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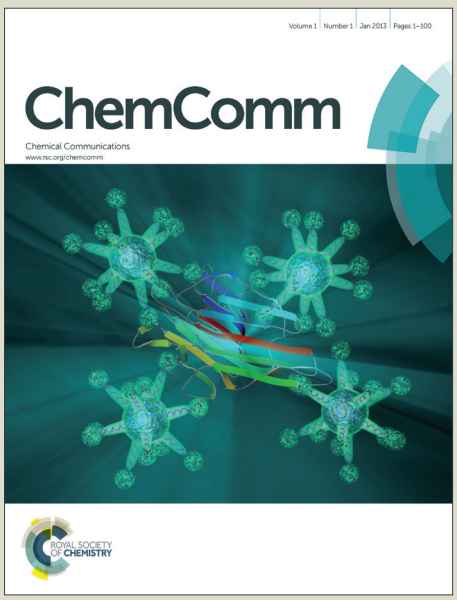

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TBHP-promoted sequential radical silylation and aromatisation of aryl isonitriles with silanes†

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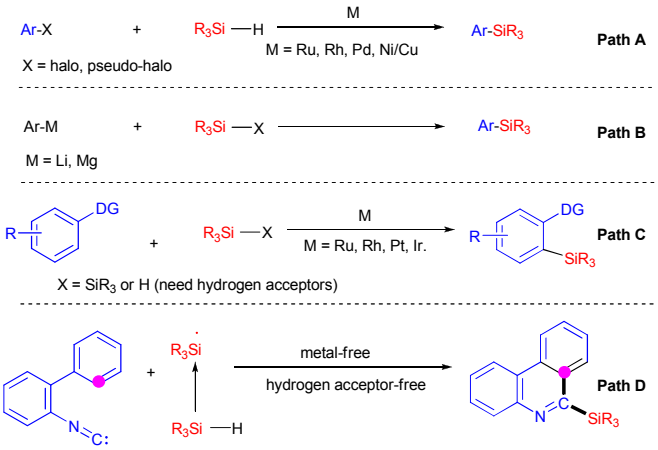
The *tert*-butyl hydroperoxide (TBHP) promoted sequential silylation and aromatisation of isonitriles was developed, where the silyl was regioselectively installed onto the 6-position of phenanthridines. This procedure tolerates a series of functional groups, such as fluoro, chloro, acetyl, methoxy carbonyl, cyano and trifluoromethyl. The addition of silyl radical to the isonitrile followed by an intramolecular aromatic cyclization was involved in this transformation.

The construction of aromatic C-Si bond is an important transformation in organic chemistry because the silylated products are useful intermediates leading to complex organic moleculars.[1] Compared with the silylation of aromatic C-X (X = halo or pseudo-halo) bond[2] and the reaction of aryl Grignard reagents or aryllithium compounds with silicon electrophiles[3] (Scheme 1, path A and B), the direct silylation of arene C-H bond represents more sustainable and higher atom-economy (Scheme 1, path C). As a result, much attention has been paid to such transformation that catalyzed by Rh,[4] Ru,[5] Pt[6] or Ir.[7] However, expensive metal catalysts were used and in the case of silane, generally, one or more equivalents of sacrificial alkenes were required as the dihydrogen acceptors. To overcome these drawbacks, Hou reported the scandium-catalyzed *ortho*-selective C-H bonds silylation of various alkoxy-substituted benzene derivatives without hydrogen acceptors.[8] Oestreich and coworkers also developed the regioselective silylation of indole C-H bond activated by a polar Ru-S bond under neutral conditions via Friedel-Crafts mechanism.[9]

The unique property of isonitrile compounds inspired us to develop a fundamentally different pathway to install the silyl group onto the aromatic ring, proceeding through the sequential radical silylation and aromatisation (Scheme 1, path D). Such a similar radical strategy has been developed in the synthesis of a series of 6-substituted phenanthridine compounds,[10] which is widely found in natural and pharmaceutical products.[11] However, the installation of hetero containing groups onto the phenanthridine rings was less studied. As far as we know, there is only one example involved the cascade reaction between 2-isocyanobiphenyls and P-radical precursors to synthesis 6-phosphorylated phenanthridines reported by Studer and co-works.[10a] Herein, we wish to report our study on the direct silylation of 2-aryl arylisonitriles to produce 6- silyl phenanthridines. This procedure is featured with: 1) transition-metal free reaction conditions; 2) no requirement of hydrogen acceptors; 3) regioselectively installation of silyl groups onto the 6- position of phenanthridines.

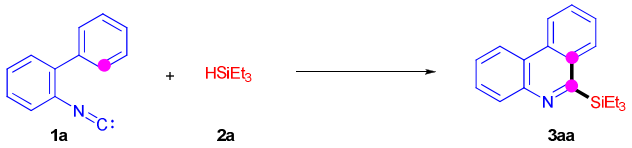
Scheme 1 The silylation of arenes.



The reaction of thermal-generated *tert*-butoxy radicals with tri-substituted silanes has been used extensively for the production of silyl radicals in organic synthesis.[12] As a result, our reaction started with the combination of 2-isocyanobiphenyl (**1a**) with triethyl silane (**2a**) in the presence of the radical initiator *tert*-butyl hydroperoxide (TBHP, 70% in water) in acetonitrile. Unfortunately, no product was detected (entry 1, Table 1). However, the addition of base increased the yields and 6-(triethylsilyl)phenanthridine (**3aa**) was successfully produced (entries 2-12, Table 1). After screening of a series of bases, such as K_3PO_4, Na_2CO_3, K_2CO_3 and Cs_2CO_3 using TBHP as the radical initiator, Cs_2CO_3 was found to be the best choice (entry 5, Table 1) and **3aa** was obtained in 55% yield. Other peroxides, di-*tert*-butyl peroxide (DTBP), for example, showed poorer efficiency under exactly the same reaction conditions (entry 6, Table 1). Solvent also affect the overall yield of this transformation and the mixed solvent (MeCN : PhH = 2 : 1, 3 mL) gave a high yield of 70%

(entry 8, Table 1). Adding a catalytic amount of benzoquinone (BQ) could further increase the yield to 75% (entry 10, Table 1). Other similar oxidants, such as DDQ (2,3-Dichloro-5,6-dicyano-1,4-benzoquinone) or chloranil failed to further increase the overall yield (entries 11 and 12, Table 1). The reaction could conduct under air but with a slightly lower yield, which was consistent with the fact that O_2 may inhibit the radical reaction (entry 10, Table 1). Blank experiment showed that no reaction took place in the absence of any oxidants (entry 9, Table 1). The yield of **3aa** was dramatically decreased using fewer amounts of peroxides or silanes (entries 13 and 14, Table 1).

Table 1. Selected results for screening the optimized reaction conditions.[a]

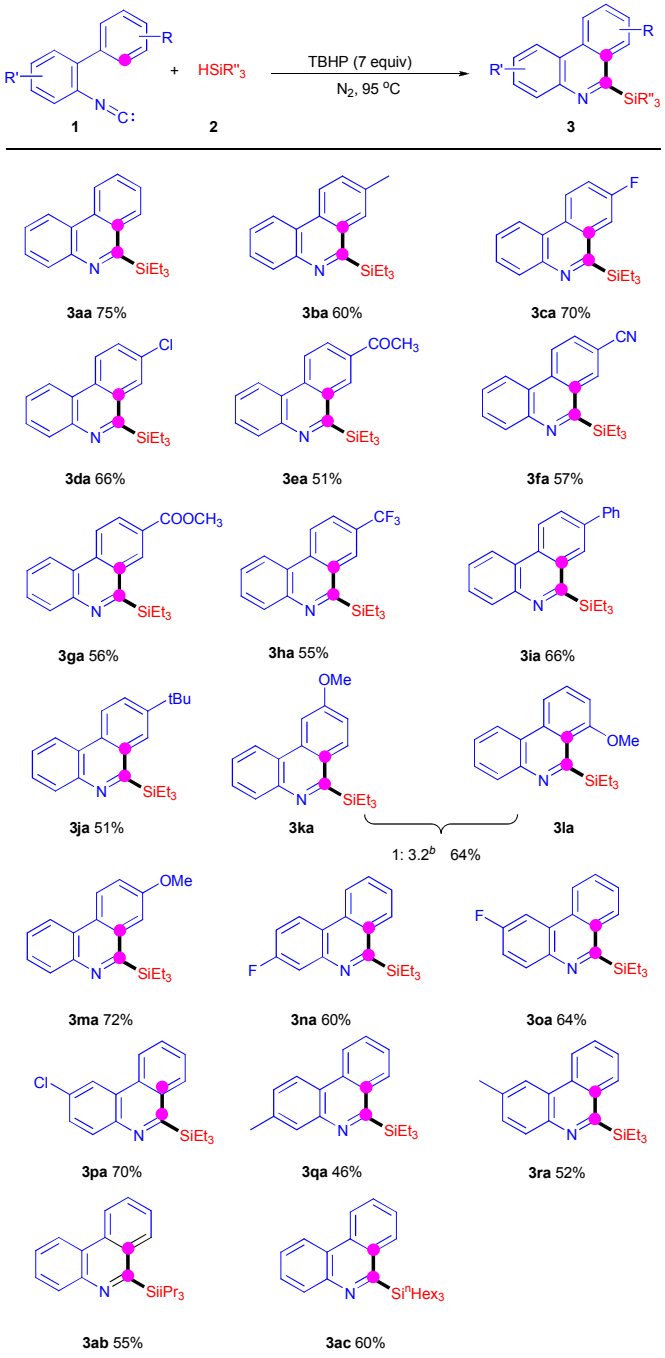


entry	base	oxidant	solvent	yield (%)[b]
1	--	TBHP	MeCN	0
2	Na_2CO_3	TBHP	MeCN	10
3	K_3PO_4	TBHP	MeCN	45
4	K_2CO_3	TBHP	MeCN	49
5	Cs_2CO_3	TBHP	MeCN	55
6	Cs_2CO_3	DTBP	MeCN	25
7	Cs_2CO_3	TBHP	PhH	32
8	Cs_2CO_3	TBHP	MeCN + PhH	70
9	Cs_2CO_3	--	MeCN + PhH	0
10	Cs_2CO_3	TBHP/BQ[c]	MeCN + PhH	75 (65)[d]
11	Cs_2CO_3	TBHP/DDQ[c]	MeCN + PhH	54
12	Cs_2CO_3	TBHP/chloranil[c]	MeCN + PhH	63
13[e]	Cs_2CO_3	TBHP/BQ[c]	MeCN + PhH	63
14[f]	Cs_2CO_3	TBHP/BQ[c]	MeCN + PhH	54

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (1.0 mmol, 5 equiv), peroxide (1.4 mmol, 7 equiv), base (0.6 mmol, 3 equiv), solvent 3 mL, 95 °C, under N_2 for 12 h. [b] Isolated yield. [c] Oxidant (0.06 mmol, 30 mol %). [d] Under air. [e] TBHP (1.0 mmol, 5 equiv). [f] 2a (0.6 mmol, 3 equiv).

To explore the substrate scopes of this protocol, this optimized reaction conditions were applied to a series of 2-isocyanobiaryl compounds and silanes as shown in Table 2. As expected, all substrates ran smoothly to give 6- silyl phenanthridines in moderate to good yields. The reaction was not sensitive to the electronic nature of the substituent on the cyclized phenyl ring or the phenyl ring bearing the isocyanide group. Various functional groups as methyl, methoxyl, fluoro, chloro, trifluoromethyl, acetyl, methoxy carbonyl, cyano, phenyl and *tert*-butyl were tolerated and the corresponding 6-silyl phenanthridines were produced (**3aa-3ra**, Table 2). Notably, halogens were tolerable, which make the further functionalization possible. The regioselectivity of the cyclization process was investigated utilizing 2-isocyano-3'-methoxybiphenyl (**1k**), and the reaction afforded a mixture of two regioisomers (1 : 3.2) in 64% yield, which favored the more steric hindered form (**3la**, Table 2). To our delight, when triisopropyl silane and trihexyl silane were employed, the reaction also ran well to afford the desired products in moderate yields (**3ab** and **3ac**, Table 2).

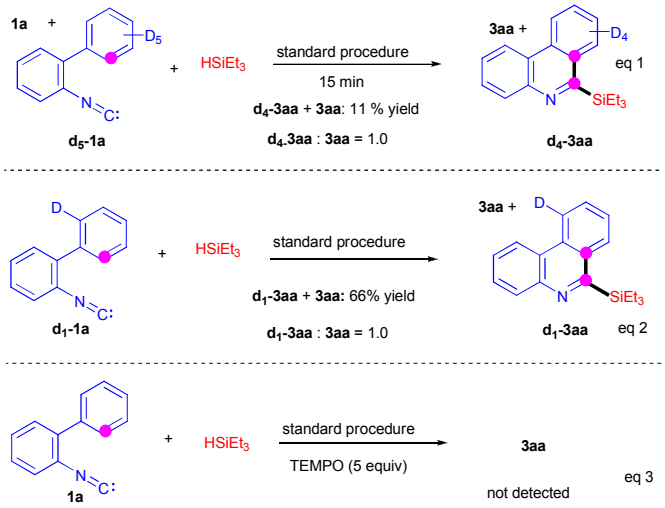
Table 2. Substrate scopes of isonitriles and silanes.[a]



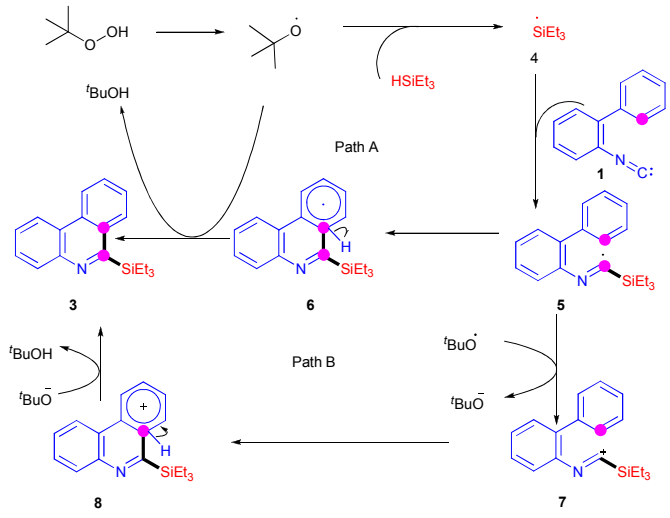
[a] Reaction conditions: **1** (0.2 mmol), **2** (1.0 mmol, 5 equiv), TBHP (7 equiv), Cs_2CO_3 (3 equiv), BQ (30 mol %), solvent (MeCN + PhH, 2 : 1), 3 mL, under N_2 at 95 °C for 12 h, isolated yield. [b] The ratio of isomers was determined by ^1H NMR analysis of the isolated products.

In order to understand the reaction mechanism of this sequential silylation and cyclization process, some reactions are carried out. Firstly, the intermolecular and intramolecular kinetic isotope effect was investigated, and no kinetic isotope effect (k_H/k_D = 1.0, 1.0, respectively, see ESI† for details) was observed (Scheme 2, eqs 1 and 2), indicating the cleavage of arene C-H bond was not the rate-determining step and either electrophilic aromatic substitution mechanism or free radical pathway is involved. Secondly, the reaction could be completely inhibited through adding 5 equivalents of TEMPO (Scheme 2, eq 3), which is in favor of the free radical mechanism.

Scheme 2. Preliminary mechanism studies.

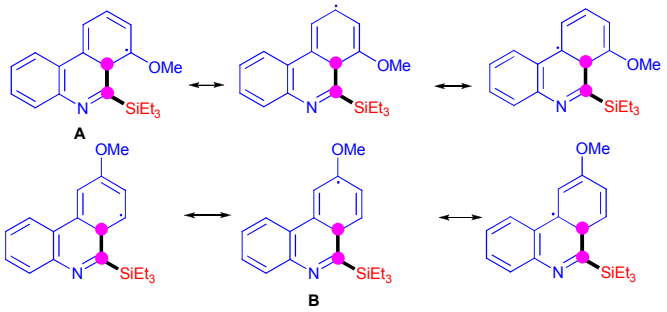


Scheme 3. The proposed mechanism.



Based on these experimental results, the proposed mechanism is illustrated in Scheme 3. Firstly, the thermal promoted cleavage of TBHP produces the *tert*-butoxy radical $^tBuO\cdot$, which abstracts the hydrogen from triethyl silane to form the triethyl silyl radical **4**.[12] Then, the addition of **4** to isonitrile produces another radical intermediate **5**. Subsequently, the intramolecular radical cyclization of intermediate **5** takes place to form the radical intermediate **6**. Finally, with the assistant of *tert*-butoxy radical, 6-triethylsilyl phenanthridine is formed by aromatisation, along with one equivalent of *tert*-butanol (Scheme 3, Path A). The catalytic amount of benzoquinone (BQ) may assist the final step (**6**→**3**) in the procedure by accepting one electron. Alternatively, another pathway is possible. The single electron transferring (SET) between $^tBuO\cdot$ and intermediate **5** takes place to form the cationic intermediate **7**. Then, the aromatic electrophilic substitution (S_EAr) produces intermediate **8**. Finally, **3** is formed by loss of one proton (Scheme 3, Path B). At the current stage, none of these two pathways could be thoroughly ruled out. In the case of substrate with *meta*-substitutent on the cyclized phenyl ring as **1k**, the cyclization at the crowded position is preferred (**3la**, Table 2) which is due to the fact that resonance structure of radical intermediate **A** is more stable than that of **B** (Scheme 4).[10f,13]

Scheme 4. Resonance structure of radical intermediate for substrate **1k**.



Conclusions

In summary, we have demonstrated a novel approach to the synthesis of 6- silyl phenanthridines with 2-isocyanobiaryls and silanes promoted by TBHP. Various 6- silyl phenanthridines were obtained in moderate to good yields. The procedure involved C-C and C-Si bond formation through radical pathway. Indeed, this work represents a facile and straightforward protocol leading to 6- silyl phenanthridines.

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Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

1 For reviews, please see: (*a*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077-1101. (*b*) J. F. Hartwig, *Acc. Chem. Res.*, 2012, **45**, 864-873. (*c*) S. E. Denmark and R. F. Sweis,

Organosilicon Compounds in Cross-Coupling Reactions. In *Metal-Catalyzed Cross-Coupling Reactions*; A. de Meijere and F. Diederich, Eds.; Wiley-VCH Verlag GmbH: Weinheim, 2008; pp 163-216. (*d*) G. R. Jones and Y. Landais, *Tetrahedron,* 1996, **52**, 7599–7662. (*e*) T. Hiyama and E. Shirakawa *Top. Curr. Chem.,* 2002, **219**, 61–85. (*f*) Z. Rappoport and Y. Apeloig, Eds. *Chemistry of organosilicon Compounds*; Wiley-VCH: New York, 2001; Vol. 3.

2 *(a)* C. Zarate and R. Martin, *J. Am. Chem. Soc.,* 2014, **136**, 2236-2239. (*b*) N. Iranpoor, H. Firouzabadi and R. Azadi *J. Organomet. Chem.,* 2010, **695**, 887-890. (*c*) A. Hamze, O. Provot, M. Alami and J.-D. Brion, *Org. Lett.,* 2006, **8**, 931-934.

3 (*a*) S. Lulinski and J. Serwatowski, *J. Org. Chem.,* 2003, **68**, 9384-9388. (*b*) K. Nishide, T. Miyamoto, K. Kumar, S. I. Ohsugi and M. Node, *Tetrahedron Lett.,* 2002, **43**, 8569-8573. (*c*) A. S. Manoso, C. Ahn, A. Soheili, C. J. Handy, R. Correira, W. M. Seganish and P. DeShong, *J. Org. Chem.,* 2004, **69**, 8305-8314. (*d*) M. Schlosser and C. Heiss, *Eur. J. Org. Chem.* 2003, 4618-4624. (*e*) M. Oestreich, G. Auer and M. Keller, *Eur. J. Org. Chem.* 2005, 184-195.

4 (*a*) C. Cheng and J. F. Hartwig, *Science*, 2014, **343**, 853-857. (*b*) P. I. Djurovich, A. R. Dolich and D. H. Berry, *J. Chem. Soc., Chem. Commun.,* 1994, 1897–1898.

5 (*a*) H. Ihara and M. Suginome, *J. Am. Chem. Soc.,* 2009, **131**, 7502-7503. (*b*) F. Kakiuchi, M. Matsumoto, K. Tsuchiya, K. Igi, T. Hayamizu, N. Chatani and S. Murai, *J. Organomet. Chem*., 2003, **686**, 134–144. (*c*) F. Kakiuchi, K. Tsuchiya, M. Matsumoto, E. Mizushima and N. Chatani, *J. Am. Chem. Soc*., 2004, **126**, 12792–12793.

6 (*a*) N. Tsukada and J. F. Hartwig, *J. Am. Chem. Soc*., 2005, **127**, 5022-5023. (*b*) M. Murata, N. Fukuyama, J.-i. Wada, S. Watanabe and Y. Masuda, *Chem. Lett*., 2007, **36**, 910–911.

7 (*a*) T. Ishiyama, K. Sato, Y. Nishio and N. Miyaura, *Angew. Chem., Int. Ed.,* 2003, **42**, 5346-5348. (*b*) T. Ishiyama, K. Sato, Y. Nishio, T. Saiki and N. Miyaura, *Chem. Commun.,* 2005, 5065-5067. (*c*) G. Choi, H. Tsurugi and K. Mashima, *J. Am. Chem. Soc.,* 2013, **135**, 13149-13161. (*d*) E. M. Simmons and J. F. Hartwig, *J. Am. Chem. Soc.,* 2010, **132**, 17092-17095. (*e*) T. Saiki, Y. Nishio, T. Ishiyama and N. Miyauya, *Organometallics,* 2006, **25**, 6068-6073. (*f*) E. M. Simmons and J. F Hartwig, *Nature*, 2012, **483**, 70-73. (*g*) B. Lu and J. R. Falck, *Angew. Chem., Int. Ed.,* 2008, **47**, 7508-7510.

8 J. Oyamada, M. Nishiura and Z. Hou, *Angew. Chem., Int. Ed*., 2011, **50**, 10720-10723.

9 H. F. T. Klare, M. Oestreich, J.-i. Ito, H. Nishiyama, Y. Ohki and K. Tatsumi, *J. Am. Chem. Soc*., 2011, **133**, 3312-3315.

10 (*a*) B. Zhang, C. G. Daniliuc and A. Studer, *Org. Lett.,* 2014, **16**, 250-253. (*b*) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang and S. Yu, *Angew. Chem., Int. Ed*., 2013, **52**, 13289-13292. (*c*) J.-J. Cao, T.-H. Zhu, S.-Y. Wang, Z.-Y. Gu, X. Wang and S.-J. Ji, *Chem. Commun*., 2014, **50**, 6439-6442. (*d*) Q. Wang, X. Dong, T. Xiao and L. Zhou, *Org. Lett*., 2013**, 15**, 4846-4849. (*e*) L. Gu, C. Jin, J. Liu, H. Ding and B. Fan, *Chem. Commun*., 2014, **50**, 4643-4645. (*f*) L. Wang, W. Sha, Q. Dai, X. Feng, W. Wu, H. Peng, B. Chen and J. Cheng, *Org. Lett*., 2014, **16**, 2088-2091. (*g*) C. Pan, J. Han, H. Zhang and C. Zhu, *J. Org. Chem*., 2014, **79**, 5374-5378. (*h*) D. Leifert, C. Gabriel and A. Studer, *Org. Lett*., 2013, **15**, 6286-6289. (*i*) Z. Xia, J. Huang, Y. He, J. Zhao, J. Lei and Q. Zhu, *Org. Lett.,* 2014, **16**, 2546-2549. (*j*) Z. Li, F. Fan, J. Yang and Z.-Q. Liu, *Org. Lett*., 2014, **16**, 3396-3399. (*k*) J. Lui, C. Fan, H. Yin, C. Qin, G. Zhang, X. Zhang, H. Yi and A. Lei, *Chem. Commun*., 2014, **50**, 2145-2147. (*l*) Z. Li, F. Fan, J. Yang and Z.-Q. Liu, *Org. Lett.,* 2014, **16**, 3396-3399. (*m*) W. Sha, J.-T. Yu, H. Yang and J. Cheng, *Chem. Commun.,* 2014, **50**, 9179-9181. (*n*) T. Xiao, L. Li, G. Lin, Q. Wang, Z.-W. Mao and L. Zhou, *Green Chem.,* 2014, **16**, 2418-2421. (*o*) Z.-Z. Zhu, T.-T. Wang, P. Bai and Z.-Z. Huang, *Org. Biomol. Chem.,* 2014, **12**, 5839-5842.

11 (a) T. C. Johnstone, S. M. Alexander, W. Lin and S. J. Lippard, *J. Am. Chem. Soc*., 2014, **136**, 116-118. (*b*) S. Simeon, J. L. Rios and A. Villar, *Pharmazie*, 1989, **44**, 593–597. (*c*) I. Slaninova, K. Pencikova, J. Urbanova, J. Slanina and E. Taborska, *Phytochem. Rev*., 2014, **13**, 51-68. (*d*) W. K. Brewster, D. E. Nichols, R. M. Riggs, D. M. Mottola, T. W. Lovenberg, M. H. Lewis and R. B. Mailman, *J. Med. Chem*., 1990, **33**, 1756–1764. (*e*) H. Chen, H. Long, X. Cui, J. Zhou, M. Xu and G. Yuan, *J. Am. Chem. Soc*., 2014, **136**, 2583-2591. (*f*) T. Nakanishi, T. Suzuki, A. Saimoto and T. Kabasawa, *J. Nat. Prod*., 1999, **62**, 864–867. (*g*) L. Sripada, J. A. Teske and A. Deiters, *Org. Biomol. Chem*., 2008, **6**, 263–265. (*h*) O. B. Abdel-Halim, T. Morikawa, S. Ando, H. Matsuda and M. Yoshikawa, *J. Nat. Prod.,* 2004, **67**, 1119–1124. (*i*) M. Tobisu, K. Koh, T. Furukawa and N. Chatani, *Angew. Chem., Int. Ed*., 2012, **51**, 11363-11366.

12 C. Chatgilialoglu, *Chem*. *Rev*., 1995, **95**, 1229-1251.

13 H. Zipse, *Top. Curr. Org*., 2006, **263**, 163−189.

