Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2018, **16**, 886

Received 12th December 2017,
Accepted 10th January 2018

DOI: 10.1039/c7ob03081a

rsc.li/obc

t-BuONa-mediated direct C–H halogenation of electron-deficient (hetero)arenes†

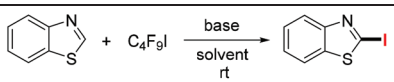
Xia Liu,[a,b] Xin Zhao,[a] Fushun Liang *[a,b] and Baoyi Ren *[c]

An efficient halogenation of electron-deficient (hetero)arenes is described. The reaction utilizes common *t*-BuONa as a catalyst (for iodination) or a promoter (for bromination and chlorination), and perfluorobutyl iodide, CBr_4 or CCl_4 as the readily-available halogenating agents, respectively. The protocol features broad scope, high efficiency, mild conditions and gram scalability. An ionic pathway involving halogen bond formation and halophilic attack is proposed. The utility of the resulting iodinated heteroarenes is demonstrated in visible light-mediated C_{aryl}–C_{aryl} cross-coupling reaction.

(Hetero)aromatic halides are valuable and fundamental building blocks that are used to construct new carbon–carbon and carbon–heteroatom bonds in organic synthesis and drug design.[1] Quite a few important classical cross-coupling reactions such as the Heck reaction, the Suzuki reaction and the Buchwald–Hartwig reaction require aryl halides as starting materials.[2] Recently developed metal-free and electron transfer-mediated cross-coupling occurs between halogenated (hetero)aromatics and aromatics.[3] Hence, it is always an important task to develop efficient preparation methods of (hetero)aromatic halides. Until now, there have been many known methods for the preparation of haloarenes from aromatics especially from electron-rich systems. However, electron-deficient (hetero)arenes are difficult to be halogenated,[4] often suffering from harsh conditions (either strong alkyllithium bases at extremely low temperature or relatively weak bases upon heating), multi-steps and/or low yields. Among all the halogenated aromatics, aryl iodides are less accessible and particularly expensive due to the weak electrophilic nature of iodine. Based on our previous work on halogen-bonding interaction/activation,[5] herein, we would like to report an efficient halogenation of electron-deficient (hetero)arenes under mild conditions, employing common *t*-BuONa as the catalyst[6] (for iodination) or the promoter (for bromination and chlorination) with broad halogen compatibility (Cl, Br and I).

The initial optimization started from benzothiazole and perfluorobutyl iodide (Table 1). The reaction with *t*-BuONa (1.2 equiv.) proceeded efficiently in DMF at room temperature, giving 2-iodobenzothiazole (**3a**) in nearly quantitative yield in 20 min (entry 1). NaOH also worked well (entry 2), however, K_2CO_3 and DBU proved to be ineffective (entries 3 and 4). Solvent screening indicated that DMSO, MeCN, DCM and toluene were much less efficient than DMF (entries 5–8). It was interesting to note that a catalytic amount of *t*-BuONa of 50 mol% loading can drive the reaction to completion, without sacrificing the yield (entry 9). Comparatively, in the absence of *t*BuONa, no reaction was observed (entry 10). All the reactions were conducted in open air and no precaution needs to be taken to exclude moisture from the glassware.

Table 1 Optimization of the reaction conditions[a,b]



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

Entry	Base (equiv.)	Solvent	*t*	Yield[b] (%)
1	*t*-BuONa (1.2)	DMF	20 min	99
2	NaOH (1.2)	DMF	25 min	98
3	K_2CO_3 (2.2)	DMF	6 h	0
4	DBU (1.2)	DMF	6 h	Trace
5	*t*-BuONa (1.2)	DMSO	6 h	50
6	*t*-BuONa (1.2)	MeCN	6 h	Trace
7	*t*-BuONa (1.2)	DCM	6 h	0
8	*t*-BuONa (1.2)	Toluene	6 h	0
9	***t*-BuONa (0.5)**	**DMF**	**25 min**	**99**
10	—	DMF	6 h	nr

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1.1 equiv.) and base in solvent (0.5 mL). [b] Isolated yield. nr = no reaction.

[a]*College of Chemistry, Liaoning University, Shenyang 110036, China. E-mail: fsliang@lnu.edu.cn*
[b]*Department of Chemistry, Northeast Normal University, Changchun 130024, China*
[c]*College of Applied Chemistry, Shenyang University of Chemical Technology, Shenyang 110142, China. E-mail: renbaoyi@syuct.edu.cn*

†Electronic supplementary information (ESI) available: Experimental procedure, and characterization data for all compounds (PDF). See DOI: 10.1039/c7ob03081a

The survey of alternative iodination reagents revealed that *N*-iodosuccinamide, iodine and C_6F_5I were not competent in the reaction (Table 2, entries 1–3). As for bromination reaction, 2-bromobenzothiazole (**4a**) could be obtained in 71% yield, using perfluorooctyl bromide (1.1 equiv.) as the bromine source (entry 4). Thus, other brominating reagents including CBr_4, NBS and BrCN were tried (entries 5–7). Delightedly, CBr_4 can be used as an efficient bromine source, giving **4a** in 93% yield (entry 5). The same case was observed when CCl_4 was employed as the chlorine source (entries 8 and 9).

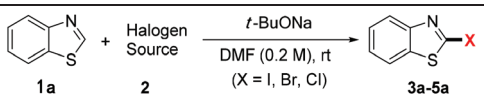
With the optimized conditions in hand, we examined the scope of the halogenation reaction (Table 3). Electron-deficient (hetero)aromatic hydrocarbons, such as benzothiazole, benzoxazole, *N*-methylbenzoimidazole and aromatics like pentafluorobenzene and 1,4-dibromo-2-nitrobenzene could be iodinated efficiently, giving products **3a–e** in high to excellent yields (81–99%). The amount of *t*-BuONa required can be as low as 50 mol%. Using 2.1 equiv. of perfluorobutyl iodide, thiazole, 5-phenyloxazole and pyridine *N*-oxide afforded diiodination products **3f–h** as the main products in excellent yields. Differently, the iodination of *N*-methylimidazole did not proceed well in DMF solution. Instead, with toluene as the solvent, the iodination reaction proceeds smoothly, giving the mono-iodination and diiodination products as a mixture. We think that the reaction performed in toluene may undergo a different pathway from that in DMF.

Monobromination for benzothiazole, benzoxazole, *N*-methylimidazole and *N*-methylimidazole (**4a–d**), as well as dibromination for thiazole and 5-phenyloxazole (**4e** and **4f**) were achieved in 63–93% yields. In the presence of 1.1 equiv. of CCl_4 and 4 equiv. of *t*-BuONa, 2-chlorobenzothiazole (**5a**) and 2-chloro-1-methylbenzoimidazole (**5b**) were obtained in 88% and 51% yields, respectively. 2,4-Dichloro-5-phenyloxazole (**5c**) was prepared with 2.1 equiv. of CCl_4 and 4 equiv. of *t*-BuONa. It is a major problem in bromination and chlorination that *t*-BuONa could not be loaded with catalytic amount, contrary to that of iodination. Noteworthily, when pentafluorobenzene was subjected to the reaction sequence, pentafluoro-6-(tribromomethyl)benzene (**6**) and pentafluoro-6-(trichloromethyl)benzene (**7**), rather than the corresponding brominated and chlorinated products, were achieved in 92% and 77% yields, respectively (eqn (1) and (2)).[7,8]

To demonstrate the practicality of this protocol, large scale reactions were conducted under otherwise identical conditions (Scheme 1). 10 g **1a** reacted with perfluorobutyl iodide (28.15 g) to give **3a** (17.57 g) in 91% yield (eqn (3)). In a mixture of **1a** (5 g, 36.99 mmol) with CBr_4 (13.49 g, 40.68 mmol) and *t*-BuONa (4 equiv.) in DMF, product **4a** (6.05 g) was obtained in 76% yield (eqn (4)).

To gain insight into the reaction mechanism, a control experiment was conducted (Scheme 2). The main question is whether radical intermediates are involved in the reaction. Thus, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), an

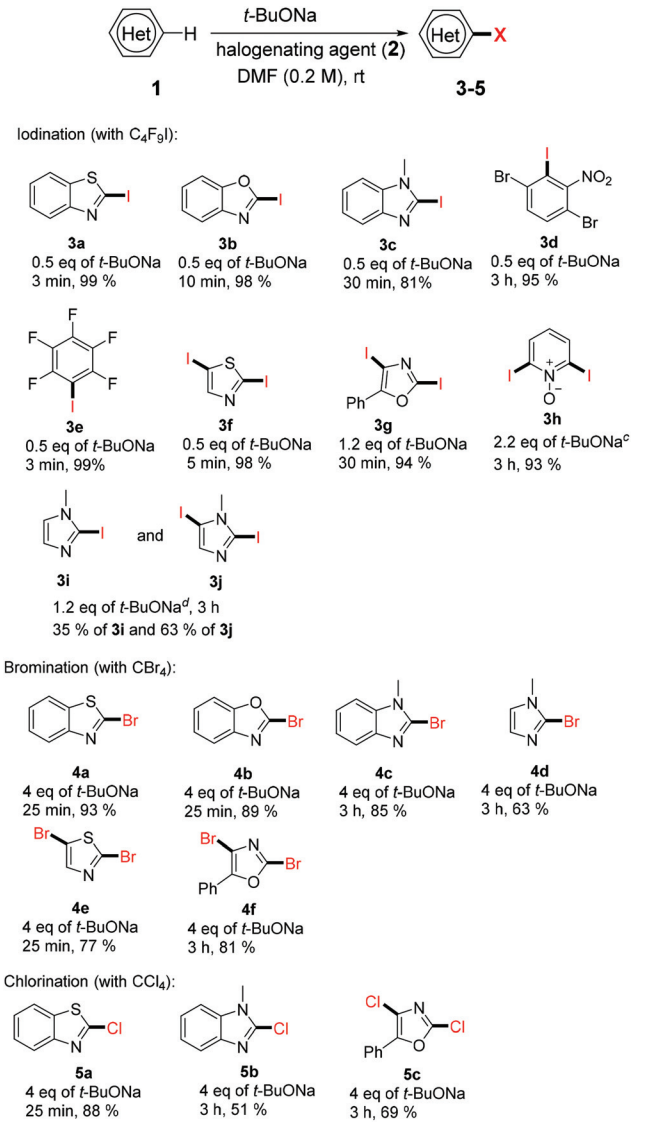
Table 2 Investigation of the halogen sources[a]



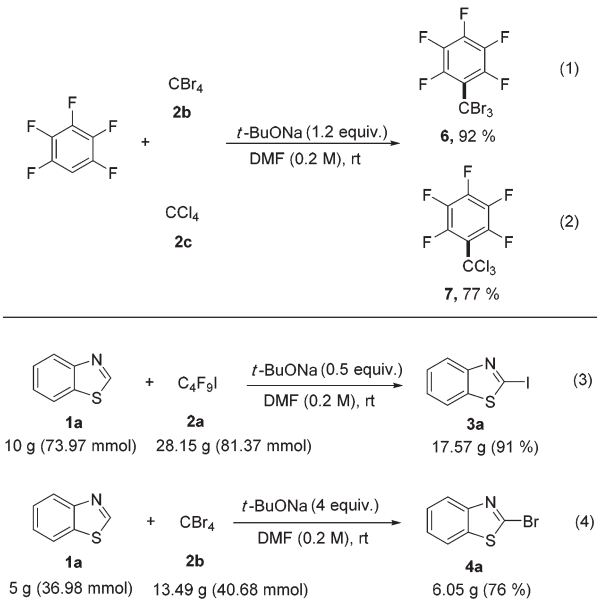
Entry	Halogen source	Yield (%)	Entry	Halogen source	Yield[b] (%)
Iodine source			5	CBr_4	93[c]
1	NIS	0	6	NBS	0
2	I_2	0	7	BrCN	Trace
3	C_6F_5I	90	Chlorine source		
Bromine source			8	CCl_4	88[c]
4	$C_8F_{17}Br$	71	9	NCP	0

[a] Reaction conditions: **1a** (0.1 mmol), **2** (1.1 equiv.) and *t*-BuONa (1.2 equiv.) in DMF (0.5 mL). [b] Isolated yield. [c] *t*-BuONa (4 equiv.) was used.

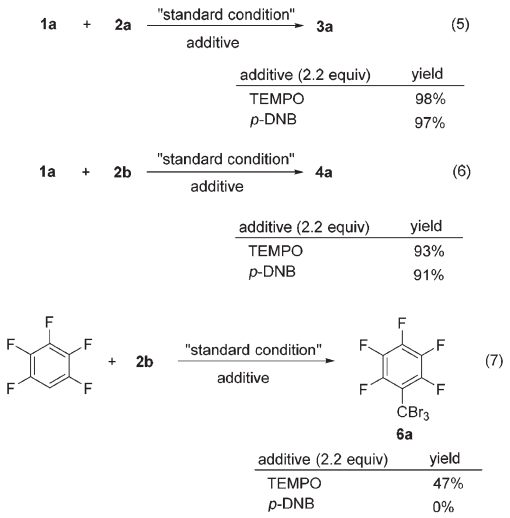
Table 3 Halogenation of heteroarenes[a,b]



[a] Reaction conditions: **1** (0.1 mmol), *t*-BuONa and **2a** (1.1 or 2.1 equiv.) in DMF (0.5 mL). [b] Isolated yields. [c] In dry DMF (0.5 mL). [d] In toluene (0.5 mL).



Scheme 1 Gram-scale reaction.

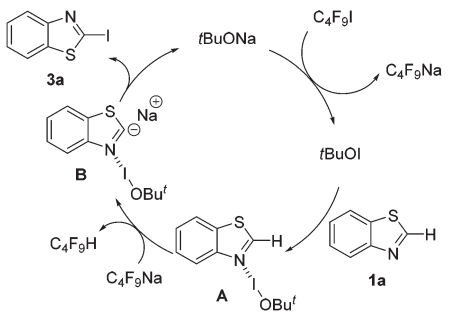


Scheme 2 Control experiment.

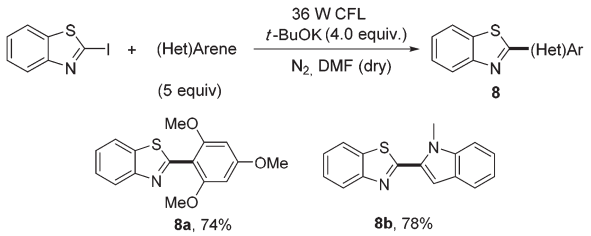
efficient free radical scavenger, was introduced as an additive under standard conditions.[9] As a result, compounds **3a** and **4a** were produced with almost the same efficiency, suggesting that TEMPO has no effect on the reactions (eqn (5) and (6)). Furthermore, we examined the reactions in the presence of a single electron transfer (SET) inhibitor, *p*-dinitrobenzene (*p*-DNB), and no yield decrease was observed. In contrast, in the case of trihalogenative methylation reaction to form compounds **6** and **7**, the reactions were partly or completely quenched in the presence of TEMPO or *p*-DNB (eqn (7), Scheme 2).

On the basis of all the experimental results, as well as the literature report,[4e] an ionic mechanism was proposed, which involves the formation of a *t*-butyl hypohalide from the metathesis of *t*BuONa and C_4F_9I[10] and subsequent halogen bond adduct **A** leading to the α-C–H of **1a** to be more acidic.[11,12] Thus, hydrogen abstraction by C_4F_9Na becomes feasible, and carbanion **B** is generated. The final iodinated product **3a** is formed *via* halophilic attack (for example, *via* a three-membered iodonium ion intermediate),[13] along with the liberation of *t*-BuONa, to complete the catalytic cycle (Scheme 3).

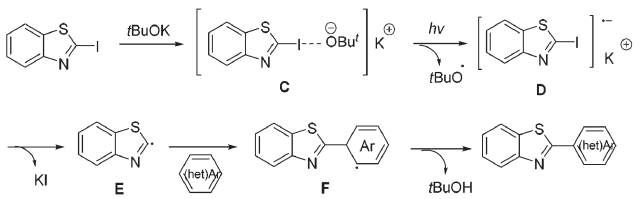
Finally, the utility of the halogenated heterocycles was illustrated by performing visible-light mediated cross-coupling reaction, which is quite attractive in current organic synthetic chemistry.[14] In the presence of *t*-BuOK (4 equiv.), the cross-coupling of 2-iodobenzothiazole with 1,3,5-trimethoxybenzene and *N*-methylindole was successful, giving the coupled products **8a** and **8b** in moderate yields (Scheme 4). The possible mechanism for the metal-free cross-coupling reaction is given in Scheme 5. A halogen bond adduct **C** can be formed between sodium *t*-butoxide and 2-iodobenzothiazole. Under the action of visible light, single-electron-transfer occurs, yielding radical anion **D** with the liberation of a *t*-BuO radical. C–I bond cleav-



Scheme 3 Proposed mechanism for the halogenation.



Scheme 4 Visible light-mediated cross-coupling of halogenated heteroaryls.



Scheme 5 Possible mechanism for the cross-coupling.

age leads to persistent benzothiazole radical **E**,[15] which would add to (hetero)aromatics, giving carbon radical **F**. Hydrogen abstraction by the *t*-BuO radical affords the final C–C coupling products. The role of *t*-BuOK in the cross-coupling is a halogen bond acceptor as well as an electron donor.[16]

Conclusions

In conclusion, we have developed a novel method for the halogenation of an array of electron-deficient (hetero)arenes. The protocol exhibits a broad scope and is efficient and practical. Among them, *t*-BuONa-catalyzed iodination by harnessing perfluorobutyl iodide as the iodination reagent was unprecedented. The utility of the halogenated products is demonstrated by visible light-mediated and metal-free cross-coupling reaction with (hetero)arenes.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

Financial support from NSFC (21172034 and 21372039) is greatly acknowledged.

Notes and references

1 (*a*) R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, New York, 1990; (*b*) P. B. De La Mare, *Electrophilic Halogenation*, Cambridge University Press, Cambridge, 1976, ch. 5.

2 (*a*) A. de Meijere, S. Bräse and M. Oestreich, *Metal Catalyzed Cross-Coupling Reactions and More*, 3 Volume Set. Wiley, 2013; (*b*) I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036.

3 For a review: see: (*a*) C. L. Sun and Z. J. Shi, *Chem. Rev.*, 2014, **114**, 9219. For selected papers: (*b*) C.-L. Sun, H. Li, D.-G. Yu, M. Yu, X. Zhou, X.-Y. Lu, K. Huang, S.-F. Zheng, B.-J. Li and Z.-J. Shi, *Nat. Chem.*, 2010, **2**, 1044; (*c*) J. Chen and J. Wu, *Angew. Chem., Int. Ed.*, 2017, **56**, 3951; (*d*) S. Yanagisawa, K. Ueda, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 4673.

4 Selected examples: (*a*) Q. Q. Shi, S. Y. Zhang, J. X. Zhang, V. F. Oswald, A. Amassian, S. R. Marder and S. B. Blakey, *J. Am. Chem. Soc.*, 2016, **138**, 3946; (*b*) G. K. S. Prakash, T. Mathew, D. Hoole, P. M. Esteves, Q. Wang, G. Rasul and G. A. Olah, *J. Am. Chem. Soc.*, 2004, **126**, 15770; (*c*) S. Usui, Y. Hashimoto, J. V. Morey, A. E. H. Wheatley and M. Uchiyama, *J. Am. Chem. Soc.*, 2007, **129**, 15102; (*d*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2011, **133**, 13577; (*e*) H.-Q. Do and O. Daugulis, *Org. Lett.*, 2009, **11**, 421; (*f*) J.-M. L'Helgoual'c, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama and F. Mongin, *J. Org. Chem.*, 2008, **73**, 177; (*g*) X. Zhao, F. Ding, J. Li, K. Lu, X. Lu, B. Wang and P. Yu, *Tetrahedron Lett.*, 2015, **56**, 511; (*h*) C. Boga, E. Del Vecchio, L. Forlani and P. E. Todesco, *J. Organomet. Chem.*, 2000, **601**, 233; (*i*) I. Popov, H.-Q. Do and O. Daugulis, *J. Org. Chem.*, 2009, **74**, 8309; (*j*) L. Li, W. Liu, H. Zeng, X. Mu, G. Cosa, Z. Mi and C.-J. Li, *J. Am. Chem. Soc.*, 2015, **137**, 8328.

5 Selected halogen bonding-mediated reactions from our group: (*a*) Y. Wei, S. Lin and F. Liang, *Org. Lett.*, 2012, **14**, 4202; (*b*) Y. Wei, S. Lin, F. Liang and J. Zhang, *Org. Lett.*, 2013, **15**, 852; (*c*) Y. Wei, F. Liang and X. Zhang, *Org. Lett.*, 2013, **15**, 5186; (*d*) M. Li, H. Yuan, B. Zhao, F. Liang and J. Zhang, *Chem. Commun.*, 2014, **50**, 2360; (*e*) H. Tan, M. Li and F. Liang, *RSC Adv.*, 2014, **4**, 33765; (*f*) L. Zhang, Y. Li, L.-Y. Jin and F. Liang, *RSC Adv.*, 2015, **5**, 65600; (*g*) R. Wang, W. Guan, Z.-B. Han, F. Liang, T. Suga, X. Bi and H. Nishide, *Org. Lett.*, 2017, **19**, 2358.

6 *t*-BuONa is abundant, inexpensive, commercially available and bench stable. For *t*-BuONa(K)-catalyzed reactions, see: (*a*) A. A. Toutov, W.-B. Liu, K. N. Betz, A. Fedorov, B. M. Stoltz and R. H. Grubbs, *Nature*, 2015, **518**, 80; (*b*) X. Shi, J. Guo, J. Liu, M. Ye and Q. Xu, *Chem. – Eur. J.*, 2015, **21**, 9988.

7 A radical pathway is most possibly involved in the reaction. P. R. Schreiner, O. Lauenstein, I. V. Kolomitsyn, S. Nadi and A. A. Fokin, *Angew. Chem., Int. Ed.*, 1998, **37**, 1895. See Scheme S1† for the possible mechanism.

8 A. Orlinkov, I. Akhrem, S. Vitt and M. Vol'pin, *Tetrahedron Lett.*, 1996, **37**, 3363.

9 For alkane radical iodination by *t*-BuOI, see: R. Montoro and T. Wirth, *Org. Lett.*, 2003, **5**, 4729.

10 A distinct coloration was observed when mixing *t*BuONa and C_4F_9I in DMF solution. For the formation of *t*BuOI, see: (*a*) C. Walling and B. B. Jacknow, *J. Am. Chem. Soc.*, 1960, **82**, 6108; (*b*) C. Walling and A. Padwa, *J. Org. Chem.*, 1962, **27**, 2976; (*c*) S. Zhu, C. Qing, C. Zhou, J. Zhang and B. Xu, *J. Fluorine Chem.*, 1996, **79**, 77; (*d*) P. Feng, K. N. Lee, J. W. Lee, C. Zhan and M.-Y. Ngai, *Chem. Sci.*, 2016, **7**, 424; (*e*) S. Okumura, C.-H. Lin, Y. Takeda and S. Minakata, *J. Org. Chem.*, 2013, **78**, 12090.

11 For the halogen bond adduct formation, see: P. Metrangolo and G. Resnati, *Halogen Bonding: Fundamentals and Applications*, Springer, Berlin, 2008. In some cases, the strength of halogen bonding is comparable to that of Ag(I) coordination. See: S. M. Walter, F. Kniep, E. Herdtweck and S. M. Huber, *Angew. Chem., Int. Ed.*, 2011, **50**, 7187.

12 S. I. Gorelsky, *Organometallics*, 2012, **31**, 794. Direct hydrogen abstraction was difficult, by comparing the pK_a values of benzothiazole and benzoxazole and the base used. The pK_a values of benzothiazole and benzoxazole are 24.4 and 27.0 (in DMSO), while the pK_a of *t*-BuOH (conjugate acid of *t*BuONa) is 29.4 in DMSO. See: (*a*) F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456; (*b*) K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568. Thus, we think that the formation of a halogen bond adduct in the

first step, followed by deprotonation and iodination, would be much reasonable.

13 N. S. Zefirov and D. I. Makhon'kov, *Chem. Rev.*, 1982, **82**, 615.

14 For visible light-induced C–C coupling, see: (*a*) A. Arora and J. D. Weaver, *Acc. Chem. Res.*, 2016, **49**, 2273; (*b*) J. Xuan, Z.-G. Zhang and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2015, **54**, 15632; (*c*) F. Yang, J. Koeller and L. Ackermann, *Angew. Chem., Int. Ed.*, 2016, **55**, 4759; (*d*) I. Ghosh, R. S. Shaikh and B. König, *Angew. Chem., Int. Ed.*, 2017, **56**, 8544.

15 (*a*) H. Fischer, *Chem. Rev.*, 2001, **101**, 3581; (*b*) J. Ke, Y. Tang, H. Yi, Y. Cheng, C. Liu, A. Lei and Y. Li, *Angew. Chem., Int. Ed.*, 2015, **54**, 6604.

16 J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 7402.

