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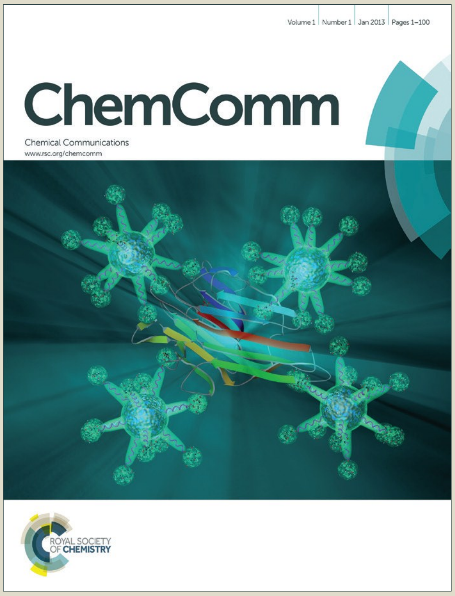

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Copper-catalyzed intramolecular aryl-bicyclization of diynes with diaryliodonium salts via vinyl cations

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A novel protocol for synthesis of polycyclic compounds from linear diynes and diaryliodonium salts has been realized. The reaction proceeded through Cu-catalyzed arylation of alkyne to generate vinyl carbocation intermediates twice that subsequently reacted with arene group to form fused ring containing diene moiety.

Ring-fused backbones widely exist in natural products, pharmaceuticals and opto-electronic materials (Fig. 1).[1] Thus the methodology of constructing ring-fused backbones are very worthy of being studied. Various cyclization reactions, such as Diels-Alder reaction with alkenes or alkynes, transition-metal catalyzed single or multiple carbometallation reactions have been well established to synthesize polycyclic compounds.[2] In the past few decades the electrophilic cyclization has proven to be most efficient ways to build up polycyclic compounds. [3,4] As a result, various electrophiles were applied for the synthesis of cyclic compounds. This electrophiles triggered reaction featured mild reaction conditions, simple operation and easily available linear substrates. Nevertheless, the electrophiles used to initiate the cyclization were narrowly limited to H^+, Lewis acids, halogen and phosphine derivatives.[3a,4] By utilizing linear diynes, previous works showed various ways to construct ring-fused backbones such as metal-promoted cycloaddition (Scheme 1a).[5] Recently, cyclization using highly reactive boron reagents has also received much attention (Scheme 1b, c). [6,1c]

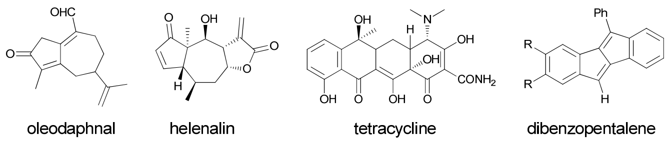
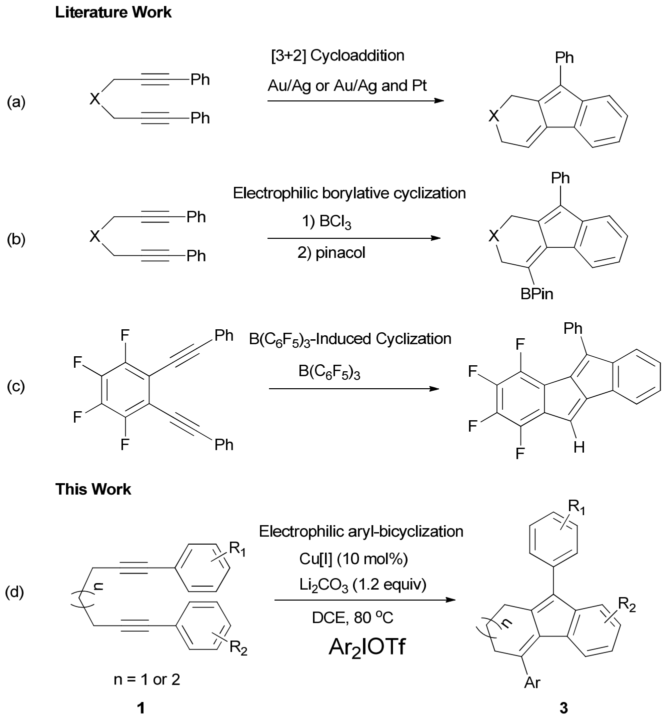


Fig. 1 Significance of ring-fused backbones.



Scheme 1 Synthesis of specified ring-fused backbones.

However, the employment of C-electrophiles to promote poly-cyclization is rarely reported, but undoubtedly important. Herein, we would like to report a poly-cyclization initiated by C-electrophiles, generated from diaryliodonium salts (Scheme 1d). The diaryliodonium salts, as environmentally friendly benign C-electrophiles, are often used to react with alkenes and alkynes to form functionalized or complex carbocations, which underpin a wide range of chemical transformations.[7,8] The progress disclose a novel and efficient pathway to construct polycyclic molecules with diaryliodonium salts.

Based on precedent studies of cyclization reactions triggered by diaryliodonium salts,[9,10] we envisioned that the linear diyne substrates **1** could form the vinyl carbocation twice during the electrophilic cyclization which consequently gives possibility to construct ring-fused backbones. The ring-fused backbone of desired product **3** was found in natural

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†Electronic Supplementary Information (ESI) available: Experimental procedures, full characterization including ^1H NMR and ^{13}C NMR datas and spectras for all new compounds and X-ray crystal structure of **3ae**. CCDC 1471734. For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/x0xx00000x

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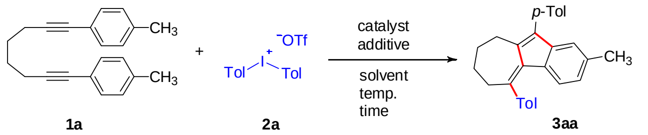
products such as insecticidal agent.[11] We developed a novel and simple protocol to synthesize such polycyclic hydrocarbons by using the benign C-electrophile: Ar_2IOTf. It is notable that the designed substrates could be extended to 1,7-diyne which results in azulene derivatives and the target product **3** is aryl-functionalized (Scheme 1d).

Initially, we attempted to perform the reaction by treating 1,8-di-*p*-tolyl-1,7-octadiyne **1a** and diaryliodonium triflate **2a** with CuBr (10 mol%) in dry dichloromethane at 80 °C for 12 h. The reaction solution colour turned from colorless to yellow and then black. The desired product was found trace in GC-MS (Table 1, entry 1). When additive Li_2CO_3 (1.2 eq.) was added to the reaction, to our delight, the desired product azulene derivative **3aa** was observed in 65% yield (entry 2). In the following trials, different solvents were applied to this hydrocarbon cyclization reaction (entry 3-7), and **3aa** was formed in a comparative higher yield of 73% (isolated 66%) when dichloroethane (DCE) was used (entry 7). Prolonging reaction time didn't give any better results (entry 8). In addition, several other additives were investigated in this study (entry 9-14), but most of them didn't produce the expected product. The results indicate that the base Li_2CO_3 could possibly promote the cyclization or neutralize the acid generated in the reaction. Different copper salts were screened for this reaction and CuBr proved to be the best one (entry 15-17). The product yield was not improved when temperature altered (entry 18, 19). So far as we tried, the optimal reaction condition is listed as entry 7 showed.

Table 1 Optimization of reaction conditions[a]

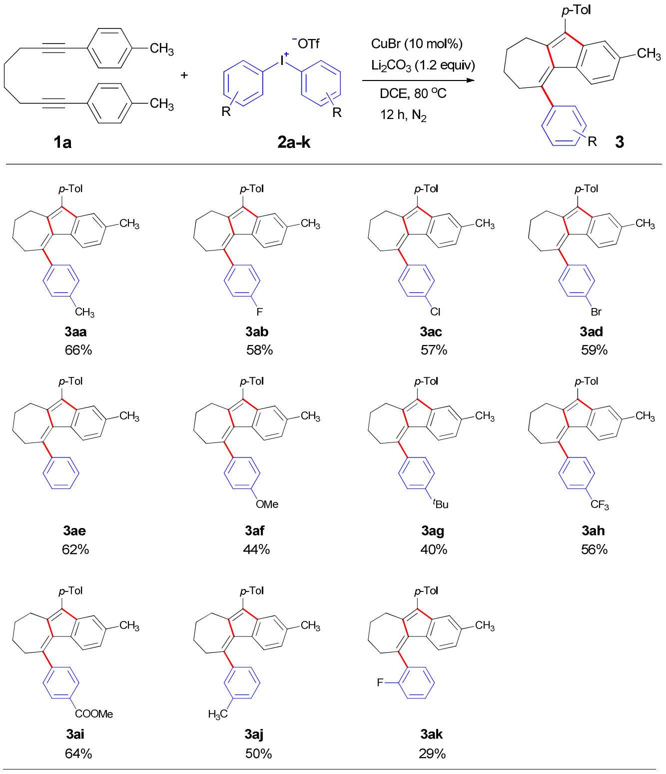


entry	catalyst	additive	solvent	temp(°C)	time(h)	yield(%)[b]
1	CuBr	—	DCM	80	12	trace
2	CuBr	Li_2CO_3	DCM	80	12	65
3	CuBr	Li_2CO_3	CH_2BrCH_2Br	80	12	37
4	CuBr	Li_2CO_3	$CHCl_3$	80	12	50
5	CuBr	Li_2CO_3	Mixed solvent[c]	80	12	58
6	CuBr	Li_2CO_3	1,4-dioxane	80	12	trace
7	CuBr	Li_2CO_3	DCE	80	12	73(66)[d]
8	CuBr	Li_2CO_3	DCE	80	64	68
9	CuBr	t-BuOLi	DCE	80	12	trace
10	CuBr	$LiPF_6$	DCE	80	12	trace
11	CuBr	LiCl	DCE	80	12	0
12	CuBr	LiBr	DCE	80	12	0
13	CuBr	Cs_2CO_3	DCE	80	12	trace
14	CuBr	Na_2CO_3	DCE	80	12	NR[e]
15	$Cu(OTf)_2$	Li_2CO_3	DCE	80	12	20
16	CuI	Li_2CO_3	DCE	80	12	51
17	CuCl	Li_2CO_3	DCE	80	12	56
18	CuBr	Li_2CO_3	DCE	70	12	61
19	CuBr	Li_2CO_3	DCE	90	12	25

[a]Unless noted, reaction were performed with **1a** (0.2 mmol), **2a** (1.2 eq.), catalyst (10 mol%), additive (1.2 eq.), in the solvent (2 mL) at the preceding temperature. [b]NMR yield using trichloroethylene as an internal standard. [c]1 mL DCM and 1 mL DCE. [d]isolated yield. [e]no reaction.

With the optimal reaction condition in hand, the scope of diaryliodonium salts with different substituents on the phenyl ring were explored. As shown in Scheme 2, the aromatic rings bearing electron-withdrawing groups such as F, Cl, Br were tolerated well in the process (**3ab**-**3ad**), and these untouched halogen substituents render the cyclic-products for further transformations. Likewise, substrates containing electron-withdrawing groups such as trifluoromethyl (**2h**) and ester (**2i**) group were effectively converted to the expected products in moderate yields. Moreover, substrates with electron-donating groups were tried. It turned out that substrate with the methyl group (**2a**) was transformed smoothly under the standard condition and substrate with methoxy group (**2f**) led to a low yield which might be attributed to electronic effect. In the case of *para*-substitued bulky isobutyl group of the substrate (**2g**), the yield was reduced to 40% (**3ag**). For substrates with *meta*-substitued methyl (**2j**), the product yield was reduced to 50% (**3aj**) compared to **3aa**. Similarly, if substrate with *ortho*-substitued fluorine (**2k**) was used, the yield was dramatically reduced to 29% (**3ak**). The results indicated that the steric hindrance showed great effects on the outcome of the cyclization products. To further confirm the structure of the product, a single crystal of product **3ae** was characterized by XRD (Fig.2 CCDC 1471734).

Encouraged by the above study, the scope of diynes were further explored by varying the substituents on the phenyl moities. Under the optimized conditions for the amazing intramolecular aryl-bicyclization, other analogues of **1a** with 4-



Standard conditions: **1a** (0.2 mmol), **2** (1.2 eq.), CuBr (10 mol%), Li_2CO_3 (1.2 eq.), in the dichloroethane (2 mL) at 80 °C, 12 h under N_2 atmosphere. Yields provided above were isolated.

Scheme 2 Scope of copper-catalyzed electrophilic cyclization of **1a** with diaryliodonium salts.

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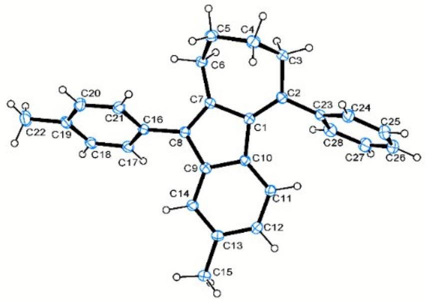


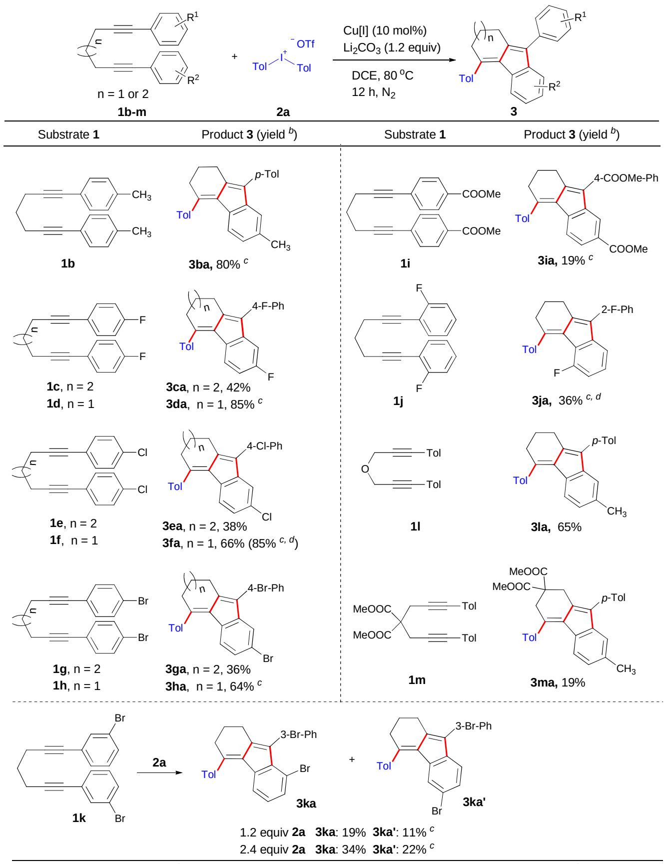
Fig.2 Crystal structure of **3ae** (CCDC No.: 1471734) .

CH_3-, 4-F-, 4-Cl-, and 4-Br-substituents on the phenyl ring also worked well to give products **3ba**-**3ha**, respectively (Table 2). Moreover, the diynes with three carbons aliphatic chain such as **1b**, **1d**, **1f**, **1h** (n=1) were transformed to give the desired product **3ba**, **3da**, **3fa**, **3ha** in higher yields compared with **3aa**, **3ca**, **3ea**, **3ga** (n=2). It was a delightful result that the product yield of **3fa** was greatly improved to 85% when Ar_2IOTf was increased to 2.4 equivalent. Diynes **1i** and **1j** proceeded the reaction to form **3ia** and **3ja** in low yields, which was due to the electronic and steric effect. When diyne **1k** with 3-Br-substituent on phenyl ring was conducted, both isomers of **3ka** and **3ka'** were formed by different reaction site during the intramolecular cyclization. It didn't make any difference to the ratio of **3ka** and **3ka'** by increasing the quantity of Ar_2IOTf. It is hard to isolate the two isomers. On the other hand, when the aliphatic chain of the diyne was inserted by heteroatom (**1l**), the target product **3la** was obtained in 65% yield. For diyne **1m** with two ester groups substituted on the chain, the yield of the product **3ma** is very low on account of the ester groups inhibiting the formation of the six-membered cycles.

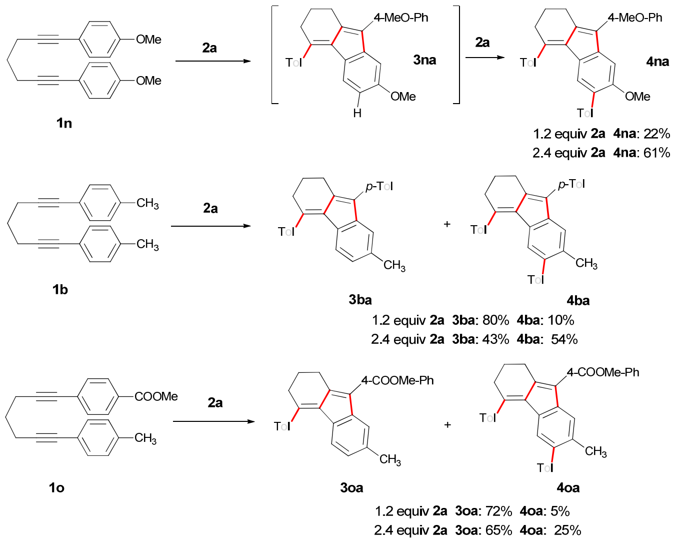
Interestingly, When diyne (n=1) with 4-MeO-substituent on the phenyl ring (**1n**) was conducted under the optimal reaction condition (Scheme 3), the corresponding product of **3na** was trace. Instead, a new product of **4na**, arylated by one more toluene group of **3na**, was obtained in 22% yield or 61% yield when more Ar_2IOTf was used. When diyne with a weaker electron-donating group on the phenyl ring (**1b**) was studied, **4ba** was also formed in 10% yield besides the main product **3ba**. Likewise, when more Ar_2IOTf was used, **4ba** was increased to 54% yield and **3ba** was decreased to 43% yield. The structure of **4ba** was confirmed by COSY, HMQC, HMBC spectroscopy (see supporting information). The arylation site selectivity is in accordance with the reported literature.[12] the reactivity of unsymmetrical diyne **1o** was also designed. The reaction **1o** and **2a** mainly afforded product **3oa** in 72% yield, which showed great site selectivity. When **2a** was increased to 2.4 equivalent, product **4oa** was formed in 25% yield. According to the above results, the final structure of **4** the products were greatly affected by the electronic effect because the fused benzene ring with electron-donating group was easier to be arylated by the Ar_2IOTf.

It is precedented that the diaryliodonium salts could be catalyzed by copper salt to generate reactive electrophilic species Ar-Cu(III) in situ, which is regarded as carbocation equivalents that could easily be attacked by nucleophiles.[7,13] Based on the above results, a plausible mechanism is proposed for the intramolecular bicyclization reaction (Scheme 4, exemplified with **1b**). Ar-Cu(III) is formed through electrophilic addition of Cu(I) species by Ar_2IOTf. Then Ar-Cu(III) is attacked by the alkynyl group of diyne to form intermediate **I** (favoured

Table 2 The scope investigation of diyne[a].



[a] standard condition, [b] isolated yield, [c] CuCl was used instead of CuBr, [d] 2.4 eq. diaryliodonium salts and Li_2CO_3 were used.



Standard conditions: **1** (0.2 mmol), **2a**, CuCl (10 mol%), Li_2CO_3 (In accordance with **2a**), in the dichloroethane (2 mL) at 80 °C, 12 h under N_2 atmosphere. Yields provided above were isolated.

Scheme 3 New product **4** generated under standard condition.

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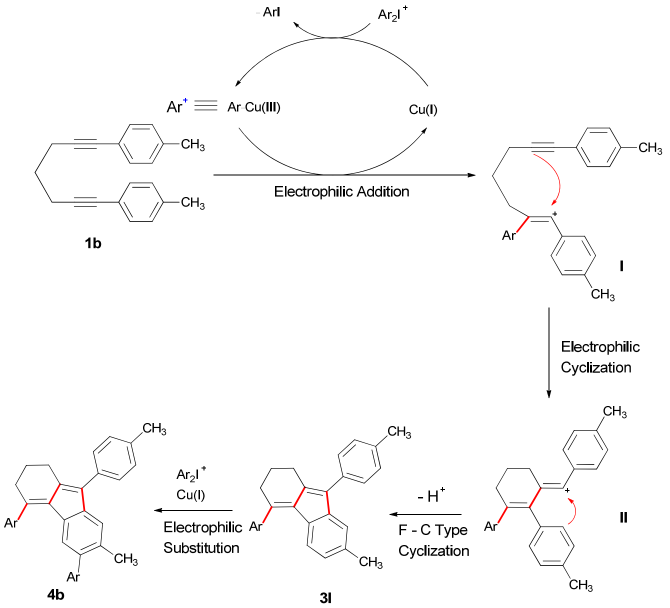

Scheme 4 Plausible mechanism of Cu-catalyzed intramolecular bicyclization.

by the conjugate effect). Vinyl-cation center **I** is highly active and easily attacked by the other alkynyl group in the same molecular to give vinyl-cation **II**. Subsequently, **II** undergoes a Friedel-Crafts type reaction to produce the final product **3**. When the fused benzene ring of **3** is substituted by electron-donating groups, a new product **4** would be formed through further electrophilic substitution of product **3**. The additive Li_2CO_3 might neutralize the acid generated in the reaction and have some coordination effect during the cyclization. According to the mechanism, the design of the diyne is artful to proceed such intramolecular bicyclization.

In summary, with a properly designed substrate diyne, we have developed a simple and efficient method to build up ring-fused backbones with diaryliodonium triflate reagents. This aryl-bicyclization was catalyzed by Cu(I) and the aryl group of the diaryliodonium triflate reagents served as the electrophilic agent. This strategy gave hint on the synthesis of complex polycyclic compounds by consecutively forming several vinyl cations.

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Notes and references

1 (a) T. P. Stockdale and C. M. Williams, *Chem. Soc. Rev.*, 2015, **44**, 7737; (b) C. Serba, R. Lagoutte and N. Winssinger, *Eur. J. Org. Chem.*, 2016, **2016**, 644; (c) C. Chen, M. Harhausen, R. Liedtke, K. Bussmann, A. Fukazawa, S. Yamaguchi, J. L. Petersen, C. G. Daniliuc, R. Frçhlich, G. Kehr and G. Erker, *Angew. Chem. Int. Ed.*, 2013, **52**, 5992.
2 (a) P. A. Inglesby and P. A. Evans, *Chem. Soc. Rev.*, 2010, **39**, 2791; (b) B. Alcaide, P. Almendros and C. Aragoncillo, *Chem. Soc. Rev.*, 2010, **39**, 783; (c) Y. Luo, X. Pan, X. Yu and J. Wu, *Chem. Soc. Rev.*, 2014, **43**, 834; (d) S. Reymond and J. Cossy, *Chem. Rev.*, 2008, **108**, 5359.
3 (a) B. Godoi, R. F. Schumacher and G. Zeni, *Chem. Rev.*, 2011, **111**, 2937; (b) R. C. Larock, *ChemInform*, 2007, **38**, 51;
4 T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277.
5 J. Lian, P. Chen, Y. Lin, H. Ting and R. Liu, *J. Am. Chem. Soc.*, 2006, **128**, 11372.
6 A. J. Warner, J. R. Lawson, V. Fasano and M. J. Ingleson, *Angew. Chem. Int. Ed.*, 2015, **54**, 11245.
7 (a) K. Aradi, B. L. Tóth, G. L. Tolnai, Z. Novák, *Synlett*, 2016, **27**, A; (b) B. Olofsson, *Top Curr Chem*, 2016, **373**, 135. (c) M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, *ARKIVOC*, 2011, 370; (d) E. A. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48**, 9052; (e) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299; (f) V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2002, **102**, 2523; (g) V. V. Grushin, *Chem. Soc. Rev.*, 2000, **29**, 315; (f) P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123.
8 R. R. Naredla and D. A. Klumpp, *Chem. Rev.*, 2013, **113**, 6905.
9 (a) Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem. Int. Ed.*, 2013, **52**, 5323; (b) X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou and M. Li, *Chem. Commun.*, 2013, **49**, 6752; (c) J. Peng, C. Chen, Y. Wang, Z. Lou, M. Li, C. Xi and H. Chen, *Angew. Chem. Int. Ed.*, 2013, **52**, 7574; (d) Y. Wang, C. Chen, S. Zhang, Z. Lou, X. Su, L. Wen and M. Li, *Org. Lett.*, 2013, **15**, 4794; (e) J. Peng, C. Chen, J. Chen, X. Su, C. Xi and H. Chen, *Org. Lett.*, 2014, **16**, 3776; (f) J. Chen, C. Chen, J. Chen G. Wang and H. Qu, *Chem. Commun.*, 2015, **51**, 1356; (g) J. Chen, H. Qu, J. Peng and C. Chen, *Chin. J. Org. Chem.*, 2015, **35**, 937; (h) J. Sheng, X. Su, C. Cao and C. Chen, *Org. Chem. Front.*, 2016, **3**, 501.
10 (a) L. L. Suarez and M. F. Greaney, *Chem. Commun.*, 2011, **47**, 7992; (b) S. Tang, P. Peng, P. Zhong and J. Li, *J. Org. Chem.*, 2008, **73**, 5476; (c) Á. Sinai, Á.Mészáros, T. Gáti, V. Kudar, A. Palló and Z. Novák, *Org. Lett.*, 2013, **15**, 5654; (d) A. J. Walkinshaw, W. Xu, M. G. Suero and M. J. Gaunt, *J. Am. Chem. Soc.*, 2013, **135**, 12532.
11 S. B. Singh, J. G. Ondeyka, H. Jayasuriya, D. L. Zink, S. N. Ha, A. Dahl-Roshak, J. Greene, J. A. Kim, M. M. Smith, W. Shoop and J. S. Tkacz, *J. Nat. Prod.*, 2004, **67**, 1496.
12 T. E. Storr and M. F. Greaney, *Org. Lett.*, 2013, **15**, 1410.
13 (a) B. Chen, X.-L. Hou, Y.-X. Li, Y.-D. Wu, *J. Am. Chem. Soc.* 2011, **133**, 7668; (b) R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong and M. J. Gaunt, *J. Am. Chem. Soc.*, 2012, **134**, 10773.

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