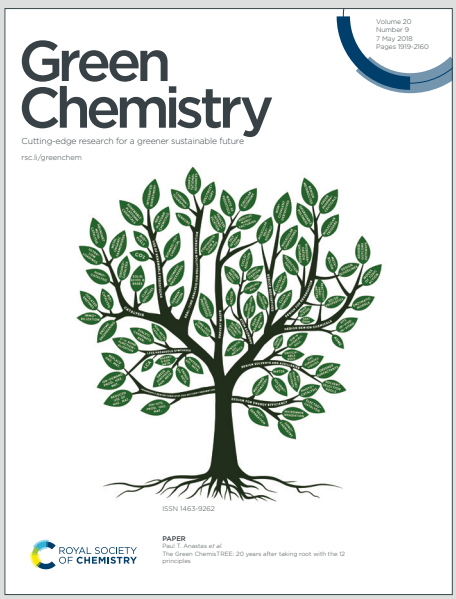
View Article Online
View Journal

Green Chemistry

Cutting-edge research for a greener sustainable future

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Zhang, X. Feng, H. Zhang, Y. Yamamoto and M. Bao, *Green Chem.*, 2019, DOI: 10.1039/C9GC02407G.



ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C9GC02407G

Journal Name

ARTICLE

Transition-Metal-Free Decarboxylative Halogenation of 2-Picolinic Acids with Dihalomethane under Oxygen Conditions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

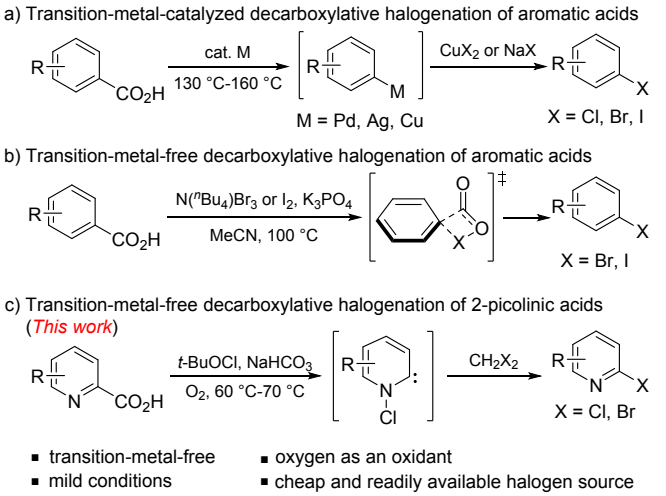
Xitao Zhang,[a] Xiujuan Feng,*[a] Haixia Zhang,[a] Yoshinori Yamamoto,[ab] and Ming Bao*[a]

A convenient and efficient method for the synthesis of 2-halogen-substituted pyridines is described. The decarboxylative halogenation of 2-picolinic acids with dihalomethane proceeded smoothly via *N*-chlorocarbene intermediates to afford 2-halogen-substituted pyridines in satisfactory to excellent yields under transition-metal-free conditions. This new type of decarboxylative halogenation is operationally simple and exhibits high functional-group tolerance.

Introduction

The 2-halogen-substituted pyridine motif is present in many important bioactive molecules and pharmaceuticals,[1] and 2-halogen-substituted pyridine derivatives can serve as useful intermediates in the synthesis of drug molecules and function materials through transition metal-catalyzed cross-coupling reactions[2] or a nucleophilic aromatic substitution reaction (S_NAr reaction)[3]. The importance of 2-halogen-substituted pyridines provides the continuous impetus for the synthetic chemists to seek simple and valid methods to construct them. Three main methods for preparing 2-halogen-substituted pyridines have been developed over the past decades. One method involves the direct chlorination of pyridine ring with chlorine gas at high temperatures.[4] This method generally results in overhalogenation and poor regioselectivity. Another method involves the substitution reaction of 2-hydroxy group with halogen atoms, with $POCl_3$, PCl_5, $POBr_3$, and PBr_3 as halogen sources.[5] The last method involves the halogenation of pyridine-*N*-oxides with almost the same halogen sources mentioned above.[6,7] However, these halogen sources are harmful, moisture sensitive, and difficult to handle. Moreover, these methods also suffer from harsh reaction conditions, limited substrate scope, and poor regioselectivity. Therefore, developing a convenient and efficient method for synthesizing 2-halogen-substituted pyridines is highly desired.

A rapidly growing number of decarboxylative coupling reactions in the formation of C–C and C–heteroatom bonds have attracted increasing attention because aromatic carboxylic acids show good stability and high commercial availability and are low cost.[8] The transition metal-catalyzed decarboxylative halogenation has been demonstrated to be a powerful method for constructing C–X bond (Scheme 1a).[9] However, this method cannot be utilized to synthesize 2-halogen-substituted pyridines because



Scheme 1. Decarboxylative Halogenation of aromatic acids.

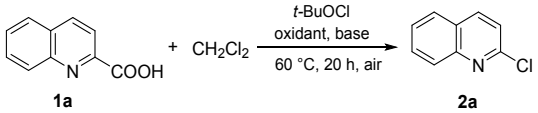
2-metallapyridine intermediates generated in situ are unstable and easily undergo protodemetalation.[10] Recently, Larrosa and co-workers disclosed a study on the transition-metal-free decarboxylative halogenation of benzoic acids with $N(^nBu_4)Br_3$ or I_2 (Scheme 1b).[11] Nevertheless, we failed to synthesize 2-halogen-substituted pyridines by this protocol. In the course of our research on the development of efficient methods for synthesizing aromatic halides,[12] we found that 2-halogen-substituted pyridines can be synthesized also through transition-metal-free decarboxylative halogenation; the decarboxylative halogenation of 2-picolinic acids proceeded smoothly via *N*-chlorocarbene intermediates (Scheme 1c). The results are reported in this paper.

In our initial study, we selected the reaction of quinoline-2-carboxylic acid (**1a**) with dichloromethane as a model reaction for optimizing reaction conditions. The results are shown in Table 1. The 2-chloroquinoline (**2a**) product was obtained in 32% yield without a base (entry 1). Several bases, including potassium carbonate (K_2CO_3), sodium acetate (NaOAc), sodium

[a]*State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116023, China. Fax: +86-0411-84986181; Tel: +86-0411-84986180; E-mail: fengxiujuan@dlut.edu.cn; mingbao@dlut.edu.cn*
[b] *WPI-AIMR (WPI-Advanced Institute for Materials Research), Tohoku University, Sendai 980-8577, Japan.*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Results and discussion

Table 1. Optimization of Reaction Conditions[a]



1a 2a

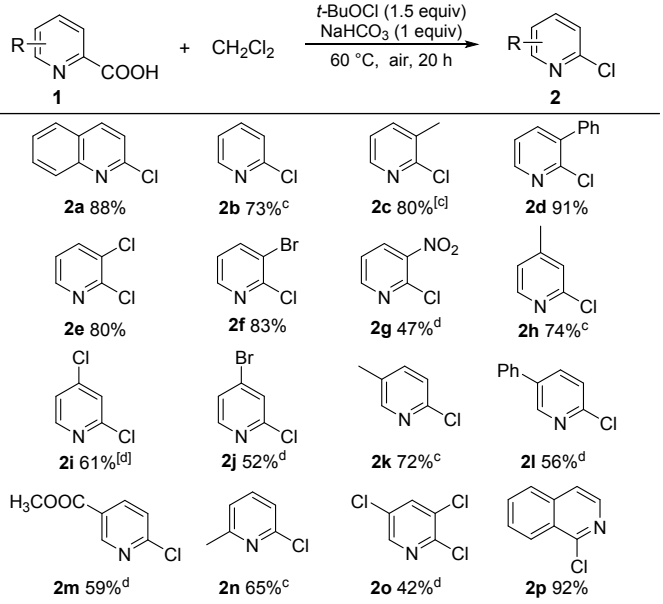
entry	base (equiv.)	oxidant (equiv.)	yield (%)[b]
1	none	air	32
2	K_2CO_3 (0.5)	air	58
3	NaOAc (1)	air	10
4	NaOH (1)	air	32
5	Et_3N (1)	air	Trace
6	Na_2CO_3 (1)	air	60
7	$NaHCO_3$ (1)	air	88
8	$NaHCO_3$ (1)	none	20
9	$NaHCO_3$ (1)	$K_2S_2O_8$ (2)	47
10	$NaHCO_3$ (1)	TBHP (2)	Trace
11	$NaHCO_3$ (1)	*p*-chloranil (2)	39
12	$NaHCO_3$ (1)	O_2	89
13[c]	$NaHCO_3$ (1)	O_2	80
14[d]	$NaHCO_3$ (1)	O_2	78

[a] Reaction conditions: 1a (0.3 mmol), *t*-BuOCl (1.5 equiv., 0.45 mmol), base, and oxidant in dichloromethane (3 mL) at 60 °C for 20 h. [b] Isolated yield. [c] The reaction was conducted at 50 °C for 20 h. [d] The reaction was conducted at 60 °C for 16 h

hydroxide (NaOH), triethylamine (Et_3N), sodium carbonate (Na_2CO_3), and sodium bicarbonate ($NaHCO_3$), were examined by using 1.5 equivalents of *t*-BuOCl as the promoter under air (entries 2–7). When $NaHCO_3$ was used as the base, a relatively high yield of product **2a** was obtained (entry 7 vs. entries 2–6). Comparatively, the reaction performed under an atmosphere of N_2 gave merely 20% product (entry 8). Oxygen in the reaction system might be beneficial for the single electron transfer process involved in the reaction.[13] Other oxidants, such as potassium persulfate ($K_2S_2O_8$), *tert*-butyl hydroperoxide (TBHP), and *p*-chloranil, were inefficient (entries 9–11). The yield of **2a** was insignificantly improved under oxygen atmosphere (entry 12 vs. entry 7). The yield of **2a** decreased along with the decreasing temperature and shorting reaction time (entries 13 and 14). Therefore, the subsequent reactions of picolinic acid substrates **1** with dichloromethane were performed in the presence of *t*-BuOCl (1.5 equiv) and $NaHCO_3$ (1 equiv) in air at 60 °C for 20 h.

The scope and limitation of this type of decarboxylative chlorination reaction were determined under optimal reaction conditions. The results are summarized in table 2. When using 2-picolinic acid (**1b**) as the substrate, the desired product **2b** was obtained in 73% yield. The reactions of 2-picolinic acids **1c–1f** bearing methyl (Me), phenyl (Ph), chloro (Cl), or bromo (Br) on 3-position gave the desired products **2c–2f** in good yields, thus indicating that steric hindrance of the 3-position did not influence the reactivity of 2-picolinic acid substrates. Meanwhile, **2g** was obtained in relatively low yield in comparison with **2b** possibly because of the strong electron-withdrawing capability of the nitro (NO_2) group. Me, Cl, and Br linked on the 4-position of pyridine ring (**1h–1j**) gave the desired products 2-chloropyridines **2h–2j** in 52%–74% yields. Moderate-to-good yields (59%–72%) were obtained when the substrates **1k–1m** bearing a substituent (Me, Ph, or COOMe) on 5-position were examined. A satisfactory yield (65%) of

Table 2. Decarboxylative Chlorination of 2-Picolinic Acids with Dichloromethane[a,b]

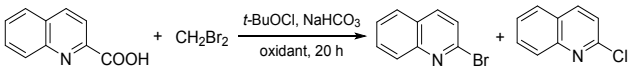


[a] Reaction conditions: 2-picolinic acid (**1**, 0.3 mmol), *t*-BuOCl (0.45 mmol), $NaHCO_3$ (0.3 mmol) in dichloromethane (3 mL) at 60 °C under air for 20 h. [b] The isolated yields were calculated based on 2-picolinic acids. [c] Yields were determined via ^1H NMR analysis using dibromomethane as an internal standard. [d] The reaction was conducted in the presence of 0.9 mmol *t*–BuOCl under O_2 atmosphere.

product **2n** was obtained when 6-methyl 2-picolinic acid (**1n**) was used as the substrate. The reaction of 3,5-dichloro-2-picolinic acid (**1o**) afforded the corresponding product 2o in 42% yield. The reaction of isoquinoline-1-carboxylic acid (**1p**) proceeded smoothly, producing the desired product **2p** in 92%.

The success in decarboxylative chlorination encouraged us to explore the decarboxylative bromination reaction. The decarboxylative bromination reaction of **1a** with dibromo methane was selected as the model reaction in the optimization of the reaction conditions. The results are shown in Table 3. The desired product, 2-bromoquinoline (**3a**), was obtained in 23% yield along with trace amounts of **2a** when

Table 3. Screening of Reaction Conditions for Decarboxylative Bromination[a]



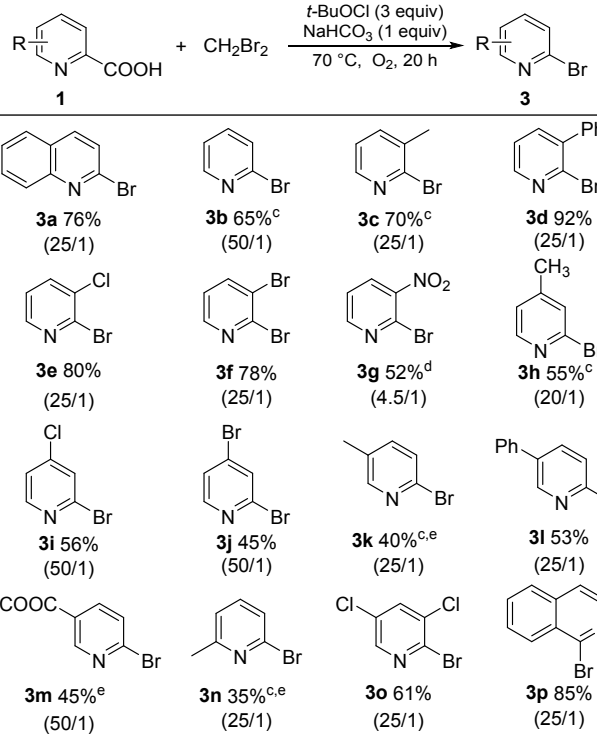
entry	equiv. of *t*-BuOCl	oxidant	yield of **3a** (%)[b]	**3a**/**2a**[c]
1	1.5	air	23	25/1
2	2.0	air	29	25/1
3	3.0	air	40	25/1
4	4.0	air	41	25/1
5	3.0	O_2	65	25/1
6[d]	3.0	O_2	76	25/1
7[e]	3.0	O_2	69	25/1

[a] Reaction conditions: **1a** (0.3 mmol), *t*-BuOCl (3 equiv, 0.9 mmol), base, oxidant in dibromomethane (2 mL) at 60 °C under air for 20 h. [b] Isolated yield. [c] The ratios of isomers were determined by crude product ^1H NMR analysis. [d] The reaction was performed at 70 °C for 20 h. [e] The reaction was performed at 70 °C for 16 h.

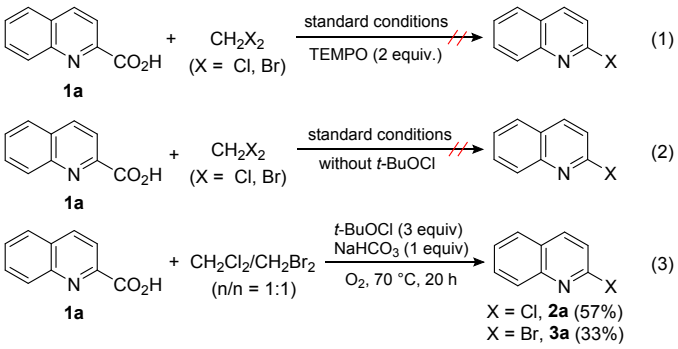
the model reaction was conducted under the standard conditions of chlorination (entry 1). The *t*-BuOCl loading was subsequently screened with $NaHCO_3$ as the base. The results obtained indicated that 3 equivalents of *t*-BuOCl is enough for obtaining **3a** in relatively high yield (entries 2–4). When the reaction was conducted under an O_2 atmosphere, the yield of **3a** was improved to 65% (entry 5). The yield of **3a** was further improved to 76% when the model reaction was performed at enhanced temperature (entry 6, 70 °C). However, reducing the reaction time to 15 h led to a decrease in product yield (entry 7). The subsequent reactions of picolinic acid substrates **1** with dibromomethane were therefore performed in the presence of *t*-BuOCl (3 equiv) and $NaHCO_3$ (1 equiv) under O_2 atmosphere at 70 °C for 20 h.

The scope of the decarboxylative bromination reaction was explored using dibromomethane as the bromine source. The results are summarized in Table 4. The desired product **3b** was obtained in 65% yield when using 2-picolinic acid (**1b**) as the substrate. The reactions of 2-picolinic acids **1c–1f** bearing methyl (Me), phenyl (Ph), chloro (Cl), or bromo (Br) on 3-position afforded the desired products in good yield (70%–92%). These results indicated that the steric hindrance of 3-position did not influence the reactivity of the 2-picolinic acid substrates. The product **3g** was obtained in a relatively low yield (52%) along with protodecarboxylation product; the low yield and poor selectivity was attributed to the strong electron-withdrawing capability of the NO_2 group. The reactions of 2-picolinic acids **1h–1j** bearing a substituent (Me, Cl, or Br) on 4-position afforded the products 2-bromopyridines **3h–3j** in moderate yields (45%–56%). Similarly, moderate yields (40%–53%) were observed in 2-picolinic acids **1k–1m** bearing a substituent (Me, Ph, or COOMe) on the 5-position. Only 35% of **3n** was obtained when 6-methyl 2-picolinic acid was used as the substrate. A satisfactory yield of 61% was obtained when 3,5-dichloro-2-picolinic acid (**1o**) was examined. Finally, the reaction of **1p** with dibromomethane was examined, and the desired product **3p** was obtained in 85% yield.

Table 4. Decarboxylative Bromination of 2-Picolinic Acids with Dibromomethane [a,b]



[a] Reaction conditions: 2-picolinic acid (**1**, 0.3 mmol), *t*-BuOCl (0.9 mmol), $NaHCO_3$ (0.3 mmol) in dibromomethane (2 mL) at 70 °C under oxygen for 20 h. The ratios of isomers were determined by ^1H NMR analysis. [b] The isolated yields were calculated based on 2-picolinic acids. [c] Yields were determined via ^1H NMR analysis using diethylene glycol dimethyl ether as an internal standard. [d] Additional NBS (0.3 mmol) was added to the reaction. [e] The reaction was conducted for 30 h.

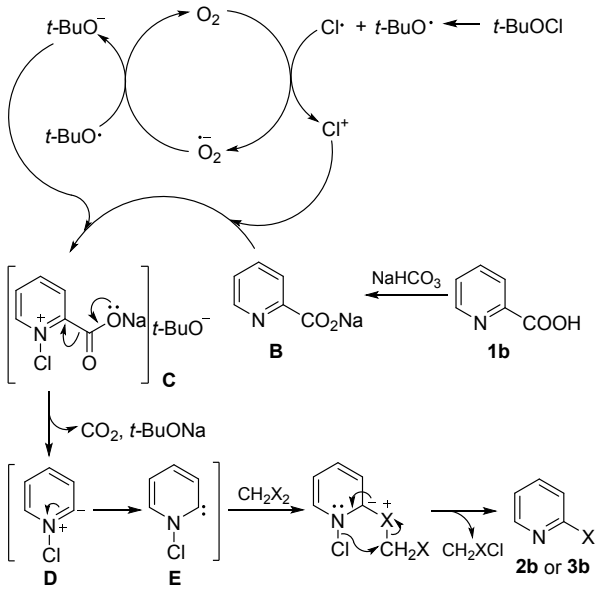


Scheme 2. Control experiments.

Control experiments were conducted to gain insights into the mechanism of this type of decarboxylative halogenation reaction (Scheme 2). No reaction was observed when the reaction of **1a** was performed in the presence of 2 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO; Scheme 4, Eq. 1). This result suggested that this transformation might involve a radical process. No decarboxylation reaction occurred when *t*-BuOCl was removed from the catalytic system, and **1a** was recovered completely (Scheme 4, Eq. 2). *t*-BuOCl was hence required for the reaction to proceed. A 1.7 ratio of **2a** to **3a** was observed when an intermolecular competition reaction between dichloromethane and dibromomethane was conducted at 70 °C (Scheme 4, Eq. 3); the reason was probably that the formation of C-Cl bond was more favorable than the formation of C-Br bond in thermodynamics.

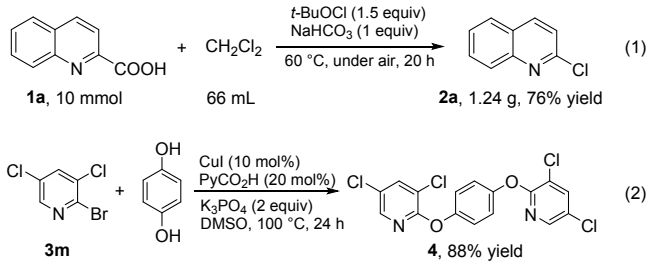
On the basis of the preliminary results and our previous reports,[14] a possible mechanism was proposed (Scheme 3). Radicals Cl· and *t*-BuO· generated from *t*-BuOCl under heating conditions were transformed to Cl^+ and *t*-BuO^- in the presence of oxygen. The reaction of sodium picolinate (**B**) with Cl^+ and *t*-BuO^- would produce intermediate *N*-chloro potassium picolinate (**C**). The intermediate **C** underwent a decarboxylation process to generate pyridine ylide (**D**), which would transform into a carbene intermediate **E**.[15] Dihalomethane reacted with the carbene intermediate **E** to form the desired product **2b** or **3b**. Bromochloromethane (CH_2ClBr) generated in the decarboxylative bromination reaction was verified by gas chromatography–mass spectrometry;[16] this is the reason for the presence of small amount of decarboxylative chlorination product in the decarboxylative bromination reaction.

View Article Online
DOI: 10.1039/C9GC02407G



Scheme 3. Proposed mechanism.

A gram-scale reaction of **1a** with dichloromethane was tested. This reaction was performed at 20 mmol scale and proceeded smoothly, affording product 2a with only a slight decrease in yield (1.24 g, 76%; Scheme 6). The potential application of 2-halogen-substituted pyridine products was explored through synthetic manipulations. As expected, 1,4-bis-(2-(3,5-dichloropyridyloxy)) benzene (**4**, TCPOBOP) was obtained in 88% yield through Buchwald's procedure.[17] TCPOBOP is an agonist ligand for constitutive androstane receptor.[18]



Scheme 4. Gram-scale synthesis and further transformations.

Conclusions

In conclusion, we have developed a convenient and efficient method for synthesizing 2-halogen-substituted pyridines under transition-metal-free conditions. The decarboxylative halogenation reaction of 2-picolinic acids with dihalomethane proceeded smoothly via *N*-chlorocarbene intermediates. The reaction afforded 2-halogen-substituted pyridines in satisfactory to excellent yields. Low-cost and readily available dihalomethane and oxygen were utilized as halogen source and oxidant, respectively, in this protocol. This advantage should make the present methodology not only highly useful but also in accordance with green chemistry principles.

Experimental

General Information

The reactions were performed in clean, oven-dried reactors fitted with air-tight stoppers. All the chemicals were used without further purification. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Avance II-400 spectrometer (400 MHz for 1H, 100 MHz for ^{13}C) or a Varian Inova-500 spectrometer (500 MHz for 1H, 125 MHz for 13C); $CDCl_3$ and TMS were used as solvent and internal standard, respectively. The chemical shifts are reported in ppm downfield (δ) from TMS, the coupling constants J are given in Hz. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. GC-MS analysis was performed on an Agilent 7890A GC interfaced to an Agilent 5975C mass-selective detector (30 m × 0.25 mm capillary column, HP-5MS). TLC was used with SiO_2 (silica gel 60 F254, Merck) as stationary phase. Spots were viewed under UV light. Flash column chromatography was performed with SiO_2 (80 mesh) as stationary phase.

General Procedure for the decarboxylative chlorination

A reaction flask was charged with a mixture of quinoline-2-carboxylic acid (**1a**, 51.9 mg, 0.3 mmol), $NaHCO_3$ (25.2 mg, 0.3 mmol), *t*-BuOCl (51 uL, 0.45 mmol), and dichloromethane (3 mL). The reaction mixture was stirred at 60 °C for 20 h, and then was cooled to room temperature. The solvent was removed under reduced pressure, and the residue obtained was purified via silica gel chromatography (eluent: ethyl acetate : petroleum ether = 1 : 10) to afford 2-chloroquinoline (**2a**) as a white solid.

Procedure for the decarboxylative bromination

A reaction flask was charged with a mixture of quinoline-2-carboxylic acid (**1a**, 51.9 mg, 0.3 mmol), $NaHCO_3$ (25.2 mg, 0.3 mmol); *t*-BuOCl (102 uL, 0.9 mmol) and dibromomethane (2 mL) was added and the mixture was charged with oxygen gas three times. The reaction mixture was stirred at 70 °C for 20 h, and then was cooled to room temperature. The solvent was removed under reduced pressure, and the residue obtained was purified via silica gel chromatography (eluent: ethyl acetate : petroleum ether = 1 : 10) to afford 2-chloroquinoline (**3a**) as a white solid.

Conflicts of interest

There are no conflicts to declare.

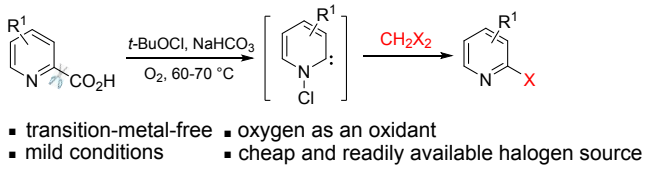
Acknowledgements

We are grateful to the National Natural Science Foundation of China (Nos. 21573032 and 21773021) for their financial support. This work was also supported by the Fundamental Research Funds for the Central Universities (DUT17ZD212).

Notes and references

1. (a) J. Latham, E. Brandenburger, S. A. Shepherd, B. R. K. Menon, *Chem. Rev*., 2018, **118**, 232; (b) A. Samadi, M. F. Revenga, C. Pérez, I. Iriepa, I. Moraleda, M. I. Rodríguez-Franco, J. Marco-Contelles, *Eur. J. Med. Chem*., 2013, **67**, 64; (c) A. Kragler, G. Höfner, K. T. Wanner, M. T. Williams, *Eur. J. Pharmacol*., 2005, **519**, 43.
2. Selected reviews: (a) M. Henrion, V. Ritleng and M. J. Chetcuti, *ACS Catal*., 2015, **5**, 1283; (b) A. Dhakshinamoorthy, A. M. Asiri and H. Garcia, *Chem. Soc. Rev*., 2015, **44**, 1922; (c) A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev*., 2014, **43**, 412; (d) F. Han, *Chem. Soc. Rev*., 2013, **42**, 5270; (e) C. A. Fleckenstein and H. Plenio, *Chem. Soc. Rev*., 2010, **39**, 694; (f) G. C. Fu, *Acc. Chem. Res*., 2008, **41**, 1555.
3. (a) P. S. Fier, K. M. Maloney, *Angew. Chem. Int. Ed*., 2017, **56**, 4478; (b) G. R. Naumiec, L. Cai, S. Lu, V. W. Pike, *Eur. J. Org. Chem.*, 2017, 6593; (c) A. Raba, M. R. Anneser, D. Jantke, M. Cokoja, W. A. Herrmann, F. E. Kühn, *Tetrahedron Lett*., 2013, **54**, 3384; (d) S. R. Inglis, C. Stojkoski, M. M. Branson, J. F. Cawthray, D. Fritz, E. Wiadrowski, S. M. Pyke, G. W. Booker, *J. Med. Chem.*, 2004, **47**, 5405.
4. For direct chlorination of pyridine rings. See: (a) V. Snieckus, *Chem. Rev*., 1990, **90**, 879; (b) W. J. Sell, F. W. Dootson, *J. Chem. Soc*., 1898, **73**, 432.
5. For substitution reaction of 2-hydroxy group with halogen atoms. See: (a) J. Wu, J. Zhou, Y. Shi, J. Zhu, *Synthetic Commun*., 2016, **46**, 1619; (b) W. Kijrungphaiboon, O. Chantarasriwong, W. Chavasiri, *Tetrahedron Lett*., 2012, **53**, 674; (c) Z. Sun, H. Wang, K. Wen, Y. Li, E. Fan, *J. Org. Chem.*, 2011, **76**, 4149; (d) Y. Kato, S. Okada, K. Tomimoto, T. Mase, *Tetrahedron Lett*., 2001, 42, 4849; (e) O. Sugimoto, M. Mori, K. Tanji, *Tetrahedron Lett*. 1999, 40, 7477.
6. For halogenation of pyridine-*N*-oxides. See: (a) D. Wang, Y. Wang, J. Zhao, L. Li, L. Miao, D. Wang, H. Sun, *Tetrahedron*, 2016, 72, 5762; (b) K. Qiao, X. Sun, K. Zhang, N. Zhu, X. Li, K. Guo, *Eur. J. Org. Chem.*, 2016, 1606; (c) D. Wang, H. Jia, W. Wang, Z. Wang, *Tetrahedron Lett*., 2014, **55**, 7130; (d) S. E. Wengryniuk, A. Weickgenannt, C. Reiher, N. A. Strotman, K. Chen, M. D. Eastgate, P. S. Baran, *Org. Lett*., 2013, **15**, 792; (e) P. Narendar, B. Gangadasu, Ch. Ramesh, B. China Raju, V. Jayathirtha Rao, *Synthetic Commun*., 2004, **34**, 1097; (f) J. C. Jung, Y. J. Jung, O. S. Park, *Synthetic Commun*., 2001, **31**, 2507.
7. Other methods for preparation of 2-halogen-substituted pyridines. See: (a) C. A. Malapit, N. Ichiishi, M. S. Sanford, *Org. Lett.*, 2017, **19**, 4142. (b) E. Bednářová, E. Colacino, F. Lamaty, M. Kotora, *Adv. Synth. Catal.*, 2016, **358**, 1916. (c) B. S. Lee, J. H. Lee, D. Y. Chi, *J. Org. Chem.*, 2002, **67**, 7884.
8. Selected reviews: (a) W. I. Dzik, P. P. Lange, L. J. Goossen, *Chem. Sci*., 2012, **3**, 2671; (b) J. D. Weaver, A. Recio, III; A. J. Grenning, J. A. Tunge, *Chem. Rev*. **2011**, *111*, 1846; (c) N. Rodríguez, L. J. Goossen, *Chem. Soc. Rev*., **2011**, *40*, 5030; d) L. J. Goossen, N. Rodríguez, K. Goossen, *Angew. Chem. Int. Ed*., 2008, **47**, 3100.
9. (a) Z. Fu, Y. Jiang, L. Jiang, Z. Li, S. Guo, H. Cai, *Tetrahedron Lett*., 2018, **59**, 4458; (b) Z. Fu, L. Jiang, Q. Zuo, Z. Li, Y. Liu, Z. Wei, H. Cai, *Org. Biomol. Chem*., 2018, **16**, 5416; (c) Z. Fu, Z. Li, Y. Song, R. Yang, Y. Liu, H. Cai, *J. Org. Chem.*, 2016, **81**, 2794; (d) X. Peng, X. F. Shao, Z. Q. Liu, *Tetrahedron Lett*., 2013, **54**, 3079; (e) Y. Luo, X. Pan, J. Wu, *Tetrahedron Lett*. 2010, **51**, 6646.
10. (a) D. Hackenberger, P. Weber, D. C. Blakemore, L. J. Goossen, *J. Org. Chem*., 2017, **82**, 3917; (b) D. Baruah, D. Konwar, *Catal. Commun*., 2015, **69**, 68; (c) X. Li, D. Zou, F. Leng, C. Sun, J. Li, Y. Wu, Y. Wu, *Chem. Commun*., 2013, **49**, 312; (d) S. Dupuy, S. P. Nolan, *Chem. Eur. J*., 2013, **19**, 14034; (e) P. Lu, C. Sanchez, J. Cornella, I. Larrosa, *Org. Lett*., 2009, **11**, 5710; (f) L. C. Campeau, S. Rousseaux, K. Fagnou, *J. Am. Chem. Soc*., 2005, **127**, 18020.
11. (a) J. M. Quibell, G. J. P. Perry, D. M. Cannas, I. Larrosa, *Chem. Sci*., 2018, **9**, 3860; (b) G. J. P. Perry, J. M. Quibell, A. Panigrahi, I. Larrosa, *J. Am. Chem. Soc.*, 2017, **139**, 11527.
12. (a) X. Feng, L. Li, X. Yu, Y. Yamamoto, M. Bao, *Catal. Today* 2016, **274**, 129; (b) X. Yu, J. Wang, Z. Xu, Y. Yamamoto, M. Bao, *Org. Lett.*, 2016, **18**, 2491; (c) X. Feng, Y. Qu, Y. Han, X. Yu, M. Bao, Y. Yamamoto, *Chem. Commun.*, 2012, **48**, 9468.
13. R. Wang, L. Wang, Q. Xu, B. Y. Ren, F. Liang, *Org. Lett*., 2019, **21**, 3072.
14. (a) X. Zhang, X. Feng, C. Zhou, X. Yu, Y. Yamamoto, M. Bao, *Org. Lett*., 2018, **20**, 7059; (b) X. Yu, M. He, J. Wu, C. Zhou, X. Feng, Y. Yamamoto, M. Bao, *Org. Lett*., 2018, **20**, 6780.
15. M. Roselló-Merino, J. Díez, S. Conejero, *Chem. Commun.*, 2010, **46**, 9247 and references therein.
16. The CH_2BrCl is determined by GC-MS, and its spectrum is available in the Supporting Information
17. H. Kinuta, M. Tobisu, N. Chatani, *J. Am. Chem. Soc*., 2015, **137**,1593.
18. M. Qatanani, D. D. Moore, *Curr. Drug Metab.* 2005, **6**, 329

View Article Online
DOI: 10.1039/C9GC02407G



- transition-metal-free
- mild conditions
- oxygen as an oxidant
- cheap and readily available halogen source

The reaction of 2-picolinic acids with *tert*-butyl hypochlorite and sodium hydrogen carbonate in the presence of oxygen proceeded smoothly to generate heterocyclic carbene intermediates, which subsequently reacted with methylene halide to produce 2-halide pyridines in satisfactory to good yields under transition-metal-free conditions.