Organic & Biomolecular Chemistry

Accepted Manuscript

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

COMMUNICATION

Cu-Mediated Direct Regioselective C-2 Chlorination of Indoles

Jing Zhao,[a] Xiuzhi Cheng,[a] Jun Le,[a] Wei Yang,[c] Fengtian Xue,[c] Xuan Zhang[b] and Chao Jiang[a]*

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

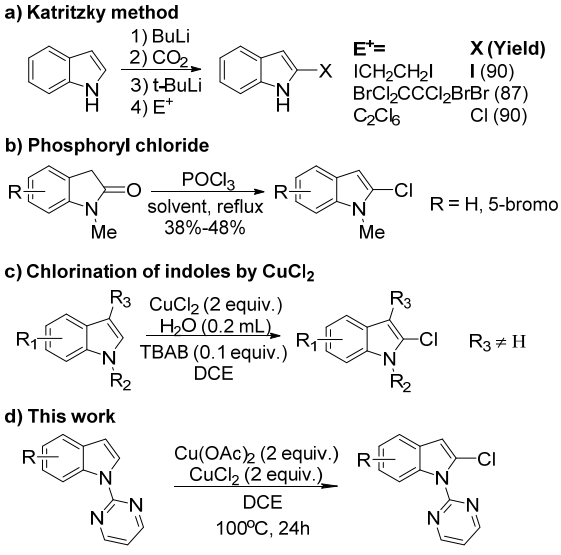
DOI: 10.1039/x0xx00000x

www.rsc.org/

Cu-mediated C-2 chlorination of indoles were accomplished with copper(II) chloride through the use of a directing pyrimidyl protection group. A highly regioselective manner can be achieved on a range of indole substrates with excellent functional group tolerance.

Transition-metal-catalyzed C-H halogenation of (hetero)arenes, in the past decade, has emerged rapidly as a straightforward and efficient synthetic protocol for halogenated (hetero)arenes, which are versatile building blocks in organic synthesis[1] and key structural motifs in numerous natural products and drugs.[2] However, the reported protocols generally depend on precious palladium catalysts.[3] It is strongly desired to develop new reactions mediated by other economically sustainable transition metals.[4] Thus, significant attention has recently been focused on copper catalysts as inexpensive and potentially effective alternatives.[5] Since the first report on copper-catalyzed direct C-H halogenation of 2-arylpyridines by Yu and co-workers in 2006[6a], copper-catalyzed/mediated aryl C-H halogenation with different directing groups using various different halogen sources, such as acyl chlorides, lithium halides, and N-halosuccinimides (NXS), has been reported.[6]

Halogenated indoles are found in nature[7] and used as starting materials for the synthesis of a large number of alkaloids.[8] They are also present in biologically active compounds, for example, 2-chloro-4-fluoroindole nucleoside was designed as shape mimics of 8-oxopurines and used as mechanistic probes of cellular responses to DNA damage.[9] A series of trichlorinated indole nucleosides exhibit potent and selective activity against human cytomegalovirus (HCMV).[10] Thus, C-H halogenation, especially chlorination of indoles has received great attention from synthetic chemists. Due to the electron-rich character of indoles, 3-haloindoles are mainly obtained in eletrophilic halogenation reactions.[11] Development of selective halogenation protocols for the synthesis of 2-haloindoles is still highly challenging.[12] One early example is the Katritzky method that involves lithiation at C-2 position, followed by trapping with halogenating agents (Scheme 1a).[13] Another common procedure comes from the conversion of *N*-substituted oxindole derivatives to 2-haloindoles using phosphoryl chloride (Scheme 1b).[14] Although C-2 chlorination of indole by copper(II) chloride was reported, it required the presence of a substitution at the C-3 position (Scheme 1c).[15] Thus, it is significant to develop an efficient and selective approach toward 2-chloroindoles with mild condition, simple operations and good yields. Herein, we introduce a copper-mediated C-2 chlorination of indoles with excellent regioselectivity, inexpensive and low-toxin copper(II) chloride as the chlorine source. In order to alter the regioselectivity from C-3 to C-2 C−H bonds, a removable pyrimidyl directing group is introduced to the indole nitrogen atom (Scheme 1d). To the best of our knowledge, direct C-

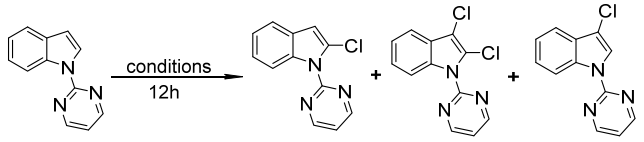


Scheme 1. The synthesis of 2-chloroindoles

[a] *Department of Pharmaceutical Engineering, School of Chemical Engineering, Nanjing University of Science and Technology, Nanjing, Jiangsu, 210094, China E-mail: chaojiang@njust.edu.cn*
[b] *Jiangsu Key Laboratory of Chemical Pollution Control and Resources Reuse, Nanjing University of Science & Technology, Nanjing, Jiangsu, 210094, China*
[c] *Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Baltimore, Maryland 21201, United States*
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Organic & Biomolecular Chemistry Accepted Manuscript

Table 1. Optimization studies for C−2 chlorination of indole



1a **2a** **3a** **4a**

Entry	Conditions[a]	Yield(%)[b] of **2a/3a/4a**
1	$Pd(OAc)_2$ (5 %), NCS (1.1 eq), AcOH, 120°C	0/3/92
2	$Pd(OAc)_2$ (10 %), NCS (1.1 eq), DCE, 100°C	0/12/75
3	$Pd(OAc)_2$ (10 %), NCS (1.1 eq), MeCN, 100°C	0/7/77
4	$Pd(OAc)_2$ (10 %), LiCl (2 eq), $K_2S_2O_8$ (2 eq), AcOH, 120°C	0/15/0
5	$Pd(OAc)_2$ (10 %), LiCl (2 eq), $NaIO_3$ (2 eq), AcOH, 120°C	0/5/14
6	$Pd(OAc)_2$ (10 %), LiCl (2 eq), PIDA (2 eq), AcOH, 120°C	0/8/25
7	$Pd(OAc)_2$ (10 %), $CuCl_2$ (2 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	70/12/0
8	**$CuCl_2$ (2 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C**	**79/10/0**
9	$CuCl_2$ (2 eq), DCE, 100°C	0/18/46
10	NaCl (2 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	n.r.
11	KCl (2 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	n.r.
12	CsCl (2 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	n.r.
13	NH_4Cl (2 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	21/0/0
14	Bu_4NCl (2 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	36/0/0
15	$CuCl_2$ (2 eq), $Cu(OAc)_2$ (1.5 eq), DCE, 100°C	73/14/0
16	$CuCl_2$ (2 eq), $Cu(OAc)_2$ (1 eq), DCE, 100°C	62/23/0
17	$CuCl_2$ (1.5 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	65/7/0
18	$CuCl_2$ (1 eq), $Cu(OAc)_2$ (2 eq), DCE, 100°C	53/6/0

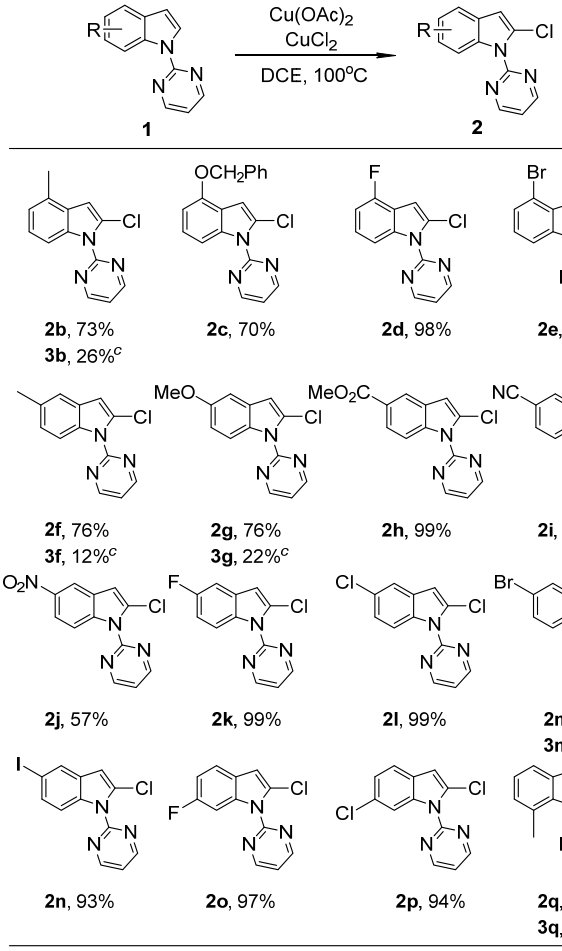
[a] Reaction conditions: **1a** (0.2 mmol), catalyst, chloride and additives as specified, solvent (0.2 M), 12h. [b] Determined by ^{1}H NMR spectroscopy. n.r. = no reaction.

2 chlorination of indoles is not disclosed in the literature.

Initially, we examined the reaction of *N*-pyrimidyl indole **1a** with *N*-chlorosuccinimide (NCS) using $Pd(OAc)_2$ as the catalyst[16] (Table 1). However, only trace amount of desired product **2a** was detected with different solvents, and the major product **4a** came from the direct electrophilic addition of NCS (Entries 1-3). Then, non-electrophilic chlorine source LiCl in combination with an oxidant was used in place of NCS in the reaction, but the results were not improved (Entries 4-6). Subsequently, inspired by Shi's work[3e], we investigated the reaction using $Pd(OAc)_2$ in DCE with $CuCl_2$ as the chlorinating reagent and $Cu(OAc)_2$ as the oxidant. Gratifyingly, the reaction gave the desired product in 70% yield (Entry 7). Then we conducted the reaction in the absence of $Pd(OAc)_2$, to our delight, the chlorinated product **2a** was observed in 79% yield together with 10% of double chlorination product **3a** (Entry 8). Further investigation revealed that $Cu(OAc)_2$ is necessary to obtain product **2a** in good yield (Entry 9). Remarkably, we also attempted to employ other chlorine sources, such as metal chlorides or organic chlorides, but no further success was achieved (Entries 10-14). Lowering the $Cu(OAc)_2$ loading decreased the ratio of **2a**/**3a** (Entries 15-16) and lowering the $CuCl_2$ loading led to the decrease of the conversion (Entries 17-18). Hence, the optimal conditions involve 2.0 equivalents of $Cu(OAc)_2$ and 2.0 equivalents of $CuCl_2$ in DCE at 100 °C for 12h (Entry 8).

With the optimized reaction conditions in hand, we then extended the reaction with a range of substrates. As illustrated in Table 2, this reaction was compatible with different substitutions at C4-, C5-, C6- or C7-positions, and afforded 2-chloroindoles in good

Table 2. The scope of C−2 chlorination of indoles[a,b]



[a] Reaction conditions: substrate (0.2 mmol), $Cu(OAc)_2$ (2.0 equiv), $CuCl_2$ (2.0 equiv), DCE (1 mL), 100°C, 24h (to ensure the completion). [b] Isolated yield. [c] Isolated yield of the double chlorination product **3**.

to excellent yields with high regioselectivity. *N*-Pyrimidyl indoles containing both electron-donating groups (methyl, **2b**, **2f** and **2q**; benzyloxy, **2c**; methoxy, **2g**) and electron-withdrawing groups (ester, **2h**; cyano, **2i**; nitro, **2j**) afforded 2-chlorinated products predominately. Indoles with electron-donating methyl, benzyloxy and methoxy groups usually gave better yields than those with electron-withdrawing cyano and nitro groups, however, significant amount of 2,3-dichloroindole (**3b**, **3f**, **3g** and **3q**) were also obtained in the reaction. Notably, the indoles possessing halogen groups (chloro, **2l** and **2p**; bromo, **2e** and **2m**; fluoro, **2d**[9], **2k** and **2o**; iodo, **2n**) tend to give much higher yields than other groups.

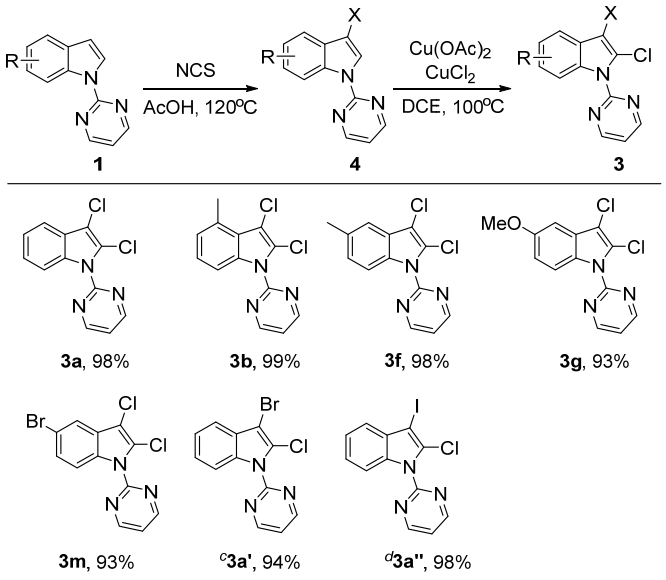
2,3-Dichloroindole motifs have been recognized as a highly valuable building block as evidenced by their presence in many pharmaceutical candidates.[17] Our chlorination protocol could also be applied to the efficient synthesis of 2,3-dichloroindoles[11a, 18](Table 3). The two-step sequence started with the direct C-3 chlorination of **1** with NCS in AcOH. Then the resulting 3-chloroindoles **4** could be converted into 2,3-dichloroindoles **3** under our optimized condition with excellent yields. It is worth noting 2,3-dichloroindoles could not be prepared in good yields by simply ove-

Organic & Biomolecular Chemistry Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins

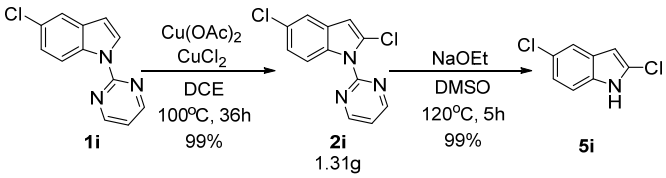
Table 3. The two step synthesis of 2,3-dichloroindoles and 2-chloro-3-bromo/iodo-indoles[a,b]



[a] Step 1, reaction conditions: substrate **1** (0.4 mmol), NCS (1.1 equiv), AcOH (1 mL), 120°C, 5h. Step 2, reaction conditions: **4** (0.2 mmol), $Cu(OAc)_2$ (2.0 equiv), $CuCl_2$ (2.0 equiv), DCE (1 mL), 100°C, 12h. [b] Isolated yield. [c, d] The synthesis of 4a' and 4a'' were different from step 1 (see supporting information).

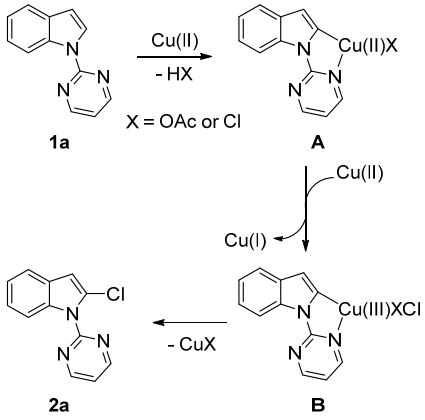
rcharging NCS (3.0 equivalents) in the first step (see supporting information). Furthermore, with 3-bromoindole and 3-iodoindole in hand, 2-chloro-3-bromoindole **3a'** and 2-chloro-3-iodoindole **3a''** could be obtained efficiently. The two-step sequence can only be applied to the electron-rich indole substrates and certain halogen substituted indoles.

Under the optimal conditions, the C-2 chlorination reaction can be carried out on a gram scale without a decrease in yield and selectivity, as illustrated by the preparation of product **2i** to demonstrate the robustness of this strategy (Scheme 2). The gram scale synthesis was achieved with increased reaction time to ensure its completion. Moreover, upon treatment of **2i** with NaOEt in DMSO at 120 °C for 5h, 2,5-chloro-1*H*-indole was isolated with excellent yield.



Scheme 2. Gram scale synthesis and deprotection.

Meanwhile, control experiments using 1*H*-indole and 1-phenylindole as starting material were conducted under the optimized conditions. The former turned into a complex mixture and the latter turned into 3-chloro-1-phenylindole in 60% yield (see supporting information). These results suggested the important role of pyrimidyl group in the C-2 chlorination protocol. Based on these



Scheme 3. Proposed mechanism for the C-H chlorination

results and recent progress on high-valent organometallic copper in catalysis,[19] a possible mechanism was proposed as shown in Scheme 3. First, the coordination of pyrimidyl group of compound **1a** to copper(II) is followed by ortho-C–H bond activation which gives the cyclometalated Cu(II) intermediate **A**. Disproportionation of Cu(II) species lead to the Cu(III) intermediate **B**. Subsequently, the reductive elimination of Cu(III) intermediate **B** can provide the corresponding chlorinated product **2a**. Nonetheless, a single electron transfer (SET) process couldn't be excluded.[6a]

Conclusions

In conclusion, we have demonstrated a versatile and highly efficient Cu-mediated direct C-2 chlorination strategy for indoles with excellent regioselectivity and functional group tolerance. This C-H chlorination protocol strongly exploits the easily removable *N*-(2-pyrimidyl) motif as the metal-directing group. It serves as a novel and alternative route for preparation of 2-chloro-1*H*-indoles. Further understanding of the reaction mechanism and application expansion of this approach to other synthetically useful substrates are ongoing in our laboratory.

This work was supported by the National Natural Science Foundation of China (NSFC) (Grant No. 21402092), Natural Science Foundation of Jiangsu Province (Grant No. BK20140775), Nanjing University of Science and Technology ("Zijin Star Program"), and the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

Notes and references

1. (a) A. F. Littke and G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4176-4211; (b) K. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed.*, 2005, **44**, 4442-4489.
2. (a) R. Stürmer, *Angew. Chem. Int. Ed.*, 1999, **38**, 3307-3308; (b) A. Butler and J. Walker, *Chem. Rev.*, 1993, **93**, 1937-1944.
3. For selected examples of palladium-catalyzed direct halogenation of C–H bonds, see: (a) F. Peron, C. Fossey, J. Sopkova-de Oliveira Santos, T. Cailly and F. Fabis, *Chem. Eur. J.*, 2014, **20**, 7507-7513; (b) Q. Zhang, F. Yang and Y. Wu, *Org. Chem. Front.*, 2014, **1**, 694-697; (c) A. S. Dudnik, N. Chernyak, C. Huang and V. Gevorgyan, *Angew. Chem. Int. Ed. Engl.*, 2010, **49**, 8729-8732; (d) A. R. Dick, K. L. Hull and M. S. Sanford, *J. Am. Chem. Soc.*, 2004,

Organic & Biomolecular Chemistry Accepted Manuscript

126, 2300-2301; (e) X. Wan, Z. Ma, B. Li, K. Zhang, S. Cao, S. Zhang and Z. Shi, *J. Am. Chem. Soc.*, 2006, **128**, 7416-7417; (f) R. B. Bedford, M. F. Haddow, C. J. Mitchell and R. L. Webster, *Angew. Chem. Int. Ed. Engl.*, 2011, **50**, 5524-5527; (g) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama and T. Tanabe, *J. Am. Chem. Soc.*, 2009, **131**, 11310-11311; (h) X. Zhao, E. Dimitrijevic and V. M. Dong, *J. Am. Chem. Soc.*, 2009, **131**, 3466-3467; (i) F. Jafarpour, H. Hazrati, S. Zarei and S. Izadidana, *Synthesis*, 2014, **46**, 1224-1228; (j) B. Song, X. Zheng, J. Mo and B. Xu, *Adv. Synth. Catal.*, 2010, **352**, 329-335; (k) C. Lu, S.-Y. Zhang, G. He, W. A. Nack and G. Chen, *Tetrahedron*, 2014, **70**, 4197-4203; (l) X. T. Ma and S. K. Tian, *Adv. Synth. Catal.*, 2013, **355**, 337-340; (m) X. C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell and J. Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 10326-10329; (n) T. S. Mei, R. Giri, N. Maugel and J. Q. Yu, *Angew. Chem. Int. Ed. Engl.*, 2008, **47**, 5215-5219; (o) L. Chu, X. C. Wang, C. E. Moore, A. L. Rheingold and J. Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 16344-16347; (p) X. Sun, G. Shan, Y. Sun and Y. Rao, *Angew. Chem. Int. Ed. Engl.*, 2013, **52**, 4440-4444; (q) E. Dubost, C. Fossey, T. Cailly, S. Rault and F. Fabis, *J. Org. Chem.*, 2011, **76**, 6414-6420; (r) R. B. Bedford, J. U. Engelhart, M. F. Haddow, C. J. Mitchell and R. L. Webster, *Dalton Trans*, 2010, **39**, 10464-10472; (s) C. Chen and X. Tong, *Org. Chem. Front.*, 2014, **1**, 439; (t) D. Sarkar, F. S. Melkonyan, A. V. Gulevich and V. Gevorgyan, *Angew. Chem. Int. Ed. Engl.*, 2013, **52**, 10800-10804; (u) R. Giri, X. Chen and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2005, **44**, 2112; (v) T. S. Mei, D. H. Wang and J. Q. Yu, *Org. Lett.*, 2010, **12**, 3040-3043; (w) D. Gao, Q. Gu and S. L. You, *ACS Catal*., 2014, **4**, 2741-2745; (x) L. Chu, K. J. Xiao and J. Q. Yu, *Science*, 2014, **346**, 451-455.

4. For selected examples of direct halogenation of C–H bonds catalyzed by other metals, see: (a) F. Mo, J. M. Yan, D. Qiu, F. Li, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed. Engl.*, 2010, **49**, 2028-2032; (b) N. Schroder, J. Wencel-Delord and F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 8298-8301; (c) L. Wang and L. Ackermann, *Chem. Commun.*, 2014, **50**, 1083-1085; (d) N. Kuhl, N. Schroder and F. Glorius, *Org. Lett*., 2013, **15**, 3860-3863; (e) H. Hwang, J. Kim, J. Jeong and S. Chang, *J. Am. Chem. Soc.*, 2014, **136**, 10770-10776; (f) G. Qian, X. Hong, B. Liu, H. Mao and B. Xu, *Org. Lett.*, 2014, **16**, 5294-5257; (g) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17722-17725.
5. For selected reviews and key papers on copper-catalyzed/mediated C-H activation, see: (a) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464-3484; (b) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas and S. S. Stahl, *J. Am. Chem. Soc.*, 2010, **132**, 12068-12073; (c) K. Hirano and M. Miura, *Chem. Commun.*, 2012, **48**, 10704-10714; (d) X. X. Guo, D.-W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2014, **115**, 1622-1651; (e) K. Hirano and M. Miura, *Chem. Lett.*, 2015, **44**, 868-873; (f) A. A. Kulkarni and O. Daugulis, *Synthesis*, 2009, 4087-4109; K. Hirano and M. Miura, *Top. Catal.*, 2014, **57**, 878-889; (g) M. Nishino, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed. Engl.*, 2012, **51**, 6993-6997.
6. For selected examples of copper-catalyzed/mediated direct halogenation of C–H bonds, see: (a) X. Chen, X.-S. Hao, C. E. Goodhue and J. Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790-6791; (b) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem. Int. Ed. Engl.*, 2011, **50**, 11062-11087; (c) S. Mo, Y. Zhu and Z. Shen, *Org. Biomol. Chem.*, 2013, **11**, 2756-2760; (d) B. Urones, A. M. Martinez, N. Rodriguez, R. G. Arrayas and J. C. Carretero, *Chem. Commun.*, 2013, **49**, 11044-11046; (e) B. Li, B. Liu and B. F. Shi, *Chem. Commun.*, 2015, **51**, 5093-5096; (f) A. M. Suess, M. Z. Ertem, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 9797-9804; (g) Z.-J. Du, L.-X. Gao, Y.-J. Lin and F.-S. Han, *ChemCatChem*, 2014, **6**, 123-126; (h) B. Yao, Z.-L. Wang, H. Zhang, D.-X. Wang, L. Zhao and M.-X. Wang, *J. Org. Chem.*, 2012, **77**, 3336-3340; (i) W. Wang, C. Pan, F. Chen and J. Cheng, *Chem. Commun.*, 2011, **47**, 3978-3980.
7. (a) G. Gribble, *J. Nat. Prod.*, 1992, **55**, 1353-1395; (b) C. C. Hughes, A. Prieto-Davo, P. R. Jensen and W. Fenical, *Org. Lett.*, 2008, **10**, 629-631; (c) G. Bartoli, G. Bencivenni and R. Dalpozzo, *Chem. Soc. Rev.*, 2010, **39**, 4449-4465; (d) R. S. Norton and R. J. Wells, *J. Am. Chem. Soc.*, 1982, **104**, 3628-3635.
8. (a) C. K. Narkowicz, A. J. Blackman, E. Lacey, J. H. Gill and K. Heiland, *J. Nat. Prod.*, 2002, **65**, 938-941; (b) M. Somei and F. Yamada, *Nat. Prod. Rep.*, 2004, **21**, 278-311; (c) G. W. Gribble, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1045-1075.
9. Y. Taniguchi and E. T. Kool, *J. Am. Chem. Soc.*, 2007, **129**, 8836-8844.
10. (a) J. J. Chen, Y. Wei, J. C. Drach and L. B. Townsend, *J. Med. Chem.*, 2000, **43**, 2449-2456; (b) J. D. Williams, J. J. Chen, J. C. Drach and L. B. Townsend, *J. Med. Chem.*, 2004, **47**, 5753-5765.
11. (a) J. Yan, T. Ni and F. Yan, *Tetrahedron Lett.*, 2015, **56,** 1096-1098; (b) S. M. Maddox, C. J. Nalbandian, D. E. Smith and J. L. Gustafson, *Org. Lett.*, 2015, **17**, 1042-1045; (c) L. Shi, D. Zhang, R. Lin, C. Zhang, X. Li and N. Jiao, *Tetrahedron Lett.*, 2014, **55**, 2243-2245; (d) W. C. Frank, Y. C. Kim and R. F. Heck, *J. Org. Chem.*, 1978, **43**, 2947-2949; (e) L. Yang, Z. Lu and S. S. Stahl, *Chem. Commun.*, 2009, 6460-6462; For the invention of a new guanidine-based chlorinating reagent, "Palau'chlor", please see: (f) R. A. Rodriguez, C. M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate and P. S. Baran, *J. Am. Chem. Soc.*, 2014, **136**, 6908-6911.
12. For recent syntheses of 2-bromoindoles (one example of 2-chloroindole was included) through cyclization, see: (a) M. Wang, P. Li, W. Chen and L. Wang, *RSC Advances*, 2014, **4**, 26918; (b) P. Li, Y. Ji, W. Chen, X. Zhang and L. Wang, *RSC Advances*, 2013, **3**, 73.
13. (a) T. Fukuda, Y. Mine and M. Iwao, *Tetrahedron*, 2001, **57**, 975-979; (b) J. Bergman and L. Venemalm, *J. Org. Chem.*, 1992, **57**, 2497-2502.
14. (a) B. Liegault, I. Petrov, S. I. Gorelsky and K. Fagnou, *J. Org. Chem.*, 2010, **75**, 1047-1060; (b) T. Yamato, H. Hiyoshi, J.-H. Do, X. Feng and T. Matsumoto, *Heterocycles*, 2011, **83**, 1017.
15. (a) E. Balogh-Hergovich and G. Speier, *J. Chem. Soc.*, 1986, 2305-2308; (b) N.-X. Wang, J.-H. Li, S. Tang and Y.-X. Xie, *Synthesis*, 2007, **10**, 1535-1541.
16. (a) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Tetrahedron*, 2006, **62**, 11483-11498; (b) D. Kalyani, A. R. Dick, W. Q. Anani and M. S. Sanford, *Org. Lett.*, 2006, **8**, 2523-2526.
17. (a) H. Dehmlow, B. Kuhn, N. Panday, H. Ratni, T. Schulz-Gasch and M. B. Wright, *Patent:* US 0245515A1, 2005; (b) S. B. Lee, S. Y. Peak, S. K. Yoon, S. H. Yoon and J. S. Choi, *Patent:* WO 073904A1, 2014; (c) L. B. Townsend and J. C. Drach, *Patent:* WO 034943A1, 2005; (d) P. Burton, A. Kozakiewicz, J. A. Morris, C. J. Mathews and S. Shanahan, *Patent:* WO 160126A1, 2013; (e) J. Gary, A. Johan, R. Rune, *Patent:* WO 003703A1, 2008.
18. (a) H. Hamamoto, H. Umemoto, M. Umemoto, C. Ohta, M. Dohshita and Y. Miki, *Synlett*, 2010, **2010**, 2593-2596; (b) S. A. Amelichev, L. S. Konstantinova, K. A. Lyssenko, O. A. Rakitin and C. W. Rees, *Org. Biomol. Chem.*, 2005, **3**, 3496-3501; (c) L. S. Konstantinova, O. A. Rakitin and C. W. Rees, *Chem. Commun.*, 2002, 1204-1205; (d) M. R. Brennan, K. L. Erickson, F. S. Szmalc, M. J. Tansey and J. M. Thornton, *Heterocycles*, 1986, **24**, 2879-2885; (e) K. Erickson, M. Brennan and P. Namnum, *Synth. Commun.*, 1981, **11**, 253-259.
19. A. J. Hickman and M. S. Sanford, *Nature*, 2012, **484**, 177-185.

Organic & Biomolecular Chemistry Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

Please do not adjust margins