Synthetic Methodology

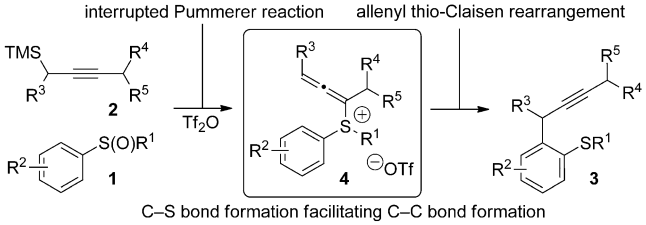
DOI: 10.1002/anie.201300223

Nucleophilic *ortho*-Propargylation of Aryl Sulfoxides: An Interrupted Pummerer/Allenyl Thio-Claisen Rearrangement Sequence**

*Andrew J. Eberhart and David J. Procter**

Selective C–C bond formation to aromatic systems is one of the most important synthetic objectives as the resulting motifs form the core of many pharmaceuticals, agrochemicals, and functional materials. In this regard, products of propargylation[1] are valuable synthetic intermediates as they are established precursors to other functional groups, and to carbo- and heterocycles.[1] Unfortunately, direct propargylation of aromatics is often difficult and can lead to mixtures of propargyl and allenyl products. Although metal-catalyzed couplings are possible,[2] many methods rely on Friedel–Crafts-type processes that can require stoichiometric metal reagents.[3] Using activating substituents to facilitate nucleophilic substitution in aromatic systems is a relatively underexploited approach. In recent years, activation by sulfoxide substituents has been exploited in nucleophilic alkylations of electron-rich heteroaromatics[4] that proceed through Pummerer-type reactions.[5] Furthermore, Yorimitsu and Oshima[6a–d] and Maulide[6e] recently employed interrupted Pummerer reactions in approaches to targets such as benzofurans and α-aryl-β-ketoesters, while we have described an interrupted Pummerer approach for the allylation of aromatic and heteroaromatic rings.[7]

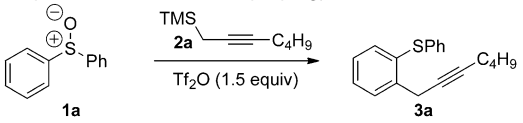
Herein we report a nucleophilic *ortho*-propargylation of aryl sulfoxides that proceeds by a new interrupted Pummerer-allenyl thio-Claisen rearrangement[8] sequence involving allenyl sulfonium salts **4** (Scheme 1).[9] The operationally simple, metal-free procedure is general, regiospecific with regard to the propargyl nucleophile, and shows complete selectivity for products of propargylation over allenylation.



Scheme 1. Nucleophilic *ortho*-propargylation of aryl sulfoxides. TMS = trimethyl silyl, Tf = 1,1,1-trifluoromethylsulfonyl.

Realizing the value of a process that would allow propargyl groups to be selectively introduced to aryl rings under metal-free conditions, we sought to develop a reaction in which intermolecular delivery of a nucleophile to sulfur is followed by an intramolecular relay to carbon (Scheme 1). We began by investigating the reaction of diphenyl sulfoxide **1a** with propargyl silane **2a** (Table 1). Using Tf_2O as an electrophilic activating agent, propargylation product **3a** was obtained in low yield (entry 1). We next compared the reaction in various solvents and obtained the best result using MeCN (entry 4).[10a] The reaction proceeded readily at room temperature in 36 h (entry 5) and the reaction time could be shortened to 1 h at 60 °C (entry 6). Addition of base significantly enhanced the reaction to give **3a** in an isolated yield of 99 % (entry 8).[10b]

Table 1: Optimization of the *ortho*-propargylation.[a]



Entry	Solvent	*t* [h]	*T* [°C]	Base	Yield **3** [%]
1	CH_2Cl_2	18	50	–	35
2	$CHCl_3$	18	50	–	28
3	toluene	18	50	–	27
4	MeCN	18	50	–	63
5	MeCN	36	RT	–	72
6	MeCN	1	60	–	73
7	MeCN	18	60	pyridine	16
8	MeCN	18	60	2,6-lutidine	99[b]
9	MeCN	18	60	2,6-DTBP	99

[a] Yields determined by ^{1}H NMR spectroscopy. Conditions: entries 7–9: base (2.5 equiv). [b] Yield of isolated product; 2,6-DTBP = 2,6-di-*tert*-butylpyridine.

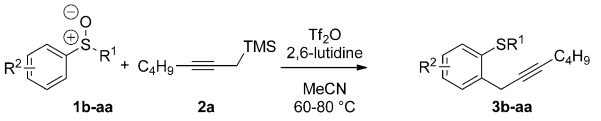
Having identified optimized reaction conditions we next investigated the substrate scope. Pleasingly the *ortho*-propargylation reaction is not restricted to diaryl sulfoxides, but works well with readily available, simple alkyl aryl sulfoxides **1b-aa** to give the corresponding products **3b-aa**, containing alkylsulfanyl groups that are of pharamaceutical relevance (Table 2). Methyl phenyl sulfoxide was easily converted to **3b** in excellent yield on a 1 gram scale. Surprisingly, the formation of classical Pummerer products (e.g. phenylthiomethyl trifluoromethanesulfonate from **1b**) was not observed, even in substrates containing electron-withdrawing

[*] A. J. Eberhart, Prof. D. J. Procter
School of Chemistry, University of Manchester
Oxford Road, Manchester, M13 9PL (UK)
E-mail: david.j.procter@manchester.ac.uk
Homepage: http://people.man.ac.uk/~mbdssdp2/

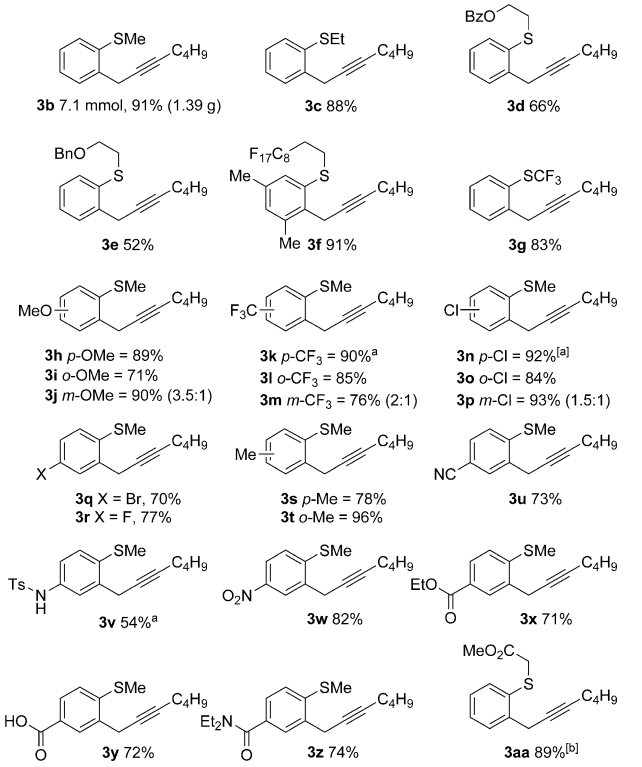
[**] We thank Merck Sharp & Dohme (CASE award to A.E.) and the EPSRC (CPhD award to A.E.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201300223.

Table 2: Aryl sulfoxide substrate scope.

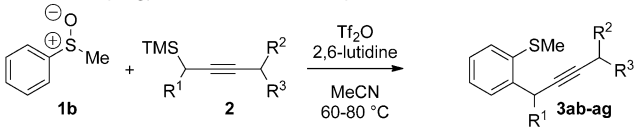


1b-aa 2a 3b-aa

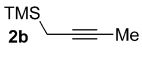
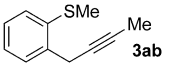
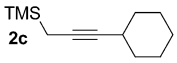
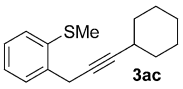
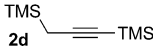
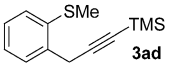
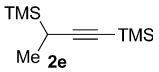
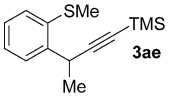
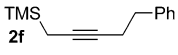
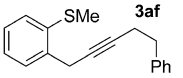
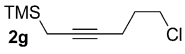
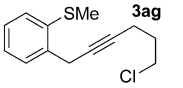


[a] 2,6-DTBP was used as the base. [b] No base.

Table 3: Propargyl silane substrate scope.



1b 2 3ab-ag

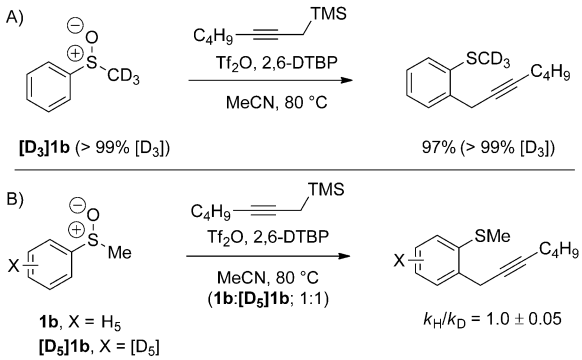
Entry	Silane	Product	Yield [%]
1	 2b	 3ab	96
2	 2c	 3ac	72
3	 2d	 3ad	92
4	 2e	 3ae	64[a]
5	 2f	 3af	88[a]
6	 2g	 3ag	95[a]

[a] 2,6-DTBP was used as the base.

alkyl chains (e.g. formation of **3d**, **3e**, **3f**, and **3aa**). Interestingly, the procedure also tolerates the synthetically important perfluorinated alkyl chain[11] in **3f** and the medicinally relevant trifluoromethyl sulfide group in **3g**.[12] The reaction is also general with respect to ring substituents: neutral, electron-rich and electron-deficient benzene rings are propargylated in high yields (**3h–z**) with no significant changes in overall reaction efficiency when substitution position was varied (**3h–p**, 71–93%). Even sterically hindered *ortho*-substituted substrates underwent propargylation to give **3l** and **3t** in 85% and 96% yield. The reaction tolerates a wide range of functional groups: Substrates containing halogens (**3n–r**), nitriles (**3u**), nitro (**3w**), and protected amines (**3v**)[13] were all readily propargylated in good to excellent yields. Furthermore, substrates bearing ester, amide and acid groups underwent successful propargylation to give **3x–z**. Importantly, a substrate known to undergo classical Pummerer chemistry,[14] gave **3aa** in 89% yield when exposed to Tf_2O in the presence of **2a**.

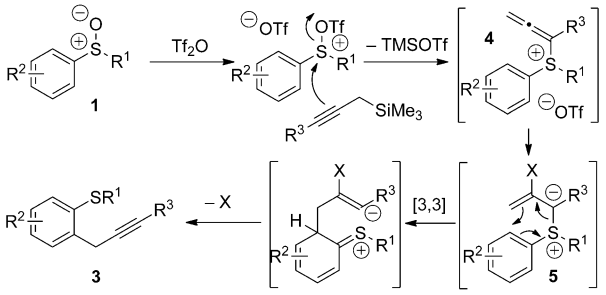
Methyl phenyl sulfoxide **1b** was exposed to propargyl silanes **2b–g** under the described conditions (Table 3). In all cases the expected products of propargylation were obtained in good to excellent yields. For example, commonly used silane **2b** (entry 1) and the protected propargyl silane **2d** (entry 3) produced products of selective propargylation in high yields. Sterically more demanding silanes (entries 2, 4), including those with substitution at both propargylic positions, and functionalized silanes (entries 5, 6) were also effective.

After activation of the sulfoxide with Tf_2O,[15] two mechanisms are possible: A nucleophile could directly attack the aromatic ring with concomitant triflate expulsion followed by rearomatization,[4a,b] or the nucleophile could react at sulfur in an interrupted Pummerer-type reaction,[7] followed by rearrangement. The former pathway would be expected to deliver, *ortho* and *para* regioisomeric products of allenylation. In contrast, our process provides products of propargylation, with no allenylation and with complete *ortho*-selectivity. This suggests that the interrupted Pummerer pathway is operational. Indeed, allenyl sulfonium salt **4** (Scheme 1) formed by reaction at sulfur can be observed when reactions are monitored by ^1H and ^{13}C NMR spectroscopy.[16,17] The formation of **4** is fast[18] and outcompetes classical thionium ion formation and Pummerer reaction. This conclusion is supported by the observation that **3aa** undergoes smooth propargylation despite the presence of acidic α-protons. In an additional experiment, labeled sulfoxide **[D_3]1b** (Scheme 2 A) was propargylated with no ^1H incorporation, further highlighting the rapid formation of allenyl sulfonium salts **4** rather than loss of a proton α to sulfur. The nature of substituents on the aryl ring, as well as their positions,[19] affect the rate of the rearrangement of **4** to products **3** as shown by preliminary rate and Hammett studies.[20] Furthermore, a competition experiment involving a 1:1 mixture of **1b** and its aryl-deuterium labeled analog **[D_5]1b** (Scheme 2 B) showed no isotope effect, suggesting that rearomatization is not the rate-determining step.



Scheme 2. Labeling experiments (yields and conversions measured by ^{1}H NMR spectroscopy).

A proposed mechanism for the selective *ortho*-propargylation is shown in Scheme 3. Interrupted Pummerer reactions, in which sulfoxides **1** activated by Tf_2O undergo nucleophilic attack by the propargyl silanes at sulfur give allenylsulfonium salts **4** (Scheme 3). These intermediates may then convert to

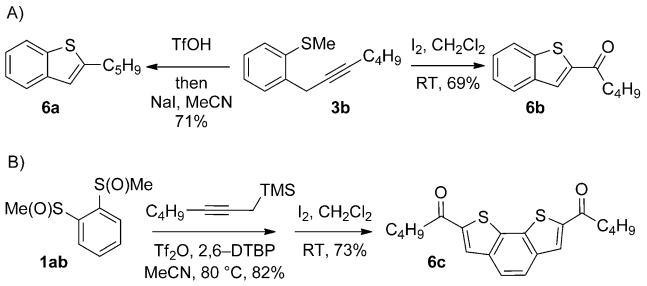


Scheme 3. Proposed mechanism for *ortho*-propargylation.

ylides **5** prior to [3,3]-sigmatropic rearrangement[8,21,22] and rearomatization to yield **3**.[23]

The products of *ortho*-propargylation are rich in synthetic potential as the combination of the propargyl[1] and organosulfanyl groups opens up a wide range of bond-forming possibilities. In particular, recent developments have shown that the C–S bond can be readily utilized in transition-metal-catalyzed cross-couplings to form C–C bonds.[6d,7,24] Preliminary studies show the potential of the dual functionality in the adducts. For example, **3b** was converted to benzothiophenes **6a** and **6b** by treatment with TfOH/NaI and I_2,[25] respectively. Furthermore, double cyclization of the adduct formed by the two-directional propargylation of bis-sulfoxide **1ab**, completed an efficient metal-free approach to **6c**, a motif found in organic semiconductors (Scheme 4).[26]

In summary, readily available aryl sulfoxides undergo *ortho*-selective propargylation by a new interrupted Pummerer/allenyl thio-Claisen rearrangement sequence. The operationally simple, metal-free procedure allows propargylic carbon nucleophiles to be added *ortho* to sulfur on a benzene ring, regiospecifically with regard to the propargyl nucleophile, and with complete selectivity for products of propargylation over allenylation. The organosulfanyl group and



Scheme 4. Manipulation of *ortho*-propargylation products.

the propargyl motif in the products are versatile handles for further manipulation.

Received: January 10, 2013
Published online: February 27, 2013

Keywords: arylsulfoxide · propargylation · Pummerer reaction · silane · thio-Claisen

[1] For reviews of propargylation, see: a) J. A. Marshall, *J. Org. Chem.* **2007**, *72*, 8153; b) M. J. Curtis-Long, Y. Aye, *Chem. Eur. J.* **2009**, *15*, 5402; c) C.-H. Ding, X-L. Hou, *Chem. Rev.* **2011**, *111*, 1914; d) N. Ljungdahl, N. Kann, *Angew. Chem.* **2009**, *121*, 652; *Angew. Chem. Int. Ed.* **2009**, *48*, 642; e) R. J. Detz, H. Hiemstra, J. H. van Maarseveen, *Eur. J. Org. Chem.* **2009**, 6263; f) Y. Nishibayashi, *Synthesis* **2012**, 489; g) E. B. Bauer, *Synthesis* **2012**, 1131; for reviews of alkyne chemistry, see: h) D. Astruc, *Organometallic Chemistry and Catalysis*, Springer, Berlin, **2007**; i) S. K. Hashmi, F. D. Toste, *Modern Gold Catalyzed Synthesis*, Wiley-VCH, Weinheim, **2012**; j) R. Chinchilla, C. Najera, *Chem. Soc. Rev.* **2011**, *40*, 5084; k) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249; l) L.-N. Guo, X.-H. Duan, Y.-M. Liang, *Acc. Chem. Res.* **2011**, *44*, 111.

[2] a) R. Martin, A. Fürstner, *Angew. Chem.* **2004**, *116*, 4045; *Angew. Chem. Int. Ed.* **2004**, *43*, 3955; b) S. Ma, Q. He, X. Zhang, *J. Org. Chem.* **2005**, *70*, 3336; c) M. Qian, E. Negishi, *Tetrahedron Lett.* **2005**, *46*, 2927; d) I. Pérez, J. P. Sestelo, L. A. Sarandeses, *J. Am. Chem. Soc.* **2001**, *123*, 4155; e) C. H. Larsen, K. W. Anderson, R. E. Tundel, S. L. Buchwald, *Synlett* **2006**, 2941; f) W.-W. Zhang, X.-G. Zhang, J.-H. Li, *J. Org. Chem.* **2010**, *75*, 5259.

[3] a) K. M. Nicholas, *Acc. Chem. Res.* **1987**, *20*, 207; b) Y. Nishibayashi, Y. Inada, M. Yoshikawa, M. Hidai, S. Uemura, *Angew. Chem.* **2003**, *115*, 1533; *Angew. Chem. Int. Ed.* **2003**, *42*, 1495; c) H. Matsuzawa, Y. Miyake, Y. Nishibayashi, *Angew. Chem.* **2007**, *119*, 6608; *Angew. Chem. Int. Ed.* **2007**, *46*, 6488; d) J. J. Kennedy-Smith, L. A. Young, F. D. Toste, *Org. Lett.* **2004**, *6*, 1325; e) C. Li, J. Wang, *J. Org. Chem.* **2007**, *72*, 7431; f) P. Rubenbauer, E. Herdtweck, T. Strassner, T. Bach, *Angew. Chem.* **2008**, *120*, 10260; *Angew. Chem. Int. Ed.* **2008**, *47*, 10106.

[4] a) S. Akai, N. Kawashita, Y. Wada, H. Satoh, A. H. Alinejad, K. Kakiguchi, I. Kuriwaki, Y. Kita, *Tetrahedron Lett.* **2006**, *47*, 1881; b) S. Akai, N. Kawashita, H. Satoh, Y. Wada, K. Kakiguchi, I. Kuriwaki, Y. Kita, *Org. Lett.* **2004**, *6*, 3793; c) S. Akai, N. Morita, K. Iio, Y. Nakamura, Y. Kita, *Org. Lett.* **2000**, *2*, 2279; d) K. S. Feldman, D. B. Vidulova, *Org. Lett.* **2004**, *6*, 1869; e) K. S. Feldman, A. P. Skoumbourdis, *Org. Lett.* **2005**, *7*, 929; f) K. S. Feldman, D. B. Vidulova, A. G. Karatjas, *J. Org. Chem.* **2005**, *70*, 6429; g) K. S. Feldman, A. G. Karatjas, *Org. Lett.* **2006**, *8*, 4137;

h) K. S. Feldman, M. D. Fodor, *J. Org. Chem.* **2009**, *74*, 3449; i) A. Padwa, S. Nara, Q. Wang, *Tetrahedron Lett.* **2006**, *47*, 595.

[5] For selected reviews of the Pummerer reaction, see: a) L. H. S. Smith, S. C. Coote, H. F. Sneddon, D. J. Procter, *Angew. Chem.* **2010**, *122*, 5968; *Angew. Chem. Int. Ed.* **2010**, *49*, 5832; b) S. Akai, Y. Kita, *Top. Curr. Chem.* **2007**, *274*, 35; c) K. S. Feldman, *Tetrahedron* **2006**, *62*, 5003; d) S. K. Bur, A. Padwa, *Chem. Rev.* **2004**, *104*, 2401.

[6] a) S. Yoshida, H. Yorimitsu, K. Oshima, *Org. Lett.* **2009**, *11*, 2185; b) T. Kobatake, D. Fujino, S. Yoshida, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2010**, *132*, 11838; c) T. Kobatake, S. Yoshida, H. Yorimitsu, K. Oshima, *Angew. Chem.* **2010**, *122*, 2390; *Angew. Chem. Int. Ed.* **2010**, *49*, 2340; d) Y. Ookubo, A. Wakamiya, H. Yorimitsu, A. Osuka, *Chem. Eur. J.* **2012**, *18*, 12690; e) X. Huang, N. Maulide, *J. Am. Chem. Soc.* **2011**, *133*, 8510.

[7] A. J. Eberhart, J. E. Imbriglio, D. J. Procter, *Org. Lett.* **2011**, *13*, 5882.

[8] For thio-Claisen rearrangements of sulfonium ylides and sulfonium salts formed by alternative approaches, see: a) X. Huang, S. Klimczyk, N. Maulide, *Synthesis* **2012**, 175; b) J. N. Harvey, H. G. Viehe, *J. Chem. Soc. Chem. Commun.* **1995**, 2345; c) V. Boyarskikh, A. Nyong, J. D. Rainier, *Angew. Chem.* **2008**, *120*, 5454; *Angew. Chem. Int. Ed.* **2008**, *47*, 5374; d) A. M. Nyong, J. D. Rainier, *J. Org. Chem.* **2005**, *70*, 746; e) A. V. Novikov, A. R. Kennedy, J. D. Rainier, *J. Org. Chem.* **2003**, *68*, 993; f) N. Furukawa, H. Shima, S. Ogawa, *Heteroat. Chem.* **1995**, *6*, 559; g) H. Shima, N. Furukawa, *Tetrahedron* **1995**, *51*, 12239; h) P. G. Gassman, G. D. Gruetzmacher, *J. Am. Chem. Soc.* **1974**, *96*, 5487; i) P. G. Gassman, T. J. van Bergen, *J. Am. Chem. Soc.* **1974**, *96*, 5508.

[9] V. G. Nenajdenko, P. V. Vertelezkij, E. S. Balenkova, *Synthesis* **1997**, 351.

[10] a) See the Supporting Information for a complete optimization table; b) the base prevents products of propargylation from undergoing acid-mediated cyclization.

[11] a) D. P. Curran in *The Handbook of Fluorous Chemistry* (Ed.: J. A. Gladysz, D. P. Curran, I. T. Horváth), Wiley-VCH, Weinheim, **2004**; b) C. J. Wallentin, J. D. Nguyen, P. Finkbeiner, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2012**, *134*, 8875.

[12] a) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312; b) C. P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183; c) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880.

[13] The presence of amines can be problematic in Pummerer reactions as they can undergo side reactions with the activating electrophile and can react as a nucleophile with other intermediates. See Ref. [5].

[14] a) R. Pummerer, *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 1401; b) H. M. Wang, M. C. Lin, L. C. Chen, *Heterocycles* **1994**, *38*, 1519.

[15] Activation of sulfoxides with electrophiles such as Tf_2O is well documented. See Ref. [5].

[16] Structure of **4** also confirmed by HRMS. See Supporting Information.

[17] As expected, the rate of formation of product **3a** through ionic intermediate **4** is accelerated by more polar solvents. See Supporting Information for an additional solvent study.

[18] See Supporting Information for a study of allenyl sulfonium salt formation using Tf_2O, TFAA and Ac_2O as activating agents.

[19] Electron-donating substituents at the *meta*-position on the benzene ring accelerate the rearrangement from **4** to **3**. See Supporting Information for further details.

[20] See Supporting Information for further details and a Hammett study. For a Hammett study of a charge-accelerated Claisen-type rearrangement, see: M. H. Weston, K. Nakajima, T. G. Back, *J. Org. Chem.* **2008**, *73*, 4630.

[21] T. H. Lambert, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2002**, *124*, 13646.

[22] X could be triflate (see Ref. [9]) although MeCN, sulfide or base can not be ruled out.

[23] Ochiai and Norton have proposed the sigmatropic rearrangement of analogous allenyliodonium salts in an *ortho*-propargylation process: a) M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, *J. Am. Chem. Soc.* **1991**, *113*, 1319; b) D. A. Gately, T. A. Luther, J. R. Norton, M. M. Miller, O. P. Anderson, *J. Org. Chem.* **1992**, *57*, 6496.

[24] For a review, see: a) S. R. Dubbaka, P. Vogel, *Angew. Chem.* **2005**, *117*, 7848; *Angew. Chem. Int. Ed.* **2005**, *44*, 7674; for recent examples, see: b) S. Kanemura, A. Kondoh, H. Yorimitsu, K. Oshima, *Synthesis* **2008**, 2659; c) J. F. Hooper, A. B. Chaplin, C. González-Rodríguez, A. L. Thompson, A. S. Weller, M. C. Willis, *J. Am. Chem. Soc.* **2012**, *134*, 2906.

[25] K. O. Hessian, B. L. Flynn, *Org. Lett.* **2003**, *5*, 4377.

[26] C. Wang, H. Dong, W. Hu, Y. Liu, D. Zhu, *Chem. Rev.* **2012**, *112*, 2208.

