediate **A**. Subsequent nitrogen intramolecular



Scheme 3 Plausible reaction pathway.

addition-cyclization forms the C3a Cu(II) pyrrolidinoindoline intermediate **B**. Then, homolytic cleavage of carbon-Cu(II) bond to generate the Cu(I) species and C3a radical intermediate **C**. The C3a radical could be oxidized by Cu<sup>II</sup> species to generate the C3a cation intermediate **D**. Subsequent nucleophilic attack of alcohol delivers the product **2a**. Meanwhile, Cu<sup>II</sup> complex was produced *in situ* through the reaction of Ln-Cu<sup>I</sup> complex with O<sub>2</sub> on the basis of the previous reports,<sup>14</sup> completing the catalytic cycle.

In conclusion, we have successfully developed copper-catalyzed alkoxy-cyclization of tryptamine under mild O<sub>2</sub> oxidation conditions, affording C3a-alkoxylation pyrrolidinoindolines in good yields with high diastereoselectivities. This protocol was proved practicable and useful by the rapid concise total synthesis of natural product CPC-1. Mechanistic studies illustrated that the copper-catalyzed carboamination cyclization was favored to form the C-3 radical pyrrolidinoindoline intermediate, then a copper-catalyzed radical alkoxylation reaction proceeded to deliver the desired product. The extension of the present catalytic protocol to other useful reactions and biological evaluation of these products are undergoing in our laboratory.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank the NSFC (22061010), Guizhou Province Science and Technology Foundation, China (QKHJC[2019]1214), CAS “Light of West China” Program, Guizhou Provincial Thousands of Innovative and Entrepreneurial Talents program (GZQ202006080) for the financial support.

## Notes and references

- (a) C. R. Jamison, J. J. Badillo, J. M. Lipshultz, R. J. Comito and D. W. C. MacMillan, *Nat. Chem.*, 2017, **9**, 1165–1169; (b) F. L. Cherblanc, K. L. Chapman, J. Reid, A. J. Borg, S. Sundriyal, L. Alcazar-Fuoli, E. Bignell, M. Demetriades, C. J. Schofield, P. A. DiMaggio Jr, R. Brown and M. J. Fuchter, *J. Med. Chem.*, 2013, **56**, 8616–8625; (c) S. Tadano, Y. Sugimachi, M. Sumimoto, S. Tsukamoto and H. Ishikawa, *Chem*, 2016, **22**, 1277–1291; (d) F.-Q. Wang, Q.-Y. Tong, H.-R. Ma, H.-F. Xu, S. Hu, W. Ma, Y.-B. Xue, J.-J. Liu, J.-P. Wang, H.-P. Song, J.-W. Zhang, G. Zhang and Y.-H. Zhang, *Sci. Rep.*, 2015, **5**, 9294.
- (a) J. Han, S.-T. Niu, Y. Liu, L. Gan, T. Wang, C.-D. Lu and T. Yuan, *Org. Chem. Front.*, 2018, **5**, 586–589; (b) A. E. M. Blom, J. Y. Su, L. M. Repka, S. E. Reisman and D. A. Dougherty, *ACS Med. Chem. Lett.*, 2020, **11**, 2204–2211; (c) U. L. Sang, Y. Asami, D. Lee, J. H. Jang, J. S. Ahn and H. Oh, *J. Nat. Prod.*, 2011, **74**, 1284–1287; (d) J. Xu and R. Tong, *Green Chem.*, 2017, **19**, 2952–2956.
- (a) S. Lepthien, M. G. Hoesl, L. Merkel and N. Budisa, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 16095–16100; (b)

- W. Zhong, J. P. Gallivan, Y. Zhang, L. Li, H. A. Lester and D. A. Dougherty, *Proc. Natl. Acad. Sci. U. S. A.*, 1998, **95**, 12088–12093.
- 4 K. Ishihara, M. Fushimi and M. Akakura, *Acc. Chem. Res.*, 2007, **40**, 1049–1055.
- 5 (a) X. Deng, K. Liang, X. Tong, M. Ding, D. Li and C. Xia, *Org. Lett.*, 2014, **16**, 3276–3279; (b) Z.-J. Liu and P.-Q. Huang, *J. Org. Chem.*, 2019, **84**, 5627–5634.
- 6 (a) D. Tu, L. Ma, X. Tong, X. Deng and C. Xia, *Org. Lett.*, 2012, **14**, 4830–4833; (b) M. Z. Wang, T. X. Si, C. F. Ku, H. J. Zhang, Z. M. Li and A. S. Chan, *J. Org. Chem.*, 2018, **84**, 831–839.
- 7 X. Lu, Y. Bai, Y. Li, Y. Shi, L. Li, Y. Wu and F. Zhong, *Org. Lett.*, 2018, **20**, 7937–7941.
- 8 (a) W. Yang, L. Huang, Y. Yu, D. Pflästerer, F. Rominger and A. S. K. Hashmi, *Chem.–Eur. J.*, 2014, **20**, 3927–3931; (b) E. C. Gentry, L. J. Rono, M. E. Hale, R. Matsuura and R. R. Knowles, *J. Am. Chem. Soc.*, 2018, **140**, 3394–3402; (c) K. Liang, X. Tong, T. Li, B. Shi, H. Wang, P. Yan and C. Xia, *J. Org. Chem.*, 2018, **83**, 10948–10958.
- 9 Y. Li, J. Guo, X. Lu and F. Zhong, *Org. Biomol. Chem.*, 2020, **18**, 32–35.
- 10 Selected examples: (a) E. S. Sherman, P. H. Fuller, D. Kasi and S. R. Chemler, *J. Org. Chem.*, 2007, **72**, 3896–3905; (b) W. Zeng and S. R. Chemler, *J. Am. Chem. Soc.*, 2007, **129**, 12948–12949; (c) T. W. Liwosz and S. R. Chemler, *J. Am. Chem. Soc.*, 2012, **134**, 2020–2023; (d) C. Qi, F. Hasenmaile, V. Gandon and D. Leboeuf, *ACS Catal.*, 2018, **8**, 1734–1739; (e) P. Shi, J. Wang, Z. Gan, J. Zhang, R. Zeng and Y. Zhao, *Chem. Commun.*, 2019, **55**, 10523; (f) T. Wdowik, S. L. Galster, R. L. L. Carmo and S. R. Chemler, *ACS Catal.*, 2020, **10**, 8535–8541.
- 11 (a) K. Jia and Y. Chen, *Chem. Commun.*, 2018, **54**, 6105–6112; (b) X. Wu, M. Wang, L. Huan, D. Wang, J. Wang and C. Zhu, *Angew. Chem., Int. Ed.*, 2018, **57**, 1640–1644; (c) H. Ren, J.-R. Song, Z.-Y. Li and W.-D. Pan, *Org. Lett.*, 2019, **21**, 6774–6778.
- 12 (a) H. Yi, X. Zhang, C. Qin, Z. Liao, J. Liu and A. Lei, *Adv. Synth. Catal.*, 2014, **356**, 2873–2877; (b) X. Gao, X. Pan, J. Gao, H. Jiang, G. Yuan and Y. Li, *Org. Lett.*, 2015, **17**, 1038–1041; (c) Z. Liao, H. Yi, Z. Li, C. Fan, X. Zhang, J. Liu, Z. Deng and A. Lei, *Chem.–Asian J.*, 2015, **10**, 96–99; (d) C. Chatalova-Sazepin, Q. Wang, G. M. Sammis and J. Zhu, *Angew. Chem., Int. Ed.*, 2015, **54**, 5443–5446.
- 13 M. Wada, T. Murata, H. Oikawa and H. Oguri, *Org. Biomol. Chem.*, 2014, **12**, 298–306.
- 14 (a) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas and S. S. Stahl, *J. Am. Chem. Soc.*, 2010, **132**, 12068–12073; (b) C. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 6174–6177; (c) Q. Li, Y. Huang, T. Chen, Y. Zhou, Q. Xu, S.-F. Yin and L.-B. Han, *Org. Lett.*, 2014, **16**, 3672–3675; (d) I. E. Markó, P. R. Giles, M. Tsukazaki, S. M. Brown and C. J. Urch, *Science*, 1996, **274**, 2044–2046; (e) M. Taki, S. Teramae, S. Nagatomo, Y. Tachi, T. Kitagawa, S. Itoh and S. Fukuzumi, *J. Am. Chem. Soc.*, 2002, **124**, 6367–6377.