DOI: 10.1002/adsc.201300026

A Copper-Catalyzed Aerobic Cascade Dehydrogenative–Dehalogenative Reaction

Lei Liang,[a] Guanyu Yang,[a] Wei Wang,[a] Fengrong Xu,[a] Yan Niu,[a] Qi Sun,[a] and Ping Xu[a,*]

[a] State Key Laboratory of Natural and Biomimetic Drugs, Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing 100191, People's Republic of China
E-mail: pingxu@bjmu.edu.cn

Received: January 12, 2013; Revised: April 9, 2013; Published online: April 30, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300026.

Abstract: A copper-catalyzed cascade dehydrogenative and dehalogenative reaction of halogenated 6-phenyl-4,5-dihydropyridazin-3(2*H*)-ones to 6-phenylpyridazin-3(2*H*)-ones has been developed. Moreover, the catalytic system consisting of copper(II) acetate/sodium carbonate/pyridine exhibits high reactivity and selectivity with oxygen as the terminal oxidant.

Keywords: copper; dehalogenation; dehydrogenation; oxygen; pyridazinones

The development of synthetic and catalytic methodology has undoubtedly made tremendous contributions to the pharmaceutical industry especially for the construction of some significant chemical bonds with high efficacy.[1] For example, pyridazinones (Figure 1a), as a vital sort of pharmacophore with use such as antagonist of G-protein-coupled-receptor (GPCR) histamine 3 receptor (H_3R), have been developed as clinical candidates and further applied into trials.[2]

There are several routes leading to pyridazin-3(2*H*)-ones, among which the dehydrogenation of the C-4–C-5 bond of 4,5-dihydropyridazin-3(2*H*)-one to a C=C bond is definitely the key step (Figure 1b). Dehydrogenative methods with high efficiency and benign circumstances have attracted tremendous attention in the past decades. However, the development of catalytic methodology for dehydrogenation remains afflicted with several limitations.[3] In previous reports, excessive amounts of hazardous oxidants were utilized including MnO_2, SeO_2, Br_2/HOAc and so on.[4] What is more, neither the efficiency nor the economy meets the demands of large-amount production or the principles of green chemistry. To solve

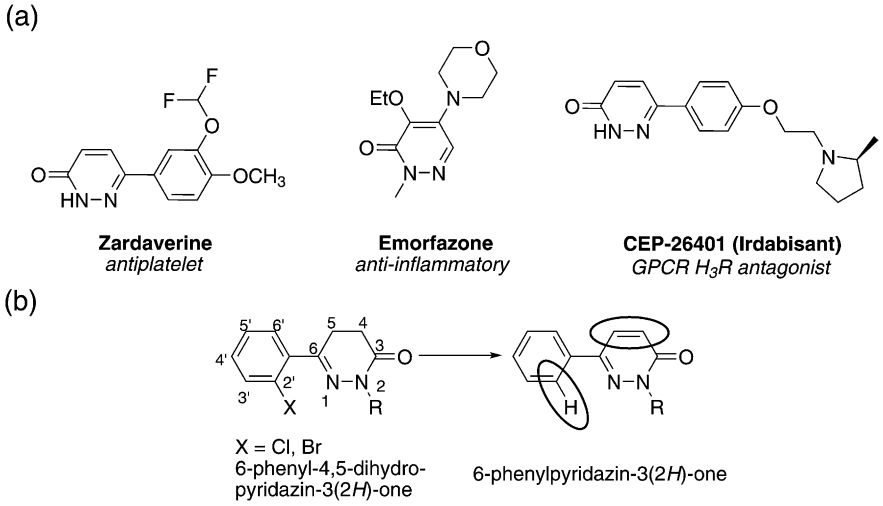


Figure 1. (a) Bioactive compounds containing the pyridazinone scaffold. (b) Structures of 6-phenyl-4,5-dihydropyridazin-3(2*H*)-one and 6-phenylpyridazin-3(2*H*)-one.

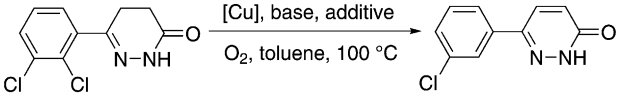
these problems, molecular oxygen has been widely used as a benign and economical source of oxidant instead of the toxic and expensive oxidants. Recently, transition metal-catalyzed oxidation in an aerobic atmosphere emerged as a powerful tool for preparation of pharmaceutical compounds.[5] Among these, palladium complexes were widely used in the dehydrogenation of unsaturated carbonyl compounds.[6] Nevertheless, the substrates accommodated to the palladium catalytic system were limited to alkanes or cycloalkanes. Heterocyclic compounds, as the most important skeleton of chemical drugs, have been less reported as substrates in metal-catalyzed dehydrogenations. In terms of the metal catalyst, copper salts are generally more economical and available compared to palladium complexes. However, there is a scarcity of reports on copper-catalyzed dehydrogenation of saturated C–C bond.[7]

On the other hand, the highly efficient and selective modification of pyridazinone derivatives provides us with abundant information about the structure-activity relationship (SAR) and the choice for design of drug candidates.[8] Accordingly, dehalogenation on the 6-phenyl ring of pyridazinone is a significant way to achieve this aim (Figure 1b). The highly efficient and selective dehalogenative reaction facilitates not only the chemical modification but also provides improvements of the pharmacokinetic/pharmacodynamic properties of pyridazinones. However, the high stability of the aryl carbon-chlorine bond renders it less reactive compared to other aryl-halogen bonds in many organic transformations and reactions.[9] In the past decades, only a limited number of methods employing metal catalysts have been reported such as Pd,[10] Ni,[11] La,[12] Rh,[13] Rh,[14] and others.[15] These systems can still be improved upon, as most suffer from expensive precious transition metal systems, unselective dechlorination, low catalytic activity, low substrate/catalyst ratio, extreme conditions (high H_2 pressure, long reaction times), and narrow functional group tolerance.

In this communication, we present a copper-catalyzed cascade dehydrogenative-dehalogenative reaction of halogenated 6-phenyl-4,5-dihydropyridazin-3(2*H*)-ones with oxygen as the oxidant.

Our investigations commenced with screening conditions using 2′,3′-dichloro-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one as substrate. The reactions were originally carried out in toluene as solvent and with oxygen as oxidant. Several sets of reactions were carried out including studies on the effects of base, ligand, catalyst and others. We first investigated the effect of base: inorganic bases such as Cs_2CO_3, K_2CO_3, Na_2CO_3 and K_3PO_4 were used and Na_2CO_3 was found to be the best inorganic base with excellent yield (Table 1, entries 1–4). Triethylamine was also used as an organic base in this reaction but merely a trace amount of product was detected with scarce conversion of substrate (Table 1, entry 5). Pyridine (Py) was identified as the most efficient ligand rather than phenanthroline (Phen), tetramethylethylenediamine (TMEDA) and bipyridine (bpy). After screening a series of copper salts including both Cu(II) and Cu(I) species and other metal salts, $Cu(OAc)_2$ was selected as the catalyst (Table 1, entries 9–13). $CuCl_2$ also gave a considerable yield compared to $Cu(OAc)_2$ (81%, Table 1, entry 9). We also investigated other metal salts including $Mn(OAc)_2$, $Fe(OAc)_2$. Both of them showed negligible conversion of substrates and poor yields (Table 1, entries 14 and 15). Control experiments revealed that the reaction could not proceed in the absence of either the copper catalyst or the base (Table 1, entries 16 and 17). Pyridine is also

Table 1. Screening of the optimized condition of the copper-catalyzed cascade dehydrogenative-dehalogenative reaction of 2′,3′-dichloro-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one.[a]



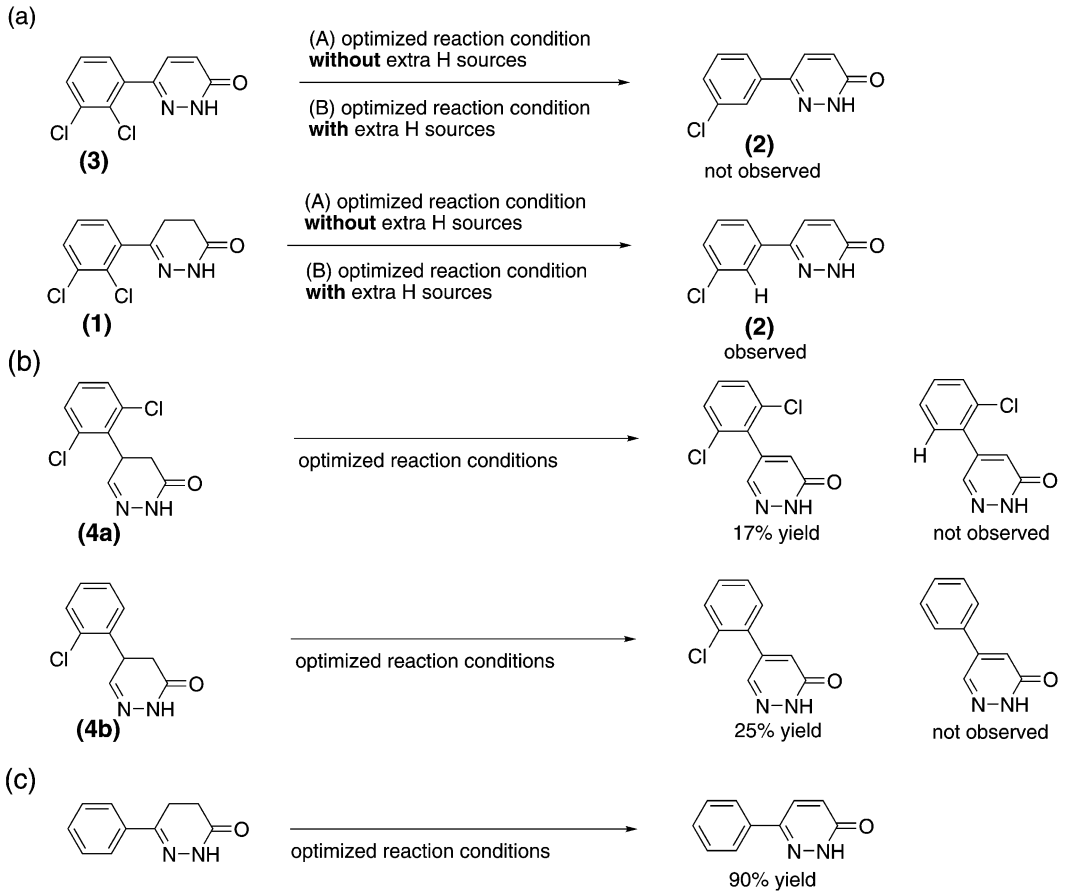
(1) **(2)**

Entry	Catalyst	Base	Additive	Yield [%][b]
1	$Cu(OAc)_2$	Cs_2CO_3	Py	74
2	$Cu(OAc)_2$	K_2CO_3	Py	70
3	**$Cu(OAc)_2$**	**Na_2CO_3**	**Py**	**87**
4	$Cu(OAc)_2$	K_3PO_4	Py	53
5	$Cu(OAc)_2$	Et_3N	Py	trace
6	$Cu(OAc)_2$	Na_2CO_3	Phen	55
7	$Cu(OAc)_2$	Na_2CO_3	TMEDA	20
8	$Cu(OAc)_2$	Na_2CO_3	Bpy	37
9	$CuCl_2$	Na_2CO_3	Py	81
10	$CuBr_2$	Na_2CO_3	Py	46
11	CuCl	Na_2CO_3	Py	18
12	CuBr	Na_2CO_3	Py	trace
13	CuI	Na_2CO_3	Py	10
14	$Mn(OAc)_2$	Na_2CO_3	Py	trace
15	$Fe(OAc)_2$	Na_2CO_3	Py	none
16	–	Na_2CO_3	Py	none
17	$Cu(OAc)_2$	–	Py	none
18	$Cu(OAc)_2$	Na_2CO_3	–	trace
19	$Cu(OAc)_2$	Na_2CO_3	Py	30[c]
20	$Cu(OAc)_2$	Na_2CO_3	Py	none[d]
21	$Cu(OAc)_2$	Na_2CO_3	Py	15[e]
22	$Cu(OAc)_2$	Na_2CO_3	Py	26[f]

[a] Reactions were carried out with 2′,3′-dichloro-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one (243.0 mg, 1.0 mmol), catalyst (10 mol%), base (2.0 equiv.), additive (2.0 equiv.), in toluene in 100 °C for 12 h without other notes.
[b] Isolated yields.
[c] In the air.
[d] Under N_2.
[e] At 25 °C.
[f] DMF as solvent.

an essential component in the catalytic system as the reaction hardly proceeded in the absence of pyridine (Table 1, entry 18). This is probably due to inactivation of copper salt without a proper ligand. The reaction slowed down in the air with lower yield (30%, Table 1, entry 19). However, no product formed when the reaction was carried out in a nitrogen atmosphere (Table 1, entry 20). Lower temperature and other common organic solvent such as DMF showed negative effects on the reaction (15% and 26%, Table 1, entries 21 and 22). Above all, the catalytic system was finally confirmed as $Cu(OAc)_2/Na_2CO_3$/pyridine with oxygen as the oxidant.

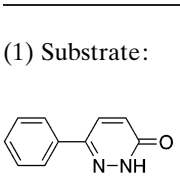
In an endeavour to expand the scope of this methodology, the catalytic system was further applied to a variety of halogenated dihydropyridazinones. To our delight, most of the substrates exclusively afforded the desired products in good to excellent yields. First of all, monochloro-substituted 6-phenyldihydropyridazinones were examined with the catalytic system and considerable results were obtained. For example, a variety of *N*-alkylated/*N*-arylated substrates, including methyl, benzyl, *n*-butyl and phenyl groups, were employed and modest to excellent yields were achieved (Table 2, **2aa–2ae**). Recently, a structurally similar drug candidate based on *N*-benzylated pyridazinone containing fluoride(s) has been developed for the treatment of allergic inflammatory diseases.[16] Herein, a series of *N*-benzylated pyridazinone compounds containing fluoride(s) were employed as substrates and excellent yields were achieved (Table 2, **2af**–**2aj**). Besides, the N(2)-benzothiazole-substituted pyridazinone was prepared with good yield (78%, Table 2, **2ak**). Moreover, 2′,3′-dichloro-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one was converted to the product with dechlorination of *ortho*-Cl and retention of *meta*-Cl selectively (Table 2, **2ba–2bj**). The catalytic system also exhibited broad substrate scope for NH substrates substituted by different groups. As we expected, *N*-arylated 2′,4′-dichloro-6-phenyl-4,5-dihydropyridazin-3(2*H*)-ones afforded the desired products with dechlorination of *ortho*-Cl and retention of *para*-Cl selectively (Table 2, **2ca** and **2cb**). Furthermore, we also observed that when both of the *ortho* positions are chlorines, only one chlorine has been replace by H, which has instructive significance for the reaction

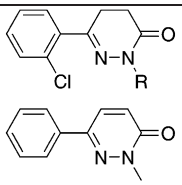


Scheme 1. Mechanistic study: (a) Reaction of 2′,3′-dichloro-6-phenylpyridazin-3(2*H*)-one and 2′,3′-dichloro-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one with/without extraneous hydrogen donors under the optimized reaction conditions. (b) Reaction of 2′,6′-dichloro-5-phenyldihydropyridazinone and 2′-chloro-5-phenyldihydropyridazinone under the optimized reaction conditions. (c) Reaction of 6-phenyl-4,5-dihydropyridazin-3(2*H*)-one under the optimized reaction conditions.

Table 2. Copper-catalyzed cascade dehydrogenative-dehalogenative reaction of various halogenated dihydropyridazinones.[b]

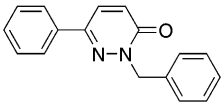
(1) Substrate:



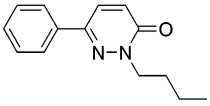


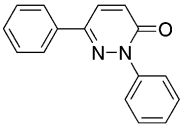
2aa: 86%

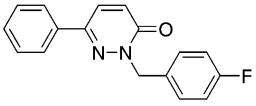
2ab: 88%



2ac: 90%



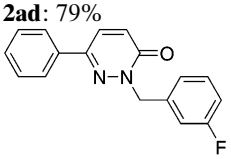


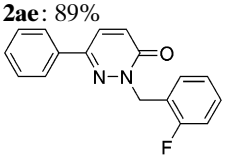


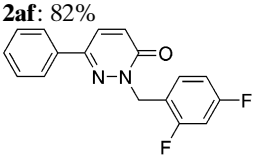
2ad: 79%

2ae: 89%

2af: 82%



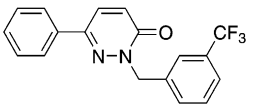


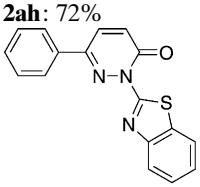


2ag: 86%

2ah: 72%

2ai: 65%



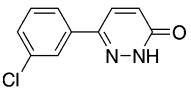


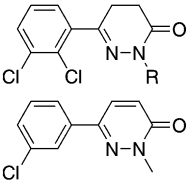
2aj: 84%

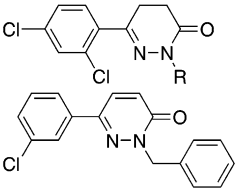
2ak: 78%

(2) Substrate:

or



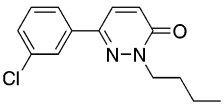


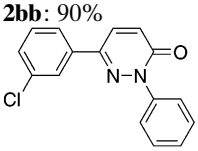


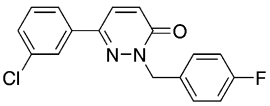
2ba: 87%[b]

2bb: 90%

2bc: 92%



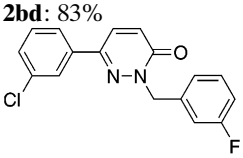


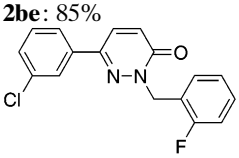


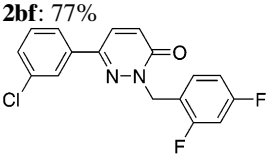
2bd: 83%

2be: 85%

2bf: 77%



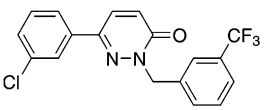


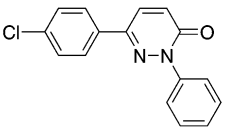


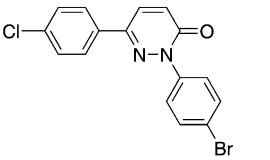
2bg: 70%

2bh: 53%

2bi: 59%





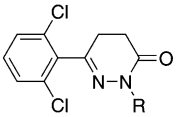


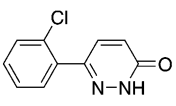
2bj: 69%

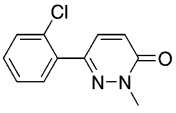
2ca: 73%

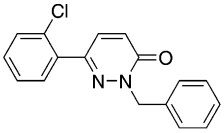
2cb: 89%

(3) Substrate:







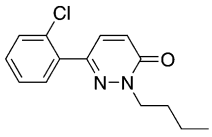


2da: 90%

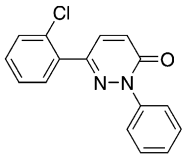
2db: 88%

2dc: 91%

Table 2. (Continued)

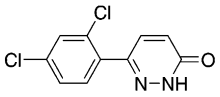


2dd: 82%

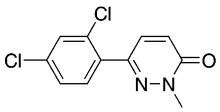


2de: 88%

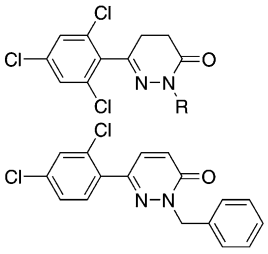
(4) Substrate:



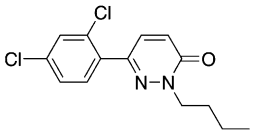
2ea: 89%



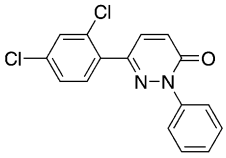
2eb: 85%



2ec: 87%

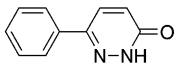


2ed: 79%

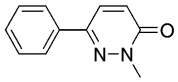


2ee: 86%

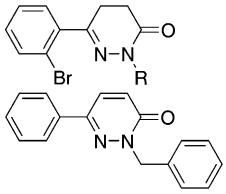
(5) Substrate:



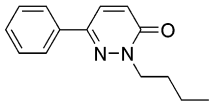
2fa: 90%



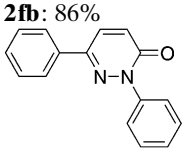
2fb: 86%



2fc: 94%



2fd: 67%

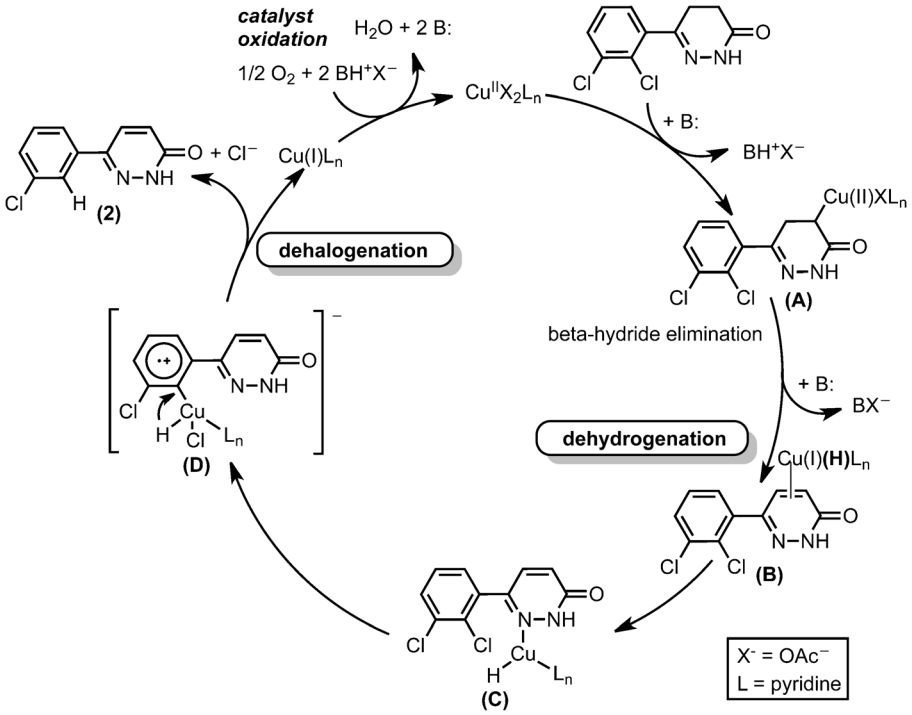


2fe: 91%

[a] Reactions were carried out with substrate (1.0 mmol), $Cu(OAc)_2$ (20.0 mg, 10 mol%), Na_2CO_3 (312.0 mg, 2.0 mmol), pyridine (159.0 mg, 2.0 mmol), in toluene in 100 °C for 12 h, all the results were calculated after column chromatography as isolated yields.

mechanism (Table 2, **2da–2de**, **2ea–2ee**). Moreover, debromination also proceeded smoothly when the 6-phenyl group was substituted by *ortho*-Br (Table 2, **2fa**–**2fe**).

To explore the mechanism of this reaction, a series of experiments was carried out. First of all, we designed a series of control experiments with 2′,3′-dichloro-6-phenylpyridazin-3(2*H*)-one (**3**) and 2′,3′-dichloro-6-phenyl-4,5-dihydropyridazin-3(2*H*)-one (**1**) as the substrates and the results are shown in Scheme 1a. For compound **3**, where the C-4−C-5 bond has already been dehydrogenated to C=C bond, no dechlorination products could be observed under our optimized conditions. Even when hydrosilanes were added as extra hydrogen sources, only trace amounts of dechlorination product could be observed. Adding other hydride sources (e.g., NaH, $LiAlH_4$) did not give any dehalogenated products. Deuterated toluene and pyridine were also used to testify if the H comes from the solvent or ligand. However, there is no proof revealing that the product contained deuterium (see Tables S1 and S2 in the Supporting Information). Moreover, if the phenyl group is shifted far away from the N-1 as shown in Scheme 1b, only dehydrogenation occurred without dechlorination. Nevertheless, yields of the dehydrogenative product were very low, possibly due to the steric effect. Finally, we found that the *ortho*-Cl is not essential for the completion of the dehydrogenation cycle, which means the substrates such as 6-phenyl-4,5-dihydropyridazinone without chlorines on the 6-phenyl ring could also be dehydrogenated by this catalytic system (Scheme 1c).



Scheme 2. Proposed mechanism for the copper-catalyzed aerobic cascade dehydrogenative and dehalogenative reaction.

On the basis of the results obtained above, a plausible mechanism is illustrated in Scheme 2. In the first step, the copper catalyst coordinates to the α-C of dihydropyridazinone resulting in complex (**A**) with assistance of the base. And then the β-H elimination is continued and complex (**A**) is converted to (**B**) that completes the formation of the C=C bond with generation of a copper(I) species. Consequently, complex (**C**) is formed owing to the coordination between copper species and N-1. Insertion of this copper species into the C–Cl bond forms the intermediate (**D**) which might explain the selective dehalogenation of the *ortho*-Cl of the 6-phenyl ring. Substitution of the *ortho*-Cl by an H atom coordinated to copper results in the product (**2**). Molecular oxygen plays a role as the oxidant to trigger the circulation of the catalytic process.[5,17] The detailed mechanism and the assignment of the H replacing the *ortho*-Cl are now under investigation in our laboratory.

In conclusion, a cascade dehydrogenative-dehalogenative reaction of halogenated 6-phenyl-4,5-dihydropyridazin-3(2*H*)-ones to 6-phenylpyridazin-3(2*H*)-ones has been developed. Moreover, the $Cu(OAc)_2$/Na_2CO_3/pyridine catalytic system exhibits high reactivity and selectivity with oxygen as the oxidant. Further work to elucidate the detailed mechanism of this reaction is underway and will be reported in due course.

Experimental Section

General Procedure

To a 20-mL Schlenk tube were added halogenated dihydropyridazinone (1.0 mmol), $Cu(OAc)_2$ (20.0 mg, 10 mol%), Na_2CO_3 (312.0 mg, 2.0 mmol), pyridine (159.0 mg, 2.0 mmol), followed by addition of toluene (2.0 mL). The mixture was heated at 100 °C under O_2 (1 atm) and stirred 12 h. On completion of the reaction, the products were purified by column chromatography on silica gel using mixtures of petroleum ether and ethyl acetate (2:1) as the eluent. All the results were measured as isolated yields.

Acknowledgements

This work was supported by the Beijing Natural Science Foundation (Design, synthesis and optimization of proteasome inhibitors as novel antitumor agents, 7112088), the National Basic Research Program of China (2012CB518000), and the National Natural Science Foundation of China (21202003/21172012).

References

[1] a) S. L. Schreiber, *Science* **2000**, *287*, 1964–1969; b) M. MacCoss, T. A. Baillie, *Science* **2004**, *303*, 1810–1813.
[2] a) I. Sircar, B. L. Duell, M. H. Cain, S. E. Bruke, J. A. Bristol, *J. Med. Chem.* **1986**, *29*, 2142–2148; b) R. Hudkins, R. Raddatz, M. Tao, J. Mathiasen, L. Aimone, N. Becknell, C. Prouty, L. Knutsen, M. Yazdanian, G.

Moachon, M. Ator, J. Mallamo, M. Marino, E. Bacon, M. Williams, *J. Med. Chem.* **2011**, *54*, 4781–4792.
[3] a) P. Xu, S. Wang, W. Liu, *Acta Pharmaceutica Sinica* **1991**, *26*, 650–655; b) W. Curran, A. Ross, *J. Med. Chem.* **1974**, *17*, 273–281; c) I. Estevez, E. Raviña, E. Sotelo, *J. Heterocycl. Chem.* **1998**, *35*, 1421–1428; d) K. A. Johnston, R. W. Allcock, Z. Jiang, I. D. Collier, H. Blakli, G. M. Rosair, P. D. Bailey, K. M. Morgan, Y. Kohno, D. R. Adams, *Org. Biomol. Chem.* **2008**, *6*, 175–186.
[4] a) E. Sotelo, E. Raviña, *Synth. Commun.* **2000**, *30*, 1–7; b) I. Sircar, B. Duell, J. Bristol, D. Evans, *J. Med. Chem.* **1985**, *28*, 1405–1413; c) R. L. Hudkins, L. D. Aimone, T. R. Bailey, R. J. Bendesky, R. Dandu, D. Dunn, J. A. Gruner, K. A. Josef, Y. Lin, J. Lyons, V. R. Marcy, J. R. Mathiasen, B. G. Sundar, M. Tao, A. L. Zulli, R. Raddatz, E. R. Bacon, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 5493–5497; d) P. Xu, S. Wang, Y. Chen, W. Liu, C. Tao, *Acta Pharmaceutica Sinica* **1991**, *26*, 656–660.
[5] a) A. N. Campbell, S. S. Stahl, *Acc. Chem. Res.* **2012**, *45*, 851–863; b) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464–3484.
[6] a) Y. Izawa, D. Pun, S. S. Stahl, *Science* **2011**, *333*, 209–213; b) T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566–14569; c) W. Gao, Z. He, Y. Qian, J. Zhao, Y. Huang, *Chem. Sci.* **2012**, *3*, 883–886.
[7] a) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068–12073; b) M. O. Simon, S. A. Girard, C. J. Li, *Angew. Chem.* **2012**, *124*, 7655–7658; *Angew. Chem. Int. Ed.* **2012**, *51*, 7537–7540; c) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem.* **2011**, *123*, 11256–11283; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062–11087.
[8] a) A. Coelho, E. Sotelo, N. Fraiz, M. Yáñez, R. Laguna, E. Cano, E. Raviña, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 321–324; b) A. Crespo, C. Meyers, A. Coelho, M. Yáñez, N. Fraiz, E. Sotelo, B. U. W. Maes, R. Laguna, E. Cano, G. L. F. Lemière, E. Raviña, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1080–1083.
[9] a) J. March, *Advanced Organic Chemistry*; Wiley-Interscience: New York, **1992**; b) T. Imamoto, in: *Comprehensive Organic Synthesis*, Vol. 8, (Eds.: B. M. Trost, I. Fleming,), Pergamon Press, London, **1991**, p 793; c) M. Hudlicky, in: *Comprehensive Organic Synthesis*, Vol. 8, (Eds.: B. M. Trost, I. Fleming), Pergamon Press, London, **1991**, p 895.
[10] a) H. Imai, T. Nishiguchi, M. Tanaka, K. Fukuzumi, *Chem. Lett.* **1976**, 855–856; b) H. Imai, T. Nishiguchi, M. Tanaka, K. Fukuzumi, *J. Org. Chem.* **1977**, *42*, 2309–2313; c) O. Navarro, H. Kaur, P. Mahjoor, S. P. Nolan, *J. Org. Chem.* **2004**, *69*, 3173–3180; d) O. Navarro, N. Marion, Y. Oonishi, R. A. Kelly III, S. P. Nolan, *J. Org. Chem.* **2006**, *71*, 685–692.
[11] a) C. Carfagna, A. Musco, R. Pontellini, *J. Mol. Catal.* **1989**, *54*, L23–L26; b) C. Desmarets, S. Kuhl, R. Schneider, Y. Forts, *Organometallics* **2002**, *21*, 1554–1559.
[12] C. Qian, D. Zhu, Y. Gu, *J. Mol. Catal.* **1990**, *63*, L1 L3.
[13] D. T. Ferrughelli, I. T. Horváth, *J. Chem. Soc. Chem. Commun.* **1992**, 806–807.
[14] a) V. V. Grushin, H. Alper, *Organometallics* **1991**, *10*, 1620–1622; b) V. V. Grushin, H. Alper, *Chem. Rev.* **1994**, *94*, 1047–1062.
[15] a) W. M. Czaplik, S. Grupe, M. Mayer, A. J. von Wangelin, *Chem. Commun.* **2010**, *46*, 6350–6352; b) C. J. Love, F. J. McQuillin, *J. Chem. Soc. Perkin Trans.* **1973**, 2509–2512; c) J. M. R. Narayanam, J. W. Tucher, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756–8757; d) R. N. Ram, T. P. Manoj, *Org. Lett.* **2008**, *10*, 2243–2246.
[16] N. Kaila, A. Huang, A. Moretto, B. Follows, K. Janz, M. Lowe, J. Thomason, T. S. Mansour, C. Hubeau, K. Page, P. Morgan, S. Fish, X. Xu, C. Williams, E. Saiah, *J. Med. Chem.* **2012**, *55*, 5088–5109.
[17] L. Liang, G. Rao, H. Sun, J. Zhang, *Adv. Synth. Catal.* **2010**, *352*, 2371–2377.

