Tetrahedron Letters 53 (2012) 7121-7124

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

New ligands for copper-catalyzed C–N coupling reactions with aryl halides

Dong Chen^{a,b,†}, Kai Yang^{b,†}, Hua Xiang^{a,*}, Sheng Jiang^{b,*}

^a Department of Medicinal Chemistry, College of Pharmacy, China Pharmaceutical University, Nanjing 210009, China
^b Laboratory of Regenerative Biology, Guangzhou Institute of Biomedicine and Health, CAS, Guangzhou 510530, China

ARTICLE INFO

Article history: Received 27 August 2012 Revised 15 October 2012 Accepted 18 October 2012 Available online 26 October 2012

Keywords: C-N coupling reactions Copper Cross-coupling 2-Carbomethoxy-3-hydroxyquinoxaline-di-N-oxide Ullmann reactions

ABSTRACT

2-Carbomethoxy-3-hydroxyquinoxaline-di-*N*-oxide was identified as an efficient novel ligand for the copper-catalyzed coupling reactions of aryl iodides, bromides, and chlorides with aliphatic amines and N-containing heterocycles under mild conditions. The catalytic system showed great functional-group tolerance and excellent chemoselectivity.

© 2012 Elsevier Ltd. All rights reserved.

etrahedro

Since their discovery 100 years ago, Ullmann-type N-arylations, as important tools for modern organic synthesis, have been involved in a wide variety of natural product syntheses and numerous industrial applications, such as the syntheses of intermediates and synthetic targets in the life science and polymer industries.¹ Ligand identification is important in improving reaction efficiency and generality during the development of copper-catalyzed Ullmann coupling reaction. Several classes of coordination ligands, such as diols,² bisamines,³ amino acids,⁴ amino alcohols,⁵ phosphoramidites,⁶ oxime-phosphine oxides,⁷ 8-hydroxyquinolin-*N*oxide,⁸ and β -diketones and β -keto esters,⁹ have been recently reported to promote the copper-catalyzed Ullmann C–N coupling reaction.¹⁰ However, significant challenges remain to be overcome in this area. For example, the use of aryl chlorides is desirable in Ullmann C–N coupling reactions to reduce costs, but most ligands fail to catalyze the reactions involving aryl chloride.

The copper-catalyzed coupling of both aliphatic amines and Ncontaining heterocycles with aryl chlorides is quite difficult because of the need for harsh reaction conditions, limited range of suitable substrates, low selectivity, and only moderate yields.¹¹ To the best of our knowledge, only one ligand can be used to promote copper-catalyzed N-arylations with aryl chlorides in crosscoupling reactions.⁸ Thus, identification of new and general ligands for copper-catalyzed cross-coupling reactions of aryl chlorides is necessary.

We presumed that 2-carbomethoxy-3-hydroxyquinoxaline-di-*N*-oxide (**L1**) might form transitional 6-membered and 5-membered rings with the Cu ion (Fig. 1). In this study, 2-carbomethoxy-3-hydroxyquinoxaline-di-*N*-oxide (**L1**) was designed as a novel potential tetradentate ligand to improve Cu-catalyzed C–N bond forming reactions of aryl halides with aliphatic amines and N-heterocyclic substrates.

The reaction of benzylamine with 4-methyl iodobenzene was initially chosen as a model reaction for the reaction condition optimization, as described in Table 1. 2-Carbomethoxy-3-hydroxyquinoxaline-di-*N*-oxide (**L1**) can successfully promote the Cucatalyzed coupling reaction with high yield (83%). Interestingly, 2-carbomethoxy-3-hydroxyquinoxaline (**L2**) showed much lower efficiency due to the absence of two oxygen atoms (entry 1). After evaluation of the catalytic efficiency of **L1** and **L2**, several bases were screened using the same model substrates and supporting ligand; cesium carbonate (Cs₂CO₃) exhibited the best result among





^{*} Corresponding authors. Tel.: +86 20 32015318; fax: +86 20 32290439. *E-mail addresses*: cpuxianghua@sina.com (H. Xiang), jiang_sheng@gibh.ac.cn (S. Jiang).

[†] These authors contributed equally to the work.

^{0040-4039/\$ -} see front matter \circledast 2012 Elsevier Ltd. All rights reserved. http://dx.doi.org/10.1016/j.tetlet.2012.10.083

7122

Table 1

Designed ligands for the copper-catalyzed C-N coupling reaction ^a



Entry	Ligand	Base	Solvent	Yield (%) ^b
1	L2	Cs ₂ CO ₃	DMF	52
2	L1	Cs ₂ CO ₃	DMF	83
4	L1	K ₂ CO ₃	DMF	39
5	L1	NEt ₃	DMF	7
6	L1	K ₃ PO ₄	DMF	28
7	L1	Cs ₂ CO ₃	DMSO	69

 a Compound **1a** (1.0 mmol), **2a** (1.5 mmol), 10 mol % Cul, 20 mol % ligand, base (2.0 mmol), solvent (2 mL), Ar, 65 °C, 12 h. b Isolated yield.

Table 2

Cul-Catalyzed Amination of Aryl lodides



^a Reaction conditions: ArI (1.0 mmol), amine (1.5 mmol), CuI (0.10 mmol, 10 mol %), and L2 (0.2 mmol, 20 mol %) in 2.0 mL of DMF at 65 °C under argon.

^b Isolated yield.

the various bases tested (entries 2-5). Thus, the following optimized reaction conditions were used: 10 mol % of Cu(I), 20 mol %

of **L1**, and 2.0 equiv of Cs_2CO_3 in 0.5 M DMF (as a solvent) under an argon atmosphere.



CuBr-catalyzed amination of aryl bromides^a



^a Reaction conditions: ArBr (1.0 mmol), amine (1.5 mmol), Cul (0.10 mmol, 10 mol %), and **L2** (0.2 mmol, 20 mol %) in 2.0 mL of DMF at 90 °C under argon. ^b Isolated yield.

The Cul/L1 catalyst system was explored under optimum conditions. Table 2 shows that the coupling reactions performed well for most substrates examined, with 78-97% yields at 65 °C. Both electron-rich and electron-deficient aryl iodides are suitable substrates for this reaction, showing similar reactivities. The reaction conditions for the coupling of aryl iodides and primary amines were extended and excellent yields (78-92%) were obtained in all cases (entries 1-4). The coupling of more hindered cyclic secondary amines, such as pyrrolidine, piperidine, and morpholine, also yielded satisfactory yields (80-83%) (entries 7 and 8). The catalyst system also showed high selectivity in the presence of multiple potentially reactive groups, which favors its potential application in the synthesis of complex molecules (entries 5 and 6). The Cul/L1 catalyst system was successfully applied in the coupling of aryl iodides with indole, with a 97% isolated yield (entry 9). Moreover, the coupling of aryl iodides with amino acid was also accomplished with high yields under the same condition (entries 10 and 11).

Extension of this amination process to aryl bromide substrates showed promising results. Table 3 shows that all examined aryl bromides coupled with primary, cyclic secondary amines, or nitrogen-containing heterocycles exhibited excellent yields at 90 °C. The reaction occurred selectively at the alkylamine when several reactive functional groups were present (entries 5 and 6). Table 4 shows that the coupling reactions for most of the substrates examined gave 51–82% yields at 115 °C. Optimized reaction conditions were applied to the coupling of aryl chlorides and primary amines, achieving good yields (51–81%) in all cases (entries 1–4). The coupling of amino acids, such as valine, with aryl chlorides also achieved excellent yields (71%) (entry 5). The catalyst system showed high selectivity in the presence of multiple potentially reactive groups, which is highly desirable in the synthesis of complex molecules (entry 6). The N-arylation of nitrogen containing heterocycles, such as pyrrole, 1*H*-benzimidazole, and indole, also achieved high yields using the Cul/L1 catalyst system (entries 7–10).

In summary, 2-carbomethoxy-3-hydroxyquinoxaline-di-*N*oxide was identified as an efficient ligand for copper-catalyzed C-N coupling reactions. To the best of our knowledge, the present catalytic system for copper-catalyzed N- and O-arylations with aryl chlorides in cross-coupling reactions is unprecedented. Our inexpensive catalytic system showed great functional group tolerance and high selectivity in the presence of multiple potentially reactive groups at moderate temperature. Efforts to extend the application of this ligand system for other types of copper-catalyzed coupling reactions are currently underway in our laboratory and will be reported in due course. Moreover, the methodology for designing new ligands, as reported in this study, will be applied in other reactions.

Table 4

Copper-catalyzed amination of aryl chlorides^a



^a Reaction conditions: ArCl (1.0 mmol), amine (1.5 mmol), Cul (0.10 mmol, 10 mol %), and L1 (0.2 mmol, 20 mol %) in 2.0 mL of DMF at 115 °C under argon. ^b Isolated yield.

° 130 °C.

Acknowledgment

We gratefully acknowledge the National Natural Science Foundation (Grant Nos. 20972160 and 21172220), the National Basic Research Program of China (Grant No. 2009CB940900), and the CSA-Guangdong Joint Foundation (Grant No. 2011B090300069) for their financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012. 10.083.

References and notes

- For recent reviews see: (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Chem. Rev. 2002, 102, 1359; (b) Thomas, A. W.; Ley, S. V. Angew. Chem., Int. Ed. 2003, 42, 5400–5449; (c) Evano, G.; Blanchard, N.; Toumi, M. Chem. Rev. 2008, 108, 3054–3131; (d) Evano, G.; Toumib, M.; Costea, A. Chem. Commun. 2009, 4166.
- (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. Org. Lett. 2002, 4, 581; (b) Job, G. E.; Buchwald, S. L. Org. Lett. 2002, 4, 3703.
- (a) Antila, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. J. Org. Chem. 2004, 69, 5578;
 (b) Klapars, A.; Antila, J. C.; Huang, X.; Buchwald, S. L. J. Am. Chem. Soc. 2001, 123, 7727;
 (c) Klapars, A.; Huang, X.; Buchwald, S. L. J. Am. Chem. Soc. 2002, 124, 7421.

- (a) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. J. Am. Chem. Soc. **1998**, 120, 12459;
 (b) Zhang, H.; Cai, Q.; Ma, D. J. Org. Chem. **2005**, 70, 5164; (c) Ma, D.; Cai, Q.;
 Zhang, H. Org. Lett. **2003**, 5, 2453; (d) Kim, J.; Chang, S. Chem. Commun. **2008**, 3052.
- (a) Lu, Z.; Twieg, R. J.; Huang, S. D. Tetrahedron Lett. 2003, 44, 6289; (b) Lu, Z.; Twieg, R. J. Tetrahedron 2005, 61, 903.
- Zhang, Z.; Mao, J.; Zhu, D.; Wu, F.; Chen, H.; Wan, B. *Tetrahedron* **2006**, *62*, 4435.
 (a) Xu, L.; Mao, J.; Zhu, D.; Wu, F.; Wang, R.; Wan, B. *Tetrahedron* **2006**, *61*, 6553;
- (b) Zhu, D.; Xu, L.; Wu, F.; Wan, B. Tetrahedron Lett. 2006, 47, 5781.
 8. (a) Yang, K.; Qiu, Y.; Li, Z.; Wang, Z.; Jiang, S. J. Org. Chem. 2011, 76, 3151; (b)
- Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. Org. Lett. **2011**, *13*, 4340; (c) Qiu, Y.; Liu, Y.; Yang, K.; Hong, W.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. Org. Lett. **2011**, *13*, 4340; (c) Qiu, Y.; Liu, Y.; Yang, K.; Hong, W.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. Org. Lett. **2011**, *13*, 3556.
- (a) Shafir, A.; Buchwald, S. L. J. Am. Chem. Soc. 2006, 128, 8742; (b) de Lange, B.; Lambers-Verstappen, M. H.; de Vondervoort, L. S.; Sereinig, N.; de Rijk, R.; de Vries, A. H. M.; de Vries, J. G. Synlett 2006, 3105; (c) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. J. Am. Chem. Soc. 2007, 129, 3490; (d) Xia, N.; Taillefer, M. Angew. Chem., Int. Ed. 2009, 48, 337.
- For other ligands on Cu-catalyzed C-N coupling, see: (a) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791; (b) Gajare, A. S.; Toyota, K.; Yoshifuji, M.; Ozawa, F. *Chem. Commun.* **1994**, 2004; (c) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672; (d) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.-Eur. J.* **2006**, *12*, 3636; (e) Wang, H.; Li, Y.; Sun, F.; Feng, Y.; Jin, K.; Wang, X. *J. Org. Chem.* **2008**, *73*, 8639; (f) Suresh, P.; Pitchumani, K. *J. Org. Chem.* **2008**, *73*, 9121; (g) Jones, K. L.; Porzelle, A.; Hall, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2008**, *10*, 797; (h) Ntaganda, R.; Dhudshia, B.; Macdonald, C. L. B.; Thadani, A. N. *Chem. Commun.* **2008**, 6200; (i) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem.-Eur. J.* **2004**, *10*, 5607.
- (a) Monnier, F.; Taillefer, M. Angew. Chem., Int. Ed. 2008, 47, 3096–3099; (b) Monnier, F.; Taillefer, M. Angew. Chem., Int. Ed. 2009, 48, 6954.