Journal Name

RSCPublishing

COMMUNICATION

Cite this: DOI: 10.1039/x0xx00000x

Cu-catalyzed Intramolecular Aryl-etherification Reactions of Alkoxyl Alkynes with Diaryliodonium Salts via Cleavage of a stable C-O Bond

Received 00th January 2012,
Accepted 00th January 2012

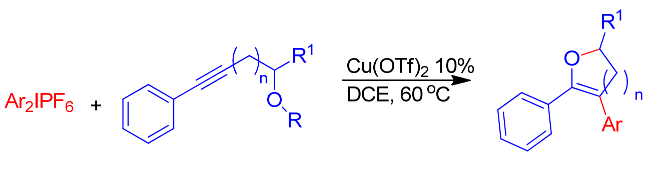
DOI: 10.1039/x0xx00000x

www.rsc.org/

Jing Chen,[a b] Chao Chen,[a*] Junjie Chen,[a] Guohua Wang,[a] Hongmei Qu[b*]

A novel Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes with diaryliodonium salts is realized. The reactions proceed smoothly to produce valuable oxo-heterocycles with readily available linear starting materials via cleavage of a stable C-O bond.

Electrophiles initiated intramolecular etherification reactions of alkynes and alkenes are versatile synthetic transformations with wide applications to prepare various oxygen containing heterocycles,[1] which are ubiquitous backbones in organic materials[2], natural products[3] and medicinal molecules[4]. In these intramolecular etherification reactions, electrophiles play significant roles and are generally applied with halogen or chalcogen onium sources, i.e. halo-etherification or chalko-etherification reactions. The analogous carbo-etherification with the formation of C-C bonds rather than C-X bonds is relatively unusual. However, this reaction is a powerful and convergent tool for oxo-heterocycle synthesis, and can allow access to a variety of analogs from readily accessible linear starting materials. Surprisingly, nearly all of the carboetherifications that have been reported, to date, are catalyzed by Pd-a novel metal complexes.[5] In this context, we would like to report a Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes with diaryliodonium salts.[6] The reactions proceed smoothly with readily available linear starting materials via the cleavage of a **stable** C-O bond (Scheme 1).



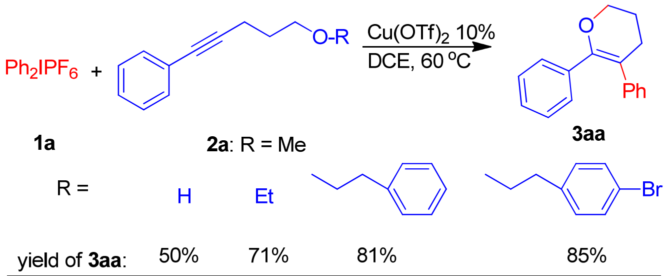
1 **2**: n = 2 **4**: n = 1 **3**: n = 2 **5**: n = 1

Scheme 1. Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes with diaryliodonium salts.

During the study of synthesizing heterocycles with diaryliodonium salts,[7-8] we attempted to realize the cyclization reaction of methoxyl alkyne **2a** with diphenyliodonium salt **1a**. Interestingly, under a simple $Cu(OTf)_2$-catalyzed condition, an aryl-etherification product **3aa** was observed,[9] apparently via selective cleavage of a stable C-O bond.[10] After various attempts, the yield of **3aa** was increased from <10% to 92% (NMR yield) under the conditions shown as entry 2 in Table 1. When other copper salt was tested as catalyst, **3aa** was formed in very low yield (entry 4-9). Expectedly, no desired product was obtained without copper catalyst (entry 10). Similarly as many reactions with diaryliodonium salts, this reaction proceeded best in dichloroethane (DCE) among common solvents (entry 11-14). The protecting group **R** on oxygen atom is essential. When methoxyl group in **2a** was replaced by -OH group, only 50% of **3aa** was observed with OH-arylated product contaminated;[11] when methyl group was replaced by other alkyl groups, the reaction also worked well, but in lower yields. *It should be noted that when diaryliodonium hexafluorophosphates **1a** were replaced by the corresponding triflates, product **3aa** was only generated in small amount (ca 30%).*

Encouraged by the successful realization of the first Cu-catalyzed intramolecular aryl-etherification reactions of alkoxyl alkynes, next, the scope of diaryliodonium salts was examined, and the results were summarized in Scheme 2. Under the optimal conditions, a variety of symmetric and unsymmetric diaryliodonium hexafluorophosphates **1** were reacted with **2a**. Symmetric diaryliodonium hexafluorophosphates with methyl and halogen substituents (**1b-1g**) reacted smoothly with **2a** producing the corresponding products **3ba-3ga**, all in excellent yields except **3da** probably due to the steric hindrance. Unsymmetric diaryliodonium salts, $ArI^{+}Mes$ were also suitable for the reaction to give desired products (**3ba**, **3ja**, **3ka**) with high chemo-selectivity. It was also pleasant to find that diaryliodonium salts could accommodate trifluoromethyl group (an electron withdrawing group) at the meta or para positions of phenyl rings to conduct the transformation to give trifluoromethylated compounds (**3ha** and **3ja**).

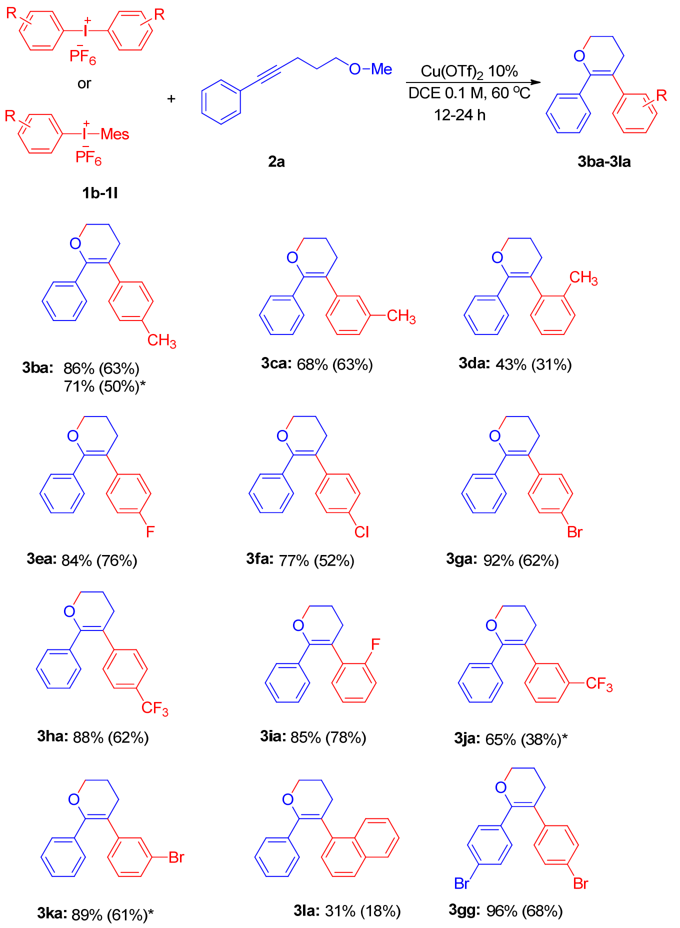
Table 1. Conditions screened for the aryl-etherification of alkoxyl alkyne **2a**.



entry	Solvent	Cat. (10%.)	Temp. (°C)	Yield[a]
1	DCE	$Cu(OTf)_2$	40	<10%
2	DCE	$Cu(OTf)_2$	60	92% (65%[b])
3	DCE	$Cu(OTf)_2$	80	34%
4	DCE	$Cu(OAc)_2$	60	0
5	DCE	CuCl	60	10%
6	DCE	CuBr	60	20%
7	DCE	CuI	60	<10%
8	DCE	Cu_2O	60	0
9	DCE	$(CuOTf)_2C_6H_6$	60	<10%
10	DCE	--	60	0
11	DCM	$Cu(OTf)_2$	60	11%
12	THF	$Cu(OTf)_2$	60	0
13	Tol	$Cu(OTf)_2$	60	21%
14	Dioxane	$Cu(OTf)_2$	60	0

[a]NMR yields with trichloroethylene (TCE) as internal standard; [b]isolated yield.

Inspired by the above results, the scope of this novel intramolecular etherification was further explored by varying the alkynes **2** (Scheme 3). It was delightful to find that alkyne **2a** could also allow various substituents on the phenyl ring to conduct the transformation to give expected products **3ab**-**3af**. The structure of **3af** was unequivocally confirmed with X-ray diffraction (Figure 1, CCDC number: 1019497).[12] When substituted 4-methoxyl-1-phenyl-1-butyne derivatives (**4a-4c**) were used as the substrates, furan derivatives **(5aa-5ac)** were obtained in synthetically useful yields.



Scheme 2. The scope investigation of diaryliodonium salts: the yields were evaluated by ^{1}H NMR with TCE as standard and isolated yields were shown in parentheses. The products with * labeled were obtained with corresponding ArI^+Mes salts.

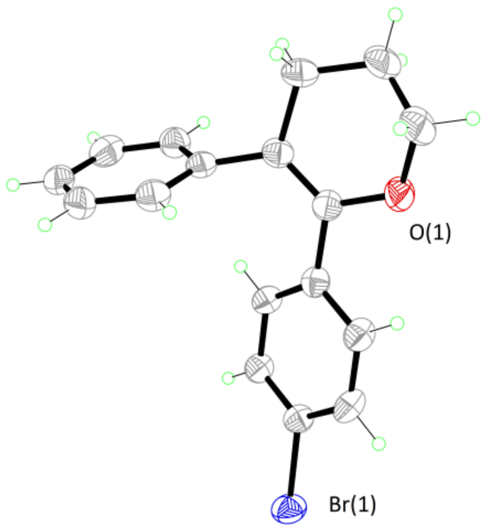
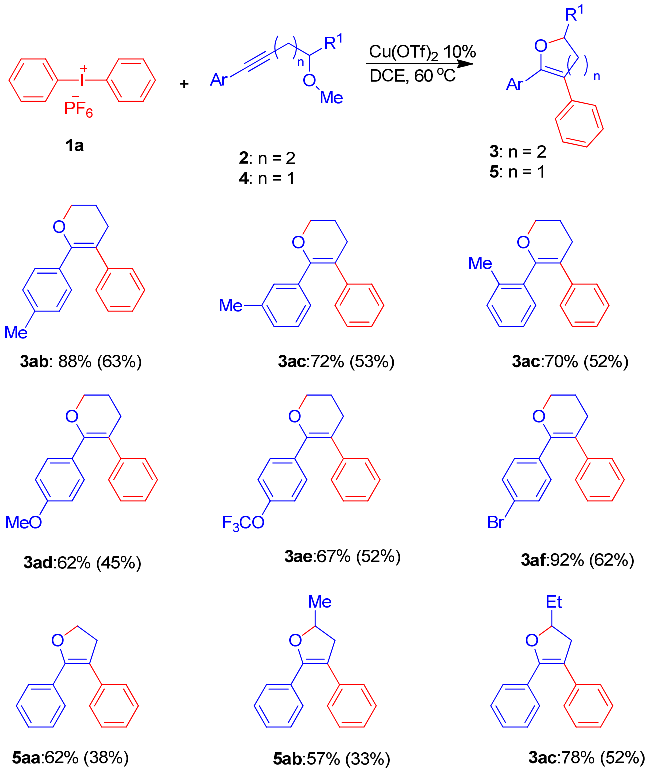
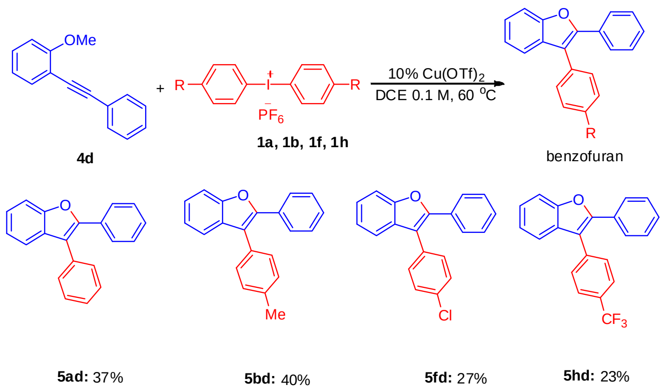


Figure 1. ORTEP drawing of **3af** with 35% probability ellipsoids.



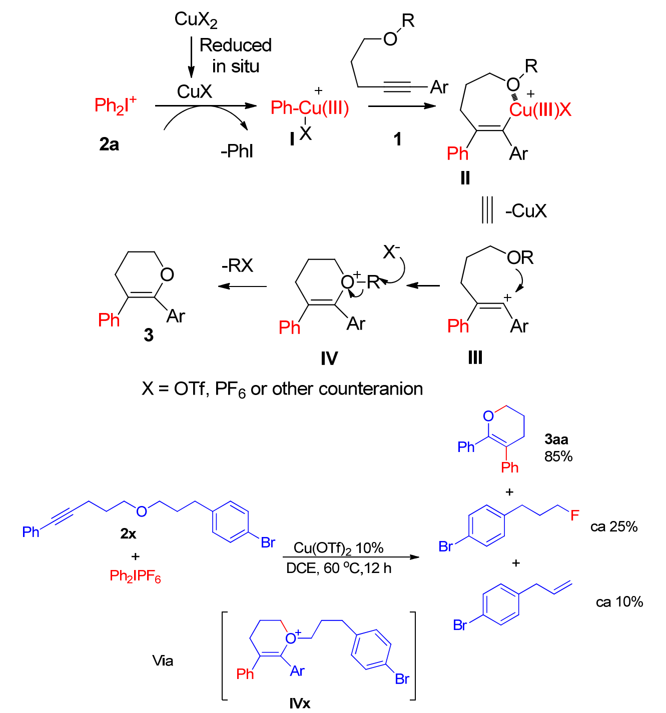
Scheme 3 The scope investigation of alkynes: the yields were evaluated by ^{1}H NMR with TCE as standard and isolated yields were shown in parentheses.

After the facile construction of oxo-heterocycles with linear alkoxyl alkynes and diaryliodonium salts, we made further attempt to benzo-fused heterocycles. For this goal, 2'-methoxyl tolane **4d** was synthesized[13] and subjected to react with a few diaryliodonium salts (scheme 4). Regretfully, the desired benzofuran products could only isolated in modest yields while the starting materials were all consumed. This may be attributed to the lower nucleophility of oxygen atom conjugated with a phenyl ring in **4d**. The usage of TMS-protected 2'-hydroxyl tolane didn't increase the yield neither (see ESI).



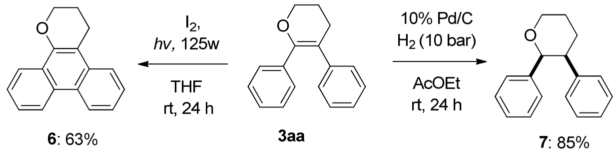
Scheme 4. The isolated yields of 1,2-diaryl benzofuran derivatives through Cu-catalyzed intramolecular aryl-etherification reaction.

It's already accepted that the diaryliodonium salts could generate highly electrophilic Ar-Cu(III) species in situ in the presence of copper salt and the Ar-Cu(III) **I** species could be easily attacked by alkynes to produce vinyl-copper(III) species **II** (Scheme 5), resembling a vinyl-cation **III**.[14] Rationally, when the alkoxyl alkynes were used as the substrates, the copper centre (followed by elimination of Cu(I)X) or vinyl cation centre was easily attacked by oxygen atom to give an oxonium intermediate **IV**. The substitution of **R** group on the electrophilic oxonium intermediate **IV** with counteranion would produce final product **3**. To seek some clues of this pathway, alkyne **2x** with 3-(4-bromophenyl)-propyl group-a larger substituent was prepared and treated with $Ph_2I^+PF_6$ under the standard condition. Interestingly, besides the product **3aa** formed in 85% yield, 3-(4-bromophenyl)-propyl fluoride and 4-allyl-phenyl bromide (or its isomer) were also observed by GC-MS in significant amount (see ESI) and this was an evidence for the presence of oxonium intermediate **IV** during the reaction.

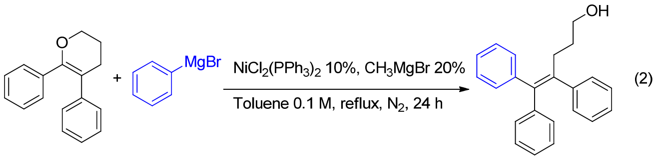


Scheme 5. Plausible mechanism for the Cu-catalyzed intramolecular aryl-etherification reaction.

To explore the further application of this Cu-catalyzed intramolecular aryl-etherification reaction, the newly formed oxo-heterocycle **3aa** was applied to a photo-cyclization reaction[15] to produce phenanthrene derivative **6** and a hydrogenation reaction[16] to give pyran **7** in high yields. Moreover, when **3aa** was treated with PhMgBr in the presence of Ni-catalyst,[17] coupling product **8**-a useful intermediate for medicinal compounds[18] was formed.



(1)



Conclusions

In summary, we reported a novel Cu-catalyzed intramolecular aryl-etherification reaction of alkoxyl alkynes with diaryliodonium salts. The reactions proceed smoothly to give useful oxo-heterocycles with readily available linear starting materials via cleavage of a stable C-O bond.

Notes and references

[a] Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China
[b] Key Laboratory of Systems Bioengineering, Ministry of Education, Department of Pharmaceutical Engineering, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China.
† This work was supported by National Natural Science Foundation of China (21102080, 21372138) and Tsinghua University Initiative Scientific Research Program (2011Z02150). Electronic supplementary Information (ESI) available: Full experimental details, including ^{1}H and ^{13}C NMR data of new compounds For ESI and crystallographic data in CIF (CCDC 1019497) of **3af** see DOI: 10.1039/c000000x/

1 For reviews, see: T. L. B. Boivin, *Tetrahedron*, 1987, **43**, 3309; G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321; K. E. Harding and T. H. Tiner, *Comp. Org. Synh.*, 1991, **4**, 363; G. Rousseau and F. Homsi, *Chem. Soc. ReV.*, 1997, **26**, 453; S. Robin and G. Rousseau, *Tetrahedron*, 1998, **54**, 13681; S. Robin and G. Rousseau, *Eur. J. Org. Chem.*, 2002, 3099; S. Ranganathan, K. M. Muraleedharan, N. K. Vaish and N. Jayaraman. *Tetrahedron*, 2004, **60**, 5273; A. N. French, S. Bissmire and T. Wirth, *Chem. Soc. Rev.*, 2004, **33**, 354; Y. Tang, J. Oppenheimer, Z. Song, L. You, X. Zhang and R. P. Hsung, *Tetrahedron*, 2006, **62**, 10785; A. M. Montana, C. Batalla and J. A. Barcia *Curr. Org. Chem.*, 2009, **13**, 919.

2 Selective examples: G.A. Sotzing, J. R. Reynolds and P. J. Steel, *Chem. Mater.*, 1996, **8**, 882; M. F. Pepitone, S. S. Hardaker and R. V. Gregory, *Chem. Mater.*, 2003, **15**, 557; C.-F. Lee, L.-M. Yang, T.-Y. Hwu, A.-S. Feng, J.-C. Tseng and T.-Y. Luh, *J. Am. Chem.* Soc.,2000. **122**, 4992; H. Chen, W. Delaunay, J. Li, Z. Wang, P.-A. Bouit, D. Tondelier, B. Geffroy, F. Mathey, Z. Duan, R. Réau and M. Hissler, *Org. Lett.*, 2013, **15**, 330.

3 Selective examples: F. Q. Alali, X.-X. Liu and J. L. McLaughlin. *J. Nat. Prod.*, 1999, **62**, 504; M. C. Zafra- Polo, B Figadere, T Gallardo, J. R. Tormo and D Cortes, *Phytochemistry*, 1998, **48**, 1087; H. C. Shen, *Tetrahedron*, 2009, **65,** 3931.

4 Selective examples: F. J. Urban and B. S. Moore, *J. Heterocycl. Chem.*, 1992, **29**, 431 and references cited therein; K. W. Hunt, J. P. Rizzi and A. Cook, PCT Int. Appl., WO 2011072064A1, 2011.

5 For reviews, see: J. P. Wolfe, *Eur. J. Org. Chem.*, 2007, 571; J. P. Wolfe, *Synlett*, 2008, 2913; M. B. Hay and J. P. Wolfe, *J. Am. Chem. Soc.*, 2005, **127,** 16468; J. P. Wolfe and M. A. Rossi, *J. Am. Chem. Soc.*, 2004, **126**, 1620; M. B. Hay and J. P. Wolfe, *Tetrahedron Lett.*, 2006, **47**, 2793; M. B. Hay, A. R. Hardin and J. P. Wolfe, *J. Org. Chem.*, 2005, **70**, 3099; A. F. Ward and J. P. Wolfe, *Org.Lett.*, 2009, **11**, 2209.

6 For reviews about diaryliodonium salts, see: M. S. Yusubov, A. V. Maskaev and V. V. Zhdankin, ARKIVOC 2011, (i), 370; E. A. Merritt and B. Olofsson, *Angew. Chem. Int. Ed.*, 2009, **48,** 9052; V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2008, **108**, 5299; V. V. Zhdankin and P. J. Stang, *Chem. Rev.*, 2002, **102**, 2523; V. V. Grushin, *Chem. Soc. Rev.*, 2000, **29**, 315; P. J. Stang and V. V. Zhdankin, *Chem. Rev.*, 1996, **96**, 1123.

7 Y. Wang, C. Chen, J. Peng and M. Li, *Angew. Chem., Int. Ed.*, 2013, **52**, 5323; J. Peng, C. Chen, Y. Wang, Z.-B. Lou, M Li. C. Xi and H. Chen, *Angew. Chem., Int. Ed.* 2013, **52**, 7574; X. Su, C. Chen, Y. Wang, J. Peng, Z.-B. Lou and M. Li, *Chem. Commun.*, 2013, **49**, 6752; Y. Wang, X. Su and C. Chen, *Synlett*, 2013, **24**, 2619.

8 A. J. Walkinshaw, W.-S. Xu, M. G. Suero and M. J. Gaunt. *J. Am. Chem. Soc.*, 2013, **135,** 12532; E. Cahard, N. Bremeyer and M. J. Gaunt. *Angew. Chem., Int. Ed.*, 2013, **52,** 9284; N. T. Vo, R. D. M. Pace, F. O'Har a and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 404.

9 C. Yu, O. H. Jamison and F. Timothy, *Angew. Chem., Int. Ed.*, 2008, **47**, 1893; C. Patrick and M. Bernard. *Tetrahedron Letters*, 1977, **17,** 1493.

10 L. V. Yudanov, A. V. Matveev, K. M. Neyman and N. Rosch. *J. Am. Chem. Soc.*, 2008, **130**, 9342; J. M. Nichols, L. M. Bishop, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*,2010, **132,** 12554; Y.-G. Zhao and V. Snieckus. *J. Am. Chem. Soc.*, 2014, **136**, 11224; D.-Y. Yu and Z.-J. Shi. *Angew. Chem., Int. Ed.*, 2011, **50**, 7097.

11 R. Ghosh and B. Olofsson. *Org. Lett.*, 2014, **16**, 1830; E. Lindstedt, R. Ghosh and B. Olofsson, *Org. Lett.*, 2013, **15**, 6070.

12 CCDC number: 1019497. The single crystal suitable for XRD was obtained by slow evaporation its solution in n-hexane.

13 S. Mandal, K. N. Parida, S. Samanta and J. N. Moorthy, *J. Org. Chem. Soc.*, 2011, **76,** 7406.

14 Selected examples: J. Peng, C. Chen, J. Chen, X. Su, C. Xi,, H. Chen, *Org. Lett.*, 2014, **16,** 3776; R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong and M. J. Gaunt, *J. Am. Chem. Soc.*, 2012, **134**, 10773; B. Chen, X.-L. Hou, Y.-X. Li and Y.-D. Wu, *J. Am. Chem. Soc.*, 2011, **133**, 7668; B. Xiao, Y. Fu, J. Xu, T.-J. Gong, J.-J. Dai, J. Yi and L. Liu, *J. Am. Chem. Soc.*, 2010, **132,** 468; R. J. Phipps and M. J. Gaunt, *Science*, 2009, **323**, 1593; R. J. Phipps, N. P. Grimster and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130,** 8172. Other metal such as Pd-catalyzed reaction of alkynes with diaryliodonium salts: S. Tang, P. Peng, P, Zhong, J.-H. Li, *J. Org. Chem.*, 2008, **73**, 5476.

15 H. R. Talele, M. J. Gohil and A. V. Bedekar, *Bull. Chem. Soc. Jpn.*, 2009, **82,** 1182; A. U. Rahmahan and B. Vuano, *J. Org. Chem.*, 1969, **34**, 763.

16 Y. M. A. Yamada, Y. Yuyama, T. Sato, S. Fujikawa and Y. Uozumi, *Angew. Chem., Int. Ed.*, 2014, **53,** 127.

17 W. Ernest, E. L. Michelott, C. S. Swindell and M. Tingoli, *J. Org. Chem.*, 1984, **49**, 4894.

18 A. B. Foster, M. Jarman, O. Leung, R. Molague, G. Leclercq and N. Devleeschouwer. *J. Med. Chem.*, 1985, **28,** 1491; L.-P. Wang, L. O. Miller, R. T. Nolte, D. P. McDonnell, T. M. Willson and W. J. Zuercher, *Bioorg. Med. Chem. Lett.*, 2006, **16,** 821.