Copper-catalyzed aerobic oxidative synthesis of aromatic carboxylic acids†

Daoshan Yang, Haijun Yang and Hua Fu*

Received 9th October 2010, Accepted 22nd November 2010
DOI: 10.1039/c0cc04319b

A simple, practical and efficient copper-catalyzed method for synthesis of aromatic carboxylic acids has been developed. The protocol uses inexpensive CuI/L-proline as the catalyst/ligand, and readily available aryl halides and malononitrile as the starting materials, and the corresponding aromatic carboxylic acids were obtained in moderate to good yields. The method is of tolerance towards functional groups in the substrates.

Aromatic carboxylic acids and their derivatives are ubiquitous in the world.[1] Oxidation of various substituted arenes is a common strategy for synthesis of aromatic carboxylic acids. The traditional methods include oxidation of alkyl arenes,[2] aryl alcohols[3] and aldehydes,[4] oxidative cleavage of aromatic alkenes,[5] alkynes,[5a,b,6] diols,[7] and diketones,[8] and these oxidative protocols are often incompatible with many functional groups because of the participation of special oxidants. The reactions of arylmetallic reagents with carbon dioxide that lead to aromatic carboxylic acids have attracted much attention. Grignard[9] and organolithium reagents[10] are strong nucleophiles that react with CO_2 directly to form valuable carboxylic acids and their derivatives. However, their poor functional group compatibility ultimately limits their use. Recently, transition metal-catalyzed carboxylation of arylzinc[11] and arylboron compounds[12] with CO_2 has made great progress, and these methods provided a new access to various functionalized aromatic carboxylic acids. However, the expensive arylzinc and arylboron reagents need previous preparation or are purchased. Obviously, the direct carboxylation of readily available aryl halides is an appealing approach to aromatic carboxylic acids. Mild palladium-catalyzed carboxylation of haloarenes with CO has been developed, and reaction efficiency highly depends on the expensive catalysts and ligands.[13] Considering the ready availability and low toxicity of copper-catalysts and their ligands,[14] the development of a cheaper copper-catalyst system enabling easy carboxylation of aryl halides has become an important goal to us. In continuation of our endeavors to develop copper-catalyzed cross couplings,[15] herein we report a simple, practical and efficient copper-catalyzed one-pot synthesis of aromatic carboxylic acids from aryl halides and malononitrile *via* sequential Ullmann-type coupling, aerobic oxidation and hydrolysis.

Before, Muria reported that the couplings of aryl halides with malononitrile under nitrogen atmosphere provided the corresponding *C*-arylation products (Fig. 1, eqn (1)). Here, we want to investigate cascade reactions of the two substrates to give the aromatic carboxylic acids under air (Fig. 1, eqn (2)).

At first, 1-iodo-4-methylbenzene was chosen as the model substrate to optimize reaction conditions including carbon sources (C sources), catalysts, ligands, bases and solvents. As shown in Table 1, four C sources (2 equiv.) were tested in DMSO at 140 °C under air applying 20 mol% of CuI as the catalyst, 20 mol% of L-proline as the ligand and 2 equiv. of Cs_2CO_3 as the base (relative to the amount of 1-iodo-4-methylbenzene) (entries 1–4), and malononitrile provided 4-methylbenzoic acid in the highest yield (55%) after 48 h reaction (entry 1). K_2CO_3 (entry 5) and K_3PO_4 (entry 6) were used as the bases, and they showed weaker activity than Cs_2CO_3. Other ligands were also investigated (entries 7–11), and L-proline gave the highest yield (entry 1). The cascade reaction provided 4-methylbenzoic acid in 42% yield in the absence of ligand (entry 12). Copper salts, CuBr and $CuCl_2$, were screened (entries 13 and 14), and CuI was proven to be a better choice (entry 1). A lower yield was provided when DMF replaced DMSO as the solvent (entry 15). We attempted one-pot two-step reactions of 1-iodo-4-methylbenzene with malononitrile as follows: the Ullmann-type coupling of 1-iodo-4-methylbenzene with malononitrile (entry 16), ethyl 2-cyanoacetate (entry 17) or diethyl malonate (entry 18) firstly produced the corresponding *C*-arylation product at 130 °C under nitrogen atmosphere for 24 h, and then an aerobic oxidation process was performed at 140 °C under air for 12 h (see Schemes 1 and 2). The one-pot two-step strategy provided the target product in slightly higher yields (compare entries 1–3 and 16–18), and the results showed that malononitrile was the best C source (entry 16). Addition of extra water led to lower yields (entries 19 and 20), and one possible reason was that malononitrile could be hydrolyzed before *C*-arylation.

The scope of copper-catalyzed carboxylation of aryl halides was investigated under two optimized conditions (Method A: using 20 mol% of CuI as the catalyst, 20 mmol% of L-proline

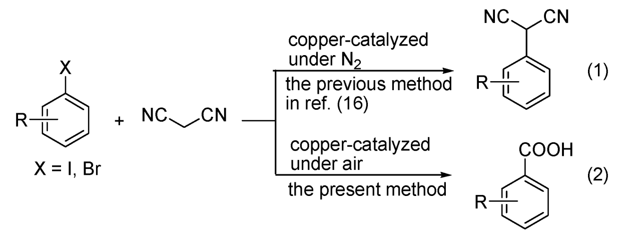


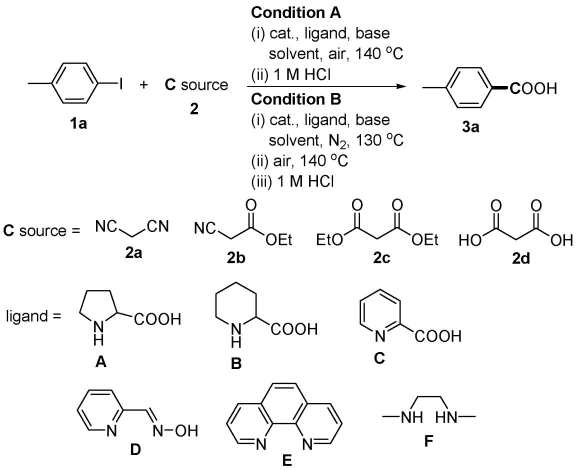
Fig. 1 Reactions of aryl halides with malononitrile under N_2 or air.

---

*Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China.
E-mail: fuhua@mail.tsinghua.edu.cn; Fax: +86 10 62781695; Tel: +86 10 62797186*

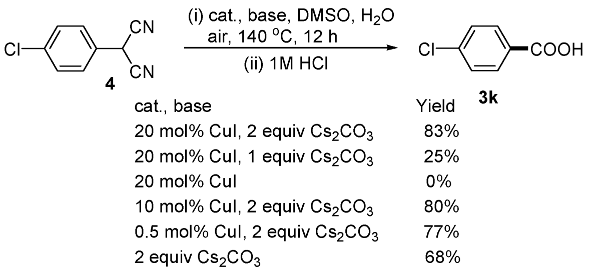
† Electronic supplementary information (ESI) available: General procedure for synthesis of compounds **3a–u**, characterization data for compounds **3a–u**, and ^1H and ^{13}C NMR spectra of compounds **3a–u**. See DOI: 10.1039/c0cc04319b

Table 1 Copper-catalyzed synthesis of 4-methylbenzoic acid *via* coupling of 1-iodo-4-methylbenzene with malononitrile followed by aerobic oxidation and hydrolysis: optimization of conditions[a]



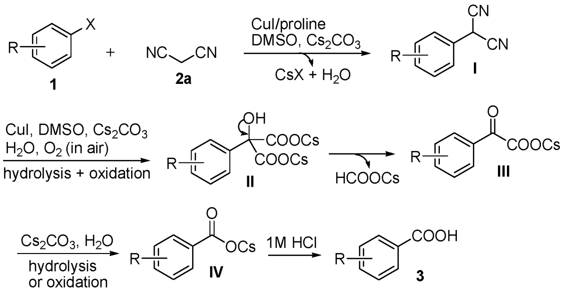
Entry	2	Cat.	L	Base	Solvent	Yield[d] (%)
1[b]	**2a**	**CuI**	**A**	**Cs_2CO_3**	**DMSO**	**55**
2[b]	**2b**	CuI	A	Cs_2CO_3	DMSO	44
3[b]	**2c**	CuI	A	Cs_2CO_3	DMSO	37
4[b]	**2d**	CuI	A	Cs_2CO_3	DMSO	0
5[b]	**2a**	CuI	A	K_2CO_3	DMSO	49
6[b]	**2a**	CuI	A	K_3PO_4	DMSO	46
7[b]	**2a**	CuI	B	Cs_2CO_3	DMSO	51
8[b]	**2a**	CuI	C	Cs_2CO_3	DMSO	53
9[b]	**2a**	CuI	D	Cs_2CO_3	DMSO	39
10[b]	**2a**	CuI	E	Cs_2CO_3	DMSO	52
11[b]	**2a**	CuI	F	Cs_2CO_3	DMSO	43
12[b]	**2a**	CuI	—	Cs_2CO_3	DMSO	42
13[b]	**2a**	CuBr	A	Cs_2CO_3	DMSO	52
14[b]	**2a**	$CuCl_2$	A	Cs_2CO_3	DMSO	47
15[b]	**2a**	CuI	A	Cs_2CO_3	DMF	45
16[c]	**2a**	**CuI**	**A**	**Cs_2CO_3**	**DMSO**	**61**
17[c]	**2b**	CuI	A	Cs_2CO_3	DMSO	47
18[c]	**2c**	CuI	A	Cs_2CO_3	DMSO	41
19[c]	**2a**	CuI	A	Cs_2CO_3	DMSO	54[e]
20[c]	**2a**	CuI	A	Cs_2CO_3	DMSO	50[f]

[a] Reaction conditions: 1-iodo-4-methylbenzene (1 mmol), catalyst (0.2 mmol), ligand (0.2 mmol), **2** (2 mmol), base (2 mmol), solvent (2 mL). [b] Condition A: reaction temperature (140 °C) in a sealed Schlenk tube with an air balloon (1 atm.). Reaction time (48 h). [c] Condition B: reacted 24 h at 130 °C in a sealed Schlenk tube with an N_2 balloon (1 atm.), and then reacted for 12 h at 140 °C under air. [d] Isolated yield. [e] Addition of 1 equiv. of water. [f] Addition of 2 equiv. of water.



cat., base	Yield
20 mol% CuI, 2 equiv Cs_2CO_3	83%
20 mol% CuI, 1 equiv Cs_2CO_3	25%
20 mol% CuI	0%
10 mol% CuI, 2 equiv Cs_2CO_3	80%
0.5 mol% CuI, 2 equiv Cs_2CO_3	77%
2 equiv Cs_2CO_3	68%

Scheme 1 Investigation on effect of catalyst and base for synthesis of aromatic carboxylic acids.



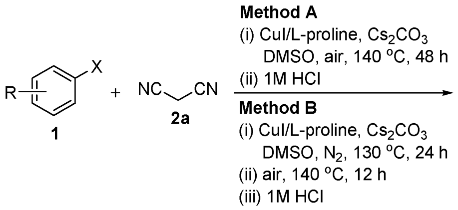
Scheme 2 Possible reaction mechanism for synthesis of aromatic carboxylic acids.

as the ligand, 2 or 3 equiv. of Cs_2CO_3 as the base and DMSO as the solvent at 140 °C under air; Method B: using 20 mol% of CuI as the catalyst, 20 mmol% of L-proline as the ligand, 2 or 3 equiv. of Cs_2CO_3 as the base and DMSO as the solvent. The first step reaction was performed at 130 °C for 24 h under nitrogen atmosphere, and the second step reaction was carried out at 140 °C for 12 h under air). As shown in Table 2, the examined substrates provided the corresponding aromatic carboxylic acids in moderate to good yields. Method B provided slightly higher yields than Method A, and a possible reason is that the copper-catalyzed Ullmann-type couplings of aryl halides with malononitrile are more efficient under nitrogen atmosphere (see reaction mechanism in Scheme 2). However, the experimental procedure of Method A was more convenient. For the aryl halides, the substrates containing electron-withdrawing groups showed higher reactivity than ones containing electron-donating groups, and the aryl iodides provided higher yields than the aryl bromides. Alkyl groups on aromatic rings were not oxidized although the cascade reactions underwent oxidation process during the formation of the aromatic carboxylic acids (see reaction mechanism in Scheme 2). The carboxylation of the aryl halides could tolerate various functional groups including ether, C–Cl bond, C–Br bond, CF_3 group, carboxyl and heterocycle.

In order to explore the carboxylation mechanism of aryl halides, the following control experiments were performed under our standard condition as shown in Scheme 1. Affect of the copper-catalyst and base was investigated in DMSO (with trace amount of water) under air at 140 °C for synthesis of 4-chlorobenzoic acid (**3k**) from 2-(4-chlorophenyl) malononitrile (**4**). Treatment of **4** provided **3k** in 83% yield in the presence of 0.2 equiv. of CuI and 2 equiv. of Cs_2CO_3, and product **3k** was obtained in 68% yield in the absence of CuI. Yields greatly decreased with reduction of Cs_2CO_3, however, amount of CuI showed insensitivity. A possible mechanism for the carboxylation of aryl halides was suggested as shown in Scheme 2. First, aryl halide and malononitrile undergoes Ullmann-type coupling to give the *C*-arylation product (**I**),[16] then hydrolysis of CN[17] and oxidization of tertiary C–H in **I** by oxygen in air in the presence of base (Cs_2CO_3) provides **II**, and desorption of HCOOCs in **II** transfers into **III**. Hydrolysis or oxidization of **III** by oxygen in air affords **IV** in base medium, and acidification of **IV** with 1 M HCl gives the target product (**3**).

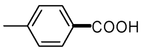
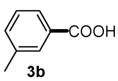
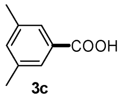
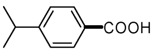
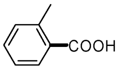
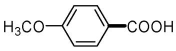
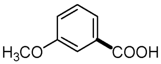
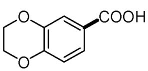
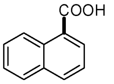
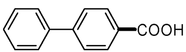
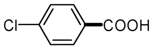
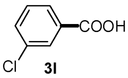
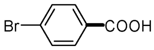
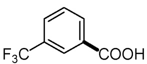
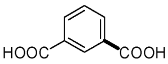
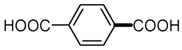
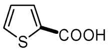
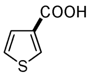
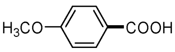
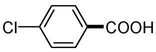
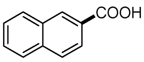
In summary, we have developed an efficient copper-catalyzed method for synthesis of aromatic carboxylic acids. The protocol uses inexpensive CuI/L-proline as the catalyst/ligand, and readily available aryl halides and malononitrile as the starting materials, the cascade reactions underwent sequential Ullmann-type coupling, aerobic oxidation and hydrolysis, and the corresponding aromatic carboxylic acids

Table 2 Copper-catalyzed synthesis of aromatic carboxylic acids[a]



Method A
(i) CuI/L-proline, Cs_2CO_3
DMSO, air, 140 °C, 48 h
(ii) 1M HCl

Method B
(i) CuI/L-proline, Cs_2CO_3
DMSO, N_2, 130 °C, 24 h
(ii) air, 140 °C, 12 h
(iii) 1M HCl

 **3a** X = I, 55% (61%)	 **3b** X = I, 50% (63%)	 **3c** X = I, 47% (60%)
 **3d** X = I, 60% (65%)	 **3e** X = I, (55%)	 **3f** X = I, 44% (51%)
 **3g** X = I, 51% (58%)	 **3h** X = I, (53%)	 **3i** X = I, 50% (54%)
 **3j** X = I, 64% (70%)	 **3k** X = I, 62% (73%)	 **3l** X = I, 59% (66%)
 **3m** X = I, (45%)	 **3n** X = I, (52%)	 **3o** X = I, 61% (70%)
 **3p** X = I, 65% (74%)	 **3q** X = I, (55%)	 **3r** X = I, (37%)
 **3s** X = Br, (48%)	 **3t** X = Br, (51%)	 **3u** X = Br, (44%)

[a] Reaction conditions: aryl halide (1 mmol), CuI (0.2 mmol), L-proline (0.2 mmol), malononitrile (2 mmol), Cs_2CO_3 (3 mmol for **3o** and **3p**, 2 mmol for others), DMSO (2 mL). For Method A, reaction temperature (140 °C) in a Schlenk tube with an air balloon (1 atm.). Reaction time (48 h). For Method B, 24 h at 130 °C in a sealed Schlenk tube under nitrogen atmosphere, and then 12 h at 140 °C under air. Isolated yield from Method A (the data in parentheses are the isolated yields from Method B).

were obtained in moderate to good yields. The method is of tolerance towards various functional groups in the substrates, and the synthesis of the aromatic carboxylic acids will attract much attention in industrial and academic researches because of their wide application in various fields.

Financial support was provided by the National Natural Science Foundation of China (Grant No. 20972083), the Ministry of Science and Technology of China (2009ZX09501-004) and the Key Subject Foundation from Beijing Department of Education (XK100030514).

Notes and references

1 (*a*) V. Karlson and R. D. Schmid, *Anal. Lett.*, 1994, **27**, 285; (*b*) P. T. Palade and R. L. Barchi, *J. Gen. Physiol.*, 1977, **69**, 879; (*c*) E. L. Larghi, M. A. Operto, R. Torres and T. S. Kaufman, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6172; (*d*) I. Navarro, C. Pöverlein, G. Schlingmann and A. G. M. Barrett, *J. Org. Chem.*, 2009, **74**, 8139.

2 (*a*) J. Fraga-Dubreuil, E. Garcia-Verdugo, P. A. Hamley, E. M. Vaquero, L. M. Dudd, I. Pearson, D. Housley, W. Partenheimer, W. B. Thomas, K. Whiston and M. Poliakoff, *Green Chem.*, 2007, **9**, 1238; (*b*) M. Gupta, S. Paul, R. Gupta and A. Loupy, *Tetrahedron Lett.*, 2005, **46**, 4957.

3 (*a*) G. Barak, J. Dakka and Y. Sasson, *J. Org. Chem.*, 1988, **53**, 3553; (*b*) J. Alvarez-Builla, J. J. Vaquero, J. L. Garcia Navio, J. F. Cabello, C. Sunkel, M. Fau de Casa-Juana, F. Dorrego and L. Santos, *Tetrahedron*, 1990, **46**, 967.

4 (*a*) P. Muller and H. Idmoumaz, *J. Organomet. Chem.*, 1988, **345**, 187; (*b*) B. Jursic, *Can. J. Chem.*, 1989, **67**, 1381; (*c*) B. R. Travis, M. Sivakumar, G. O. Hollist and B. Borhan, *Org. Lett.*, 2003, **5**, 1031.

5 (*a*) S. Samanta, L. Adak, R. Jana, G. Mostafa, H. M. Tuononen, B. C. Ranu and S. Goswami, *Inorg. Chem.*, 2008, **47**, 11062; (*b*) B. C. Ranu, S. Bhadra and L. Adak, *Tetrahedron Lett.*, 2008, **49**, 2588; (*c*) Y. Hirai, T. Kojima, Y. Mizutani, Y. Shiota, K. Yoshizawa and S. Fukuzumi, *Angew. Chem., Int. Ed.*, 2008, **47**, 5772; (*d*) S.-i. Hirashima, Y. Kudo, T. Nobuta, N. Tada and A. Itoh, *Tetrahedron Lett.*, 2009, **50**, 4328.

6 (*a*) K. Miyamoto, Y. Sei, K. Yamaguchi and M. Ochiai, *J. Am. Chem. Soc.*, 2009, **131**, 1382; (*b*) K. Lee, Y.-H. Kim, S. B. Han, H. Kang, S. Park, W. S. Seo, J. T. Park, B. Kim and S. Chang, *J. Am. Chem. Soc.*, 2003, **125**, 6844.

7 (*a*) T. Iwahama, Y. Yoshino, T. Keitoku, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2000, **65**, 6502; (*b*) Y. Ishii, K. Yamawaki, T. Ura, H. Yamada, T. Yoshida and M. Ogawa, *J. Org. Chem.*, 1988, **53**, 3587.

8 (*a*) J. Mecinović, R. B. Hamed and C. J. Schofield, *Angew. Chem., Int. Ed.*, 2009, **48**, 2796; (*b*) Y. Zhang, J. Jiao and R. A. Flowers, II, *J. Org. Chem.*, 2006, **71**, 4516; (*c*) T. Tabuchi and M. Nojima, *J. Org. Chem.*, 1991, **56**, 6591.

9 (*a*) D. J. Sheeran, J. D. Arenivar and M. Orchin, *J. Organomet. Chem.*, 1986, **316**, 139; (*b*) T. A. Van der Knaap, T. C. Klebach, F. Visser, F. Bickelhaupt, P. Ros, E. J. Baerends, C. H. Stam and M. Konijn, *Tetrahedron*, 1984, **40**, 765.

10 (*a*) C. Jones and M. Waugh, *J. Organomet. Chem.*, 2007, **692**, 5086; (*b*) A. J. Kirby and J. M. Percy, *Tetrahedron*, 1988, **44**, 6903.

11 (*a*) C. S. Yeung and V. M. Dong, *J. Am. Chem. Soc.*, 2008, **130**, 7826; (*b*) G. A. Olah, B. Török, J. P. Joschek, I. Bucsi, P. M. Esteves, G. Rasul and G. K. S. Prakash, *J. Am. Chem. Soc.*, 2002, **124**, 11379; (*c*) H. Ochiai, M. Jang, K. Hirano, H. Yorimitsu and K. Oshima, *Org. Lett.*, 2008, **10**, 2681.

12 K. Ukai, M. Aoki, J. Takaya and N. Iwasawa, *J. Am. Chem. Soc.*, 2006, **128**, 8706.

13 (*a*) Y. Uozumi and T. Watanabe, *J. Org. Chem.*, 1999, **64**, 6921; (*b*) I. Pri-Bar and O. Buchman, *J. Org. Chem.*, 1988, **53**, 624.

14 For recent reviews on copper-catalyzed Ullmann couplings, see: (*a*) A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727; (*b*) D. Ma and Q. Cai, *Acc. Chem. Res.*, 2008, **41**, 1450; (*c*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (*d*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400; (*e*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337; (*f*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054; (*g*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2009, **48**, 6954 and references cited therein.

15 (*a*) H. Rao, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 1114; (*b*) X. Liu, H. Fu, Y. Jiang and Y. Zhao, *Angew. Chem., Int. Ed.*, 2009, **48**, 348.

16 K. Okuro, M. Furuune, M. Miura and M. Nomura, *J. Org. Chem.*, 1993, **58**, 7606.

17 M. Tashiro, H. Tsuzuki, H. Goto, S. Ogasahara and S. Mataka, *J. Labelled Compd. Radiopharm.*, 1991, **29**, 475.