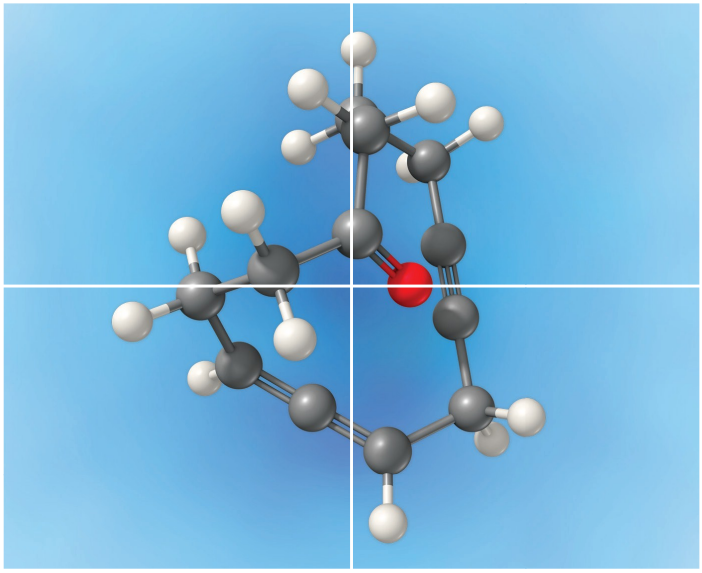
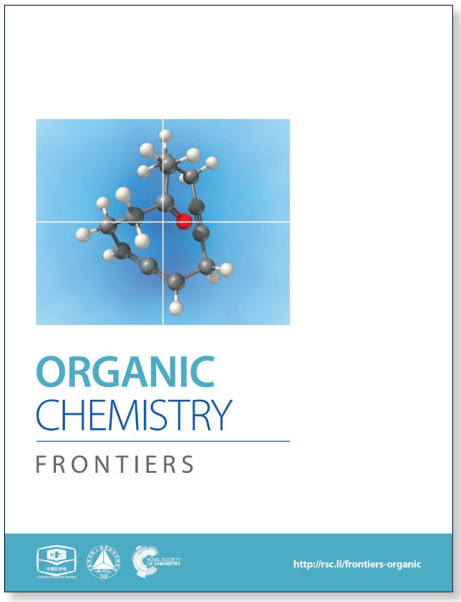
ORGANIC CHEMISTRY

FRONTIERS



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.

Journal Name

ARTICLE

Copper-catalyzed tandem arylation-cyclization of 2-alkynylaryl isothiocyanates with diaryliodonium salts: an efficient synthesis of thiochromeno[2,3-*b*]indoles

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

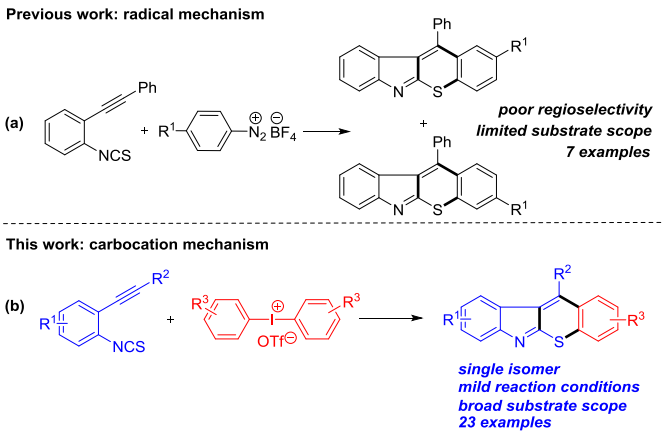
Li-Rong Wen,[a] Qiang-Yu Shen,[a] Wei-Si Guo,[a,*] and Ming Li[a,*]

A catalytic tandem arylation–cyclization approach from 2-alkynylphenyl isothiocyanates with diaryliodonium salts is described. The reaction is performed under mild conditions and the thiochromeno[2,3-*b*]indoles are obtained in moderate to good yields. This tandem protocol involves chemoselective *S*-arylation, regioselective *5-endo-trig* cyclization and Friedel–Crafts-type cyclization process. Two C–C bonds, one C–S bond, and two heterocyclic rings are formed in a single step. Preliminary mechanistic studies indicate that a carbocation mechanism is involved.

Introduction

It is found that 2,3-fused polycyclic indole derivatives widely exist in bioactive natural products,[1] which are exemplified by aspidospermine,[2] yohimbine,[3] and strychnine.[4] Over the past decade, indoles containing heteroacenes have also received much attention because of their potential application in organic field-effect transistors (OFETs) and organic light emitting diodes (OLEDs).[5] In addition, fused-thiopyran scaffolds have been found to exhibit a broad spectrum of bioactivities, such as anti-cancer,[6] anti-bacterials,[7] anti-hyperplasia activities.[8] Certain thiopyrano[2,3-*b*]indoles have also shown to possess analgesic activity.[9] Despite of various methodologies developed for the preparation of 2,3-fused indoles,[10] including thiopyrano[2,3-*b*]indoles,[11] sometimes, they suffer from tedious multistep routes and high cost transition metals. Therefore, it would be desirable to develop a more concise method.

Due to its high reactivity and low toxicity, the diaryliodonium salt has merged as an efficient arylating reagent in organic synthesis.[12] In the last three years, significant progress has been made in the tandem arylation-cyclization reactions to construct various heterocyclic compounds initiated by diaryliodonium salts.[13] Nitriles,[14] alkenes,[15] and alkynes[16] were frequently employed as substrates in these transformations. However, cyclization based on isothiocyanates is still underdeveloped.



Scheme 1 Synthesis of thiochromeno[2,3-*b*]indoles

Recently, the construction of fused heterocycles through bicyclization[17] has attracted significant attention due to their high efficiency, especially using 2-alkynylaryl isothiocyanates[18] as starting materials. In 2003, Nanni and coworkers[19] reported a radical cyclization of 2-alkynylphenyl isothiocyanates with aryl radicals, generated from diazonium tetrafluoroborates, to synthesize thiochromeno[2,3-*b*]indoles via imidoyl radicals (Scheme 1a). Only 7 examples were obtained as mixtures of isomers through competitive [4+2] and [4+1] radical cyclizations. We envisioned that the 2-alkynylphenyl isothiocyanates could be combined with a aryl carbocation generated from diaryliodonium salts, in which a single isomer of thiochromeno[2,3-*b*]indoles might be generated through [4+2] cyclization exclusively. However, control of the chemo- and regioselectivity is challenging, because alkynes are known to react with diaryliodonium salts.[20] In continuation of our previous study,[21] we report herein a Cu-catalyzed chemo- and regioselective domino arylation-cyclization approach for the synthesis of thiochromeno[2,3-*b*]indoles as single isomer from

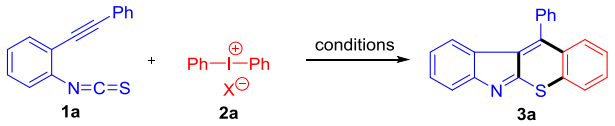
[a] *State Key Laboratory Base of Eco-Chemical Engineering, College of Chemistry and Molecular Engineering, Qingdao University of Science & Technology, Qingdao, 266042, China.*
Email: liming928@qust.edu.cn; nick8110@163.com
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

2-alkynylaryl isothiocyanates and diaryliodonium salts (Scheme 1b).

Results and discussion

Initially, we examined several different copper catalysts using 2-(2-phenylethynyl)phenyl isothiocyanate **1a** with diphenyliodonium triflate **2a** (Table 1, entries 1–4), and found that $Cu(OTf)_2$ gave the best result. The 11-phenylthiochromeno[2,3-*b*]indole **3a** was obtained in 45% yield. In the absence of Cu catalyst, no desired product was observed (entry 5). Moreover, lower yields were obtained when anions of the diphenyliodonium salts were changed to hexafluorophosphate (PF_6^-) or tetrafluoroborate (BF_4^-) (entries 6 and 7). Diminished yields were obtained at decreased or elevated temperature (entries 8 and 9). In order to further improve the yield, a base was added to quench trifluoromethanesulfonic acid formed during the reaction (entries 10–13). Pleasingly, the yield of **3a** was up to 64% when 1 equiv K_2CO_3 was added (entry 10). The yield of **3a** was not improved with the catalyst loading increased to 20 mol% or reduced to 5 mol% (entries 14 and 15). After optimization, the best conditions were established as follows: $Cu(OTf)_2$ (0.1 equiv) as the catalyst and K_2CO_3 (1.0 equiv) as the base in DCE (1.0 mL) at 50 °C under N_2 for 6 h. The structure of **3a** was confirmed by the X-ray diffraction analysis (Fig. S1 in the ESI).

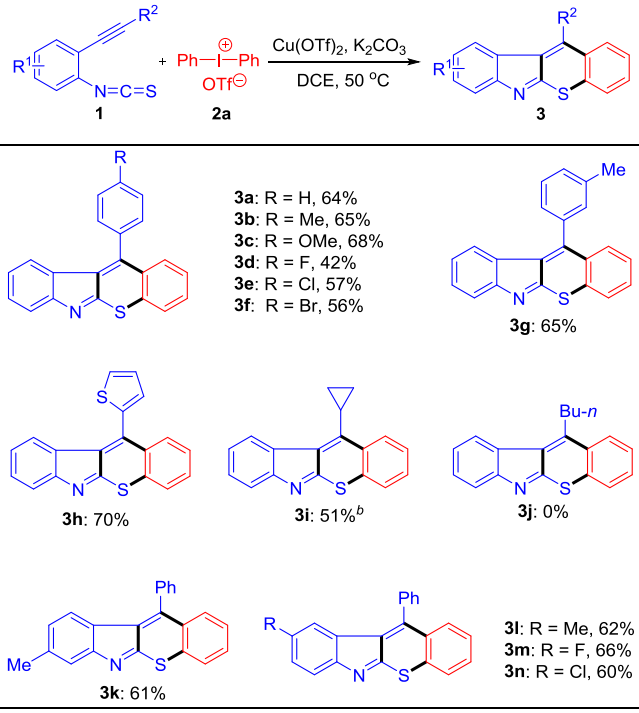
Table 1 Optimization of the reaction conditions[a]



entry	catalyst (mol %)	X	base (eq)	T [°C]	yield (%)[b]
1	CuCl (10)	OTf		50	20
2	CuBr (10)	OTf		50	32
3	$Cu(OTf)_2$ (10)	OTf		50	45
4	CuTc (10)	OTf		50	0
5	-	OTf		50	0
6	$Cu(OTf)_2$ (10)	PF_6		50	25
7	$Cu(OTf)_2$ (10)	BF_4		50	34
8	$Cu(OTf)_2$ (10)	OTf		30	26
9	$Cu(OTf)_2$ (10)	OTf		80	31
10	**$Cu(OTf)_2$ (10)**	**OTf**	**K_2CO_3 (1.0)**	**50**	**64**
11	$Cu(OTf)_2$ (10)	OTf	Na_2CO_3 (1.0)	50	37
12	$Cu(OTf)_2$ (10)	OTf	Cs_2CO_3 (1.0)	50	42
13	$Cu(OTf)_2$ (10)	OTf	DABCO (1.0)	50	0
14	$Cu(OTf)_2$ (20)	OTf	K_2CO_3 (1.0)	50	37
15	$Cu(OTf)_2$ (5)	OTf	K_2CO_3 (1.0)	50	28

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), DCE (1.0 mL), 6 h, N_2. [b]Isolated yield.

Table 2 Synthesis of thiochromeno[2,3-*b*]indoles **3a-3n** from various 2-alkynylaryl isothiocyanates **1**[a]

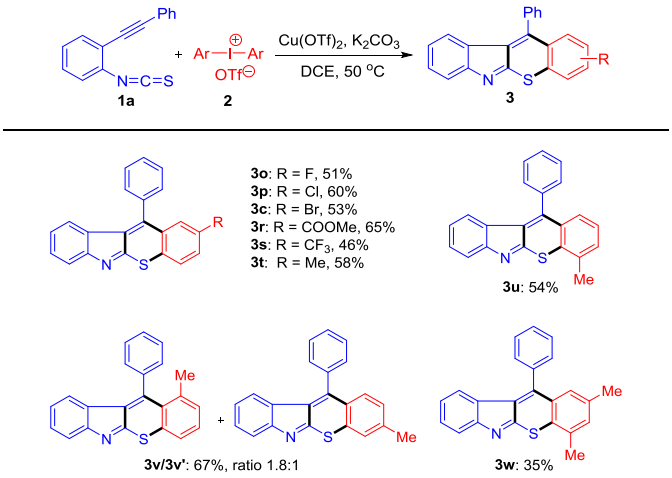


[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), $Cu(OTf)_2$ (0.1 equiv), K_2CO_3 (1.0 equiv), DCE (2.5 mL), 50 °C, 6 h, N_2. [b] Reaction time is 15 min.

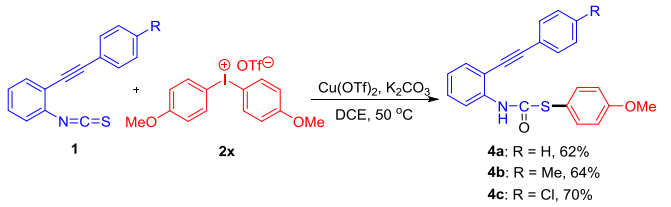
With the optimal conditions in hand, a variety of alkynylaryl isothiocyanates were tested (Table 2). The R^2 group in substrates **1** exhibited obvious electronic effects. Products **3b**, **3c** and **3g** were afforded in good yields (65–68%) when R^2 was an electron-donating aryl group such as 4-MeC_6H_4, 4-$MeOC_6H_4$ and 3-MeC_6H_4. Whereas R^2 was an electron-withdrawing aryl group, such as 4-FC_6H_4, 4-ClC_6H_4, and 4-BrC_6H_4, the reaction proceeded to generate compounds **3d-3f** in moderate yields (42–57%). Substrate with a thiophene group was also tolerated and product **3h** was isolated in 70% yield. Moreover, product **3i** was obtained in 51% yield when R^2 was a cyclopropyl group (a group can stabilize the adjacent carbocation). Unfortunately, no desired product **3j** was formed when R^2 was an *n*-butyl group, probably due to this group could not stabilize the adjacent positive charge. In addition, products **3k-3n** were obtained in good yields (60–66%), regardless of the substitution positions and electronic properties of R^1 group.

We next investigated the scope of diaryliodonium salts **2** under the optimal conditions (Table 3). Substrates bearing fluoro, chloro, bromo, ester, and trifluoromethyl groups at *para*-position of the aryl ring all worked well to produce the desired thiochromeno[2,3-*b*]indoles **3o**–**3s** in 46-65% yields. The expected products **3t**–**v** were afforded smoothly regardless of methyl position on the phenyl ring. While *meta* substituted substrate gave two inseparable isomers in 1.8:1 ratio and 67% overall yield (**3v/3v'**). Additionally, diaryliodonium salts with 2,4-dimethyl groups also afforded the desired products **3w**, albeit in lower yield.

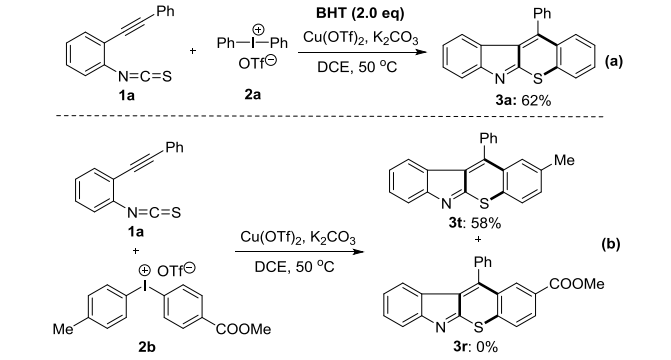
Table 3 Synthesis of thiochromeno[2,3-*b*]indoles **3o-3w** from various diaryliodonium salts **2**[a]



[a] Reaction conditions: **1a** (0.5 mmol), **2a** (1.5 equiv), $Cu(OTf)_2$ (0.1 equiv), K_2CO_3 (1.0 equiv), DCE (2.5 mL), 50 °C, 6 h, N_2.

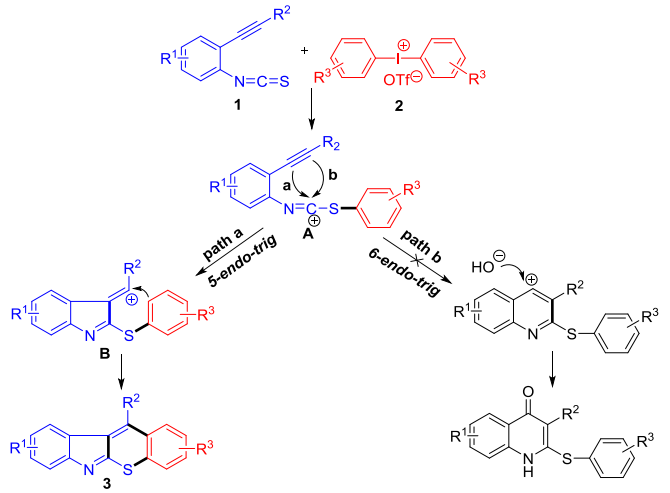


Scheme 2 The reaction of **1** with **2x**.



Scheme 3 Control experiments.

Notably, when diaryliodonium salt with strong electron-donating group (4-OMe) **2x** was used to react with **1**, the carbamothioates **4a-c** were separated in 62-70% yields rather than the desired cyclization products (Scheme 2). Moreover, when bis(2-methoxyphenyl)iodonium salt was used to react with **1**, no separable product was formed. The structures of **4** were confirmed by X-ray diffraction analysis of **4a** (Fig. S2 in the ESI). The reason that **2x** can not form the thiochromeno[2,3-*b*]indole remains unclear, however, the separation of carbamothioates **4** supports the formation of the proposed intermediate **A** (Scheme 4).



Scheme 4 Proposed reaction mechanism.

Control experiments were carried out to investigate the reaction mechanism. Initially, a radical scavenger 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added to the reaction mixture under the optimal conditions. The reaction was not inhibited and **3a** was obtained in 62% yield (Scheme 3a). In addition, a competition reaction was performed using 2-alkynylphenyl isothiocyanate **1a** with unsymmetrical diaryliodonium salt **2b** under the standard conditions, product **3t** was afforded exclusively in 58% yield and no product **3w** was detected (Scheme 3b). These results indicate that a carbocation mechanism might be involved in the reaction.[14c,22]

On the basis of our experiment results, a possible mechanism for the copper-catalyzed domino reaction was proposed (Scheme 4). According to literatures and our previous work,[16,21] both the isothiocyanate group and alkyne group in substrate **1a** could be arylated by diaryliodonium salts. In this paper, a phenyl carbocation is chemoselectively transfered by a well-established Cu(III) species[16] to the isothiocyanate group of **1a** to generate a cationic intermediate **A**. Then, intermediate **A** is captured by the vicinal alkyne group to give intermediate **B** through a regioselective *5-endo-trig* cyclization (path a). The newly formed carbocation in intermediate **B** could be stabilized by the adjacent phenyl group. Finally, the thiochromeno[2,3-*b*]indole is obtained by intramolecular Friedel–Crafts-type cyclization of intermediate **B**. Another reaction path b through *6-endo-trig* cyclization to form quinolin-4(1*H*)-ones was not observed.

Conclusions

In conclusion, an efficient copper-catalyzed tandem arylation-cyclization process is developed with readily available starting materials 2-alkynylaryl isothiocyanates and diaryliodonium salts. The tetracyclic thiochromeno[2,3-*b*]indoles are obtained in good yield through a sequence of chemoselective *S*-arylation, regioselective *5-endo-trig* cyclization, and Friedel–Crafts-type cyclization process. Moreover, this method features broad substrates scope,

simple operation, and the formation of three chemical bonds and two heterocyclic rings in a single step. Further studies to expand the scope of isothiocyanate-based cyclization with diaryliodonium salts are ongoing in our laboratory.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (21372137 and 21572110) and the Natural Science Foundation of Shandong Province (ZR2014BM006).

Notes and references

1 For selected reviews, see: (a) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 69; (b) M. Ishikura and K. Yamada, *Nat. Prod. Rep.,* 2009, **26**, 803; (c) G. R. Humphrey and J. T. Kuethe, *Chem. Rev.,* 2006, **106**, 2875; (d) T. Kawasaki and J. A. Salas, *Nat. Prod. Rep.,* 2006, **23**, 1007; (e) M. Somei and F. Yamada, *Nat. Prod. Rep.,* 2005, **22**, 73; (f) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893.

2 (a) J. E. Saxton, *Alkaloids* (Academic Press), 1998, **51**, 2. (b) J. P. Lajiness, W. Jiang and D. L. Boger, *Org. Lett.,* 2012, **14**, 2078.

3 (a) M. R. Goldberg and D. Robertson, *Pharmacological Rev.,* 1983, **35**, 143. (b) D. J. Mergott, S. J. Zuend and E. N. Jacobsen, *Org. Lett.,* 2008, **10**, 745.

4 J. Bonjoch and D. Sole, *Chem. Rev.,* 2000, **100**, 3455.

5 (a) N. Kamimoto, D. Schollmeyer, K. Mitsudo, S. Suga and S. R. Waldvogel, *Chem. Eur. J.,* 2015, **21**, 8257; (b) L. Qiu, X. Zhuang, N. Zhao, X. Wang, Z. An, Z. Lan and X. Wan, *Chem. Commun.,* 2014, **50**, 3324; (c) Y. Huang, D. Wu, J. Huang, Q. Guo, J. Li and J. You, *Angew. Chem. Int. Ed.,* 2014, **53**, 12158; (d) L. Qiu, X. Wang, N. Zhao, S. Xu, Z. An, X. Zhuang, Z. Lan, L. Wen, X. Wan, *J. Org. Chem.,* 2014, **79**, 11339.

6 (a) K. D. Berlin, D. M. Benbrook and E. C. Nelson, U.S. Patent 6586460, 2003; (b) Y. Sugita, H. Hosoya, K. Terasawa, I. Yokoe, S. Fujisawa and H. Sakagami, *Anticancer Res.,* 2001, **21**, 2629.

7 M. J. Brown, P. S. Carter, A. E. Fenwick, A. P. Fosberry, D. W. Hamprecht, M. J. Hibbs, R. L. Jarvest, L. Mensah, P. H. Milner, P. J. O'Hanlon, A. J. Pope, C. M. Richardson, A. West and D. R. Witty, *Bioorg. Med. Chem. Lett.,* 2002, **12**, 3171.

8 W. Quaglia, M. Pigini, A. Piergentili, M. Giannella, F. Gentili, G. Marucci, A. Carrieri, A. Carotti, E. Poggesi, A. Leonardi and C. Melchiorre, *J. Med. Chem.,* 2002, **45**, 1633.

9 (a) S. Takada and Y. Makisumi, *Chem. Pharm. Bull.,* 1984, **32**, 872; (b) S. Takada, N. Ishizuka, T. Sasatani, Y. Makisumi, H. Jyoyama, H. Hatakeyama, F. Asanuma and K. Hirose, *Chem. Pharm. Bull.,* 1984, **32**, 877.

10 For selected reviews, see: (a) M. Shiri, *Chem. Rev.,* 2012, **112**, 3508; (b) M. Platon, R. Amardeil, L. Djakovitchb and J. C. Hierso, *Chem. Soc. Rev.,* 2012, **41**, 3929; (c) A. Gimeno, A. Rodríguez-Gimeno, A. B. Cuenca, C. R. de Arellano, M. Medio-Simón and G. Asensio, *Chem. Commun.,* 2015, **51**, 12384. (d) T. M. Ha, B. Yao, Q. Wang and J. Zhu, *Org. Lett.,* 2015, **17**, 1750; (e) X. F. Xia, N. Wang, L. L. Zhang, X. R. Song, X. Y. Liu and Y. M. Liang, *J. Org. Chem.,* 2012, **77**, 9163; (f) S. Ali, Y. X. Li, S. Anwar, F. Yang, Z. S. Che and Y. M. Liang, *J. Org. Chem.,* 2012, **77**, 424; (g) T. Guo, Q. Jiang, F. Huang, J. Chen and Z. Yu, *Org. Chem. Front*., 2014, **1**, 707; (h) Y. S. Zhang, X. Y. Tang and M. Shi, *Org. Chem. Front*., 2015, **2**, 1516.

11 (a) M. Jha, G. M. Shelke, T. S. Cameron and A. Kumar, *J. Org. Chem.,* 2015, **80**, 5272; (b) X. Chen, Z. H. Qi, S. Y. Zhang, L. P. Kong, Y. Wang and X. W. Wang, *Org. Lett.,* 2015, **17**, 42; (c) F. M. Moghaddama, M. R. Khodabakhshi, M. Kiamehr and Z. Ghahremannejad, *Tetrahedron Lett.,* 2013, **54**, 2685; S. Majumder and P. J. Bhuyan, *Tetrahedron Lett.,* 2012, **53**, 137.

12 For selected reviews, see: (a) K. Aradi, B. L. Tóth, G. L. Tolnai and Z. Novák, *Synlett*, 2016, **27**, DOI: 10.1055/s-0035-1561369; (b) E. A. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.,* 2009, **48**, 9052; (c) V. V. Zhdankin and P. J. Stang, *Chem. Rev.,* 2008, **108**, 5299; (d) V. V. Zhdankin and P. J. Stang, *Chem. Rev.,* 2002, **102**, 2523; for selected arylation reactions, see: (e) S. G. Modha and M. F. Greaney, *J. Am. Chem. Soc.,* 2015, **137**, 1416; (f) M. G. Suero, E. D. Bayle, B. S. L. Collins and M. J. Gaunt, *J. Am. Chem. Soc.,* 2013, **135**, 5332; (g) B. S. L. Collins, M. G. Suero and M. J. Gaunt, *Angew. Chem. Int. Ed.,* 2013, **52**, 5799; (h) Q. Y. Toh, A. McNally, S. Vera, N. Erdmann and M. J. Gaunt, *J. Am. Chem. Soc.,* 2013, **135**, 3772.

13 (a) S. Zhu and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2012, **134**, 10815; (b) H. Jiang, Y. Cheng, R. Wang, Y. Zhang and S. Yu, *Chem. Commun.,* 2014, **50**, 6164; (c) Y. Wang, C. Chen, S. Zhang, Z. Lou, X. Su, L. Wen and M. Li, *Org. Lett.,* 2013, **15**, 4794.

14 (a) K. Aradi and Z. Novák, *Adv. Synth. Catal.,* 2015, **357**, 371; (b) X. Pang, C. Chen, X. Su, M. Li and L. Wen, *Org. Lett.,* 2014, **16**, 6228; (c) Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem. Int. Ed.,* 2013, **52**, 5323; (d) X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou and M. Li, *Chem. Commun.,* 2013, **49**, 6752.

15 (a) E. Cahard, H. P. J. Male, M. Tissot and M. J. Gaunt, *J. Am. Chem. Soc.,* 2015, **137**, 7986; (b) D. Holt and M. J. Gaunt, *Angew. Chem. Int. Ed.,* 2015, **54**, 7857; (c) B. Zhou, W. Hou, Y. Yang, H. Feng and Y. Li, *Org. Lett.,* 2014, **16**, 1322; (d) E. Cahard, N. Bremeyer and M. J. Gaunt, *Angew. Chem. Int. Ed.,* 2013, **52**, 9284.

16 (a) Á. Sinai, D. Vangel, T. Gáti, P. Bombicz and Z. Novák, *Org. Lett.,* 2015, **17**, 4136; (b) J. Chen, C. Chen, J. Chen, G. Wang and H. Qu, *Chem. Commun.,* 2015, **51**, 1356; (c) F. Zhang, S. Das, A. J. Walkinshaw, A. Casitas, M. Taylor, M. G. Suero and M. J. Gaunt, *J. Am. Chem. Soc.,* 2014, **136**, 8851; (d) D. Zhu, Y. Wu, B. Wu, B. Luo, A. Ganesan, F. Wu, R. Pi, P. Huang and S. Wen, *Org. Lett.,* 2014, **16**, 2350; (e) J. Peng, C. Chen, J. Chen, X. Su, C. Xi and H. Chen, *Org. Lett.,* 2014, **16**, 3776; (f) Á. Sinai, Á. Mészáros, T. Gáti, V. Kudar, A. Palló and Z. Novák, *Org. Lett.,* 2013, **15**, 5654.

17 (a) J. K. Qiu, B. Jiang, Y. L. Zhu, W. J. Hao, D. C. Wang, J. Sun, P. Wei, S. J. Tu and G. Li, *J. Am. Chem. Soc.,* 2015, **137**, 8928. (b) Z. Z. Chen, S. Liu, W. J. Hao, G. Xu, S. Wu, J. N. Miao, B. Jiang, S. L. Wang, S. J. Tu and G. Li, *Chem. Sci.,* 2015, **6**, 6654.

18 (a) W. Hao, J. Zeng and M. Cai, *Chem. Commun.,* 2014, **50**, 11686; (b) T. Saito, Y. Sonoki, T. Otani and N. Kutsumura, *Org. Biomol. Chem.,* 2014, **12**, 8398; (c) M. Kaname and H. Sashida, *Tetrahedron Lett.,* 2012, **53**, 748; (d) T. Otani, S. Kunimatsu, T. Takahashi, H. Nihei and T. Saito, *Tetrahedron Lett.,* 2009, **50**, 3853; (e) T. Saito, H. Nihei, T. Otani, T. Suyama, N. Furukawa and M. Saito, *Chem. Commun.,* 2008, **44**, 172; (f) T. Otani, S. Kunimatsu, H. Nihei, Y. Abe and T. Saito, *Org. Lett.,* 2007, **9**, 5513.

19 L. Benati, G. Calestani, R. Leardini, M. Minozzi, D. Nanni, P. Spagnolo, S. Strazzari and G. Zanardi, *J. Org. Chem.,* 2003, **68**, 3454.

20 (a) A. J. Walkinshaw, W. Xu, M. G. Suero and M. J. Gaunt, *J. Am. Chem. Soc.,* 2013, **135**, 12532. (b) R. J. Phipps, L. McMurray, S. H. Ritter, A. Duong and M. J. Gaunt, *J. Am. Chem. Soc.*, 2012, **134**, 10773.

21 W. Guo, S. Li, L. Tang, M. Li, L. Wen and C. Chen, *Org. Lett.,* 2015, **17**, 1232.

22 (a) J. Xu, P. Zhang, Y. Gao, Y. Chen, G. Tang and Y. Zhao, *J. Org. Chem.,* 2013, **78**, 8176; (b) D. D. Tanner, D. W. Reed and B. P. Setiloane, *J. Am. Chem. Soc.,* 1982, **104**, 3917.