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Stereoselective Synthesis of Alkenyl Silanes, Sulfones, Phosphine Oxides, and Nitroolefins by Radical C−S Bond Cleavage of Arylalkenyl Sulfides

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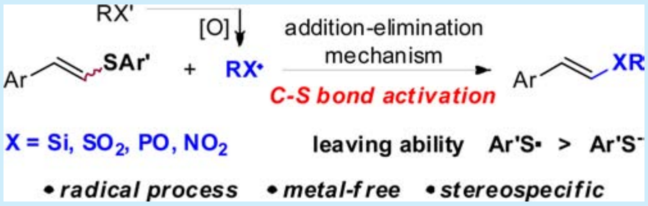
Supporting Information

ABSTRACT: A radical-mediated approach has been introduced for the C−S bond activation of arylalkenyl sulfides. The protocol provides an efficient approach for the generation of various alkenes including alkenyl silanes, sulfones, phosphine oxides, and nitroolefins. In most cases, these radical substitutions are performed under metal-free conditions with stereospecificity.



The activation and cleavage of C−S bonds for the construction of C−C bonds and C−heteroatom bonds has attracted much attention in recent years owing to the stability and ready availability of sulfur species compared to the corresponding halides used in traditional methods.[1] Among organosulfurs, alkenyl sulfides have great potential to undergo C−S bond cleavage with the simultaneous installation of an olefinic part in the products, which are important structural units in many natural products, pharmaceuticals, and organic emitter materials.[2] Therefore, the approaches have been well established for the formation of C−C bonds by C_{vinyl}−S activation using transition-metal catalysts, organometal reagents, or dithioacetal derivatives.[3]

Nevertheless, there are only a few strategies for the generation of C−X bonds (X = heteroatom) via C_{vinyl}−S bond cleavage including the preparation of enamine from dithioacetal derivatives (C−N),[4] the formation of C−O and C−S bonds using sodium alcoholates or alkanethiolates as nucleophile reagents,[5] and the synthesis of vinylsilanes using organosilicon metal reagents (C−Si).[6] Several limitations related to these approaches should be addressed: (1) reagents preprepared by multistep processes or strong basic and unstable reagents are required; (2) the substrate scope is limited; (3) the production of C−heteroatom bonds by C_{vinyl}−S bond cleavage has not been well-studied. In order to eliminate these issues, we envisaged that a radical process may be a better alternative solution than the previous nucleophilic processes, because thiyl radicals (especially aryl sulfenyl radicals) are better leaving groups than thiyl anions (Figure 1).[7]

On the other hand, the formation of olefinic compounds with β-heteroatom substituted patterns has also played an important role in the preparation of pharmaceuticals, natural products, and organic materials.[8] From this perspective, the further exploration of more practical methods for the generation of various C_{vinyl}−heteroatom bonds through C−S bond cleavage in vinyl sulfides is still desirable and appealing. Herein, we report several new metal-free radical-mediated reactions of vinyl sulfides with a wide range of substrates, which provide new access to olefinic compounds with various heteroatoms-substitution patterns. To the best of our knowledge, this is the first example of generating C_{vinyl}−X bonds by radical-mediated cleavage of C_{vinyl}−S bonds.

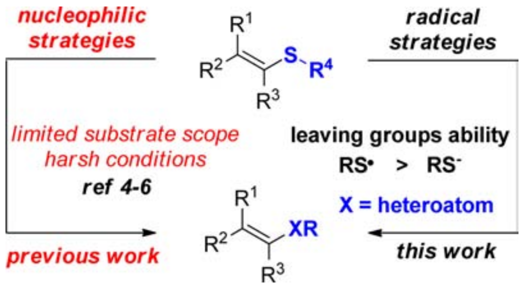


Figure 1. Strategies for the preparation of C_{vinyl}−X bonds via the cleavage of C_{vinyl}−S bonds.

Initially, we started our investigations by selecting the reaction of (4-methylphenyl)(styryl)sulfane **1a** and triphenylsilane **2a** as the model reaction (Table 1). Oxidants play a crucial role in the reaction. Peroxides are better initiators than other oxidants, presumably owing to the high reactivity of oxygen free radicals.[8e] *tert*-Butyl peroxybenzoate (TBPB) emerged as the optimal choice (entries 1−11). After screening different solvents, *t*-BuOH resulted in the best yield (entry 11). The amount of TBPB was also optimized (entries 11−14), and 3 equiv of TBPB could provide the best yield. This result indicates that the reaction may not include a radical chain cycle in which the thiyl radical is unable to abstract an H atom from a silane to generate a silyl radical.[7a] No byproduct generated by direct addition−fragmentation from the oxygen-centered radicals was detected in the protocol.

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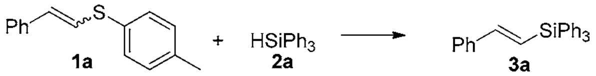
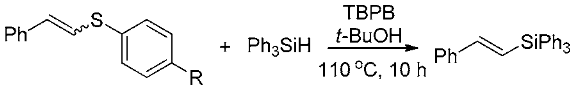
Table 1. Optimization of Reaction Conditions[a]



entry	oxidant (equiv)	solvent	yield (%)[b]
1	TBHP (3)	*t*-BuOH	45
2	TBHP (4)	*t*-BuOH	50
3	TBHP (5)	*t*-BuOH	52
4	DTBP (3)	*t*-BuOH	48
5	$K_2S_2O_8$ (3)	*t*-BuOH	trace
6	$Na_2S_2O_8$ (3)	*t*-BuOH	trace
7	H_2O_2 (3)	*t*-BuOH	14
8	*m*CPBA (3)	*t*-BuOH	11
9	I_2O_5 (3)	*t*-BuOH	nr
10	AIBN	*t*-BuOH	nr
11	TBPB (3)	*t*-BuOH	82
12	TBPB (2)	*t*-BuOH	78
13	TBPB (1)	*t*-BuOH	47
14	TBPB (0.2)	*t*-BuOH	18
15	TBPB (3)	H_2O	52
16	TBPB (3)	toluene	69
17	CHP (3)	*t*-BuOH	trace

[a]Conditions: **1a** (0.25 mmol), triphenylsilane (0.75 mmol), *t*-BuOH (1.0 mL), 110 °C, 10 h. [b]Isolated yields.

Scheme 1. Effects of Substituent Groups in *S*-Substituent Benzene Ring of Arylalkenyl Sulfides on the Reaction



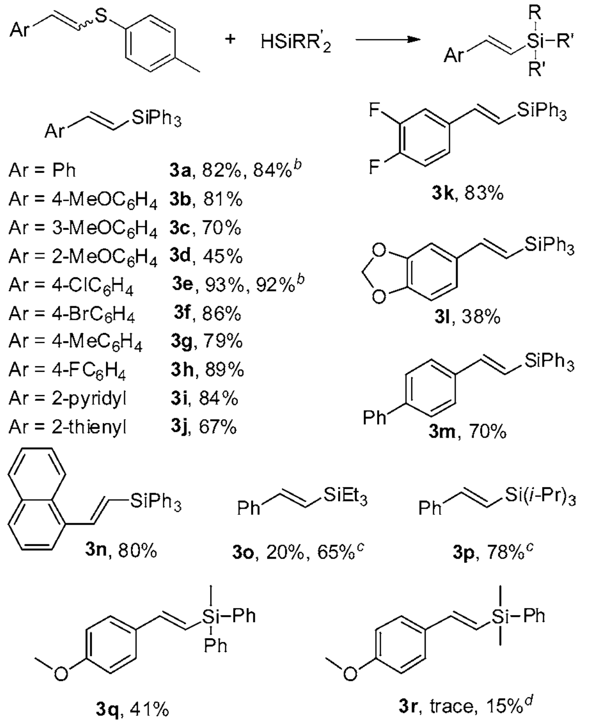
R = CH_3 **1a** (*E*/*Z* = 89/11) 82%
R = OMe **1b** (*E*/*Z* = 91/9) 71%
R = Cl **1c** (*E*/*Z* = 88/12) 83%
R = NO_2 **1d** (*E*/*Z* = 95/5) 78%

Four alkenyl sulfides were chosen to explore the effects of substituent groups on the reaction. As shown in Scheme 1, no obvious influence of *S*-substituent aryl groups in alkenes was found in the transformation, so 2-(2-(*p*-tolylthio)vinyl)arenes were employed in further studies due to consideration of price and yield.

A series of arylalkenyl sulfides with electron-donating and -withdrawing groups provided moderate to excellent yields (**3a**−**3h**, **3k**−**3m**) (Scheme 2). The electron-rich vinyl sulfides led to slightly lower yields (**3d**, **3l**). The reactions of hetero- and naphthylalkenyl sulfides also proceeded smoothly under the identical conditions (**3i**, **3j**, **3n**). Other silanes could be also applied in the protocol (**3o**−**3r**). However, only a trace yield was observed in the case of **3r**, and the reaction could be enhanced by adding cobalt(III) acetylacetonate to provide a poor yield of **3r** (15%). In the cases of **3o** and **3p**, the reactions could be enhanced by increasing the amount of silane and oxidant. It was noteworthy that *E*-alkenyl organosilanes were isolated as the only product from both *Z* and *E* starting materials in all cases.

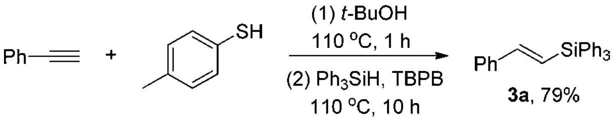
To further demonstrate the potential of this methodology, the stereospecific silylation of ethynylbenzene via a one-pot two-step route was also achieved to derive *E*-isomer **3a** (Scheme 3), in which *p*-tolylthiol was first added and then displaced. However, *Z*-isomers are the main products in various transition-metal-catalyzed reactions of alkyne with silanes.[10]

Scheme 2. Reactions of Alkenyl Sulfides with Silanes[a]



[a]Conditions: vinyl sulfides (0.25 mmol), silane (0.75 mmol), TBPB (0.75 mmol), *t*-BuOH (1.0 mL), 110 °C, 10 h, isolated yield. [b]Corresponding *Z*-**1** was used. [c]Silane (5 equiv) and TBPB (5 equiv) were used. [d]Cobalt(III) acetylacetonate 20 mol % was used.

Scheme 3. Silylation of Ethynylbenzene via a One-Pot Two-Step Process[a]

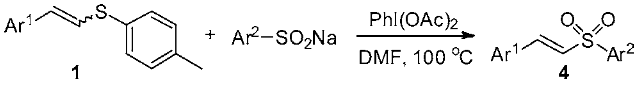


[a]Conditions: (1) ethynylbenzene (0.25 mmol), *p*-tolylthiol (0.25 mmol), *t*-BuOH (1 mL), 110 °C, 1 h; (2) Ph_3SiH (0.75 mmol), TBPB (0.75 mmol), 110 °C, 10 h, isolated yield.

Likewise, vinyl sulfones that are valuable synthetic targets and a significant motif in natural products and in drug discovery[11] could be generated from vinyl sulfides and sodium arylsulfinates in the presence of $PhI(OAc)_2$ (Table 2). To further demonstrate the versatile synthetic utility of the chemistry, other substrates including diphenylphosphine oxide, DMSO, and *tert*-butyl nitrite (TBN) were also applied in the approach to provide the desired products (**5**−**7**) (Scheme 4). All the substitution reactions are stereospecific since only *E*-products are obtained. It should be noted that no *β*-methylstyrene is observed in the reaction of DMSO and **1a**. The reason may be because the methyl radical has high reactivity, so it can react with methyl sulfinic acid or another radical quickly to form a methyl sulfonyl radical or other side products, respectively.[12]

Further radical trapping experiments were also performed. All the reactions shown in Scheme 5 were inhibited in the presence of the radical trap TEMPO. Based on these results, it could be concluded that all these transformations may involve free radical processes. As a representative example, a tentative mechanism for the reaction of triphenylsilane and arylalkenyl

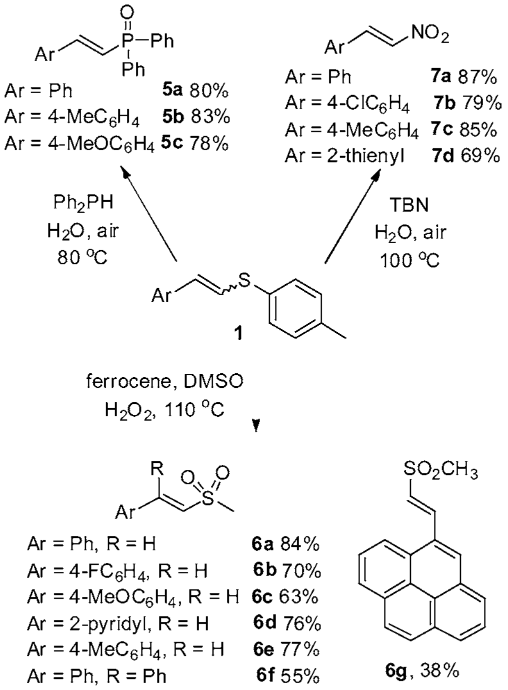
Table 2. Reactions of Alkenyl Sulfides and Sodium Arylsulfinates[a]



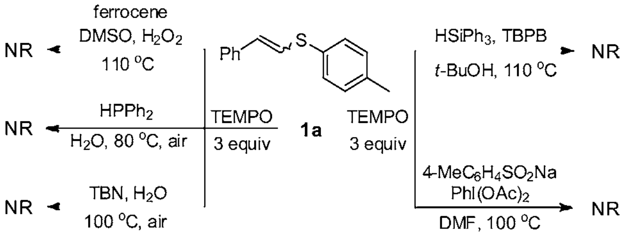
entry	Ar^1	Ar^2	4	yield (%)[b]
1	Ph	4-MeC$_6$H$_4$	**4a**	80, 78[c]
2	Ph	4-MeOC$_6$H$_4$	**4b**	42
3	Ph	4-FC$_6$H$_4$	**4c**	91
4	4-MeOC$_6$H$_4$	4-MeC$_6$H$_4$	**4d**	97
5	4-ClC$_6$H$_4$	4-MeC$_6$H$_4$	**4e**	84
6	4-FC$_6$H$_4$	4-MeC$_6$H$_4$	**4f**	95
7	2-pyridyl	4-MeC$_6$H$_4$	**4g**	63
8	Ph	4-MeC$_6$H$_4$	**4h**	37[d]
9	Ph	Ph	**4i**	74

[a] Conditions: **1** (0.25 mmol), sodium arylsulfinates (0.75 mmol), PhI(OAc)$_2$ (0.50 mmol), DMF (1 mL), 100 °C, 10 h. [b] Isolated yield. [c] **1c** instead of **1a** was used. [d] (2,2-Diphenylvinyl)(*p*-tolyl)sulfane is used as the starting material.

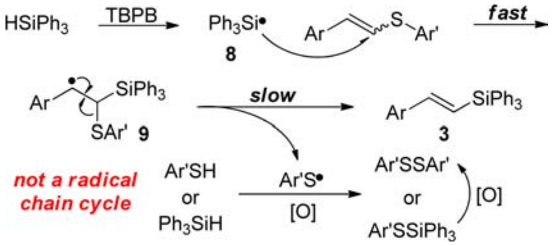
Scheme 4. Transformations of Alkenyl Sulfides 1 via C–S Bond Cleavage



Scheme 5. Radical Trapping Experiments



Scheme 6. A Tentative Pathway for the Reaction of Triphenylsilane and Arylalkenyl Sulfide



sulfide was proposed (Scheme 6), although the detailed mechanisms of these reactions remain to be elucidated. First, a silicon radical **8**[13] derived from triphenylsilane in the presence of TBPB is added to the arylalkenyl sulfide generating a radical intermediate **9**.[8e] The release of the thiyl radical from **9** results in the final product **3**. There is no radical chain cycle in the addition–elimination pathway since a stoichiometric oxidant is required in the process.[7a] The elimination step may be a slow step, and the removed thiyl radical may react with arylthiol or triphenylsilane to afford the corresponding disulfide or thiosilane in the presence of an oxidant,[14] which are observed by GC-MS as the byproducts. Other transformations may have similar mechanisms.[12,15]

In summary, a newly developed approach for stereoselective synthesis of β-heteroatom substituted arylalkenes via C–S bond cleavage has been disclosed. In most cases, these alkenes are generated through a radical process under metal-free conditions, and only *E*-products are derived in these processes. The chemistry not only provides a new application of vinyl sulfides in organic synthesis but also develops a useful method for the activation of C–S bonds, which may promote the discovery of other new types of cleavage and transformation of C–S bonds to useful motifs.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00126.

Experimental details and copies of NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 5042–5055. (b) Pan, F.; Shi, Z.-J. *ACS Catal.* **2014**, *4*, 280–288. (c) Sugahara, T.; Murakami, K.; Yorimitsu, H.; Osuka, A.

Angew. Chem., Int. Ed. **2014**, *53*, 9329–9333. (d) Uetake, Y.; Niwa, T.; Hosoya, T. *Org. Lett.* **2016**, *18*, 2758–2761.

(2) (a) Feng, C.; Loh, T.-P. *J. Am. Chem. Soc.* **2010**, *132*, 17710–17712. (b) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, *42*, 599–621. (c) Iwasaki, M.; Topolovčan, N.; Hu, H.; Nishimura, Y. G.; Gagnot, Y. G.; Nanakorn, R.; Yuvacharaskul, R.; Nakajima, K.; Nishihara, Y. *Org. Lett.* **2016**, *18*, 1642–1645. (d) Zhang, L.; Dong, J.; Xu, X.; Liu, Q. *Chem. Rev.* **2016**, *116*, 287–322.

(3) Selected reports on the formation of C–C bonds by C_{vinyl}–S activation: (a) Wang, L.; Liu, X.; Wang, M.; Liu, J. *Org. Lett.* **2016**, *18*, 2162–2165. (b) Jin, W.; Du, W.; Yang, Q.; Yu, H.; Chen, J.; Yu, Z. *Org. Lett.* **2011**, *13*, 4272–4275. (c) Yu, H.; Yu, Z. *Angew. Chem., Int. Ed.* **2009**, *48*, 2929–2933. (d) Kobatake, T.; Fujino, D.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, *132*, 11838–11840. (e) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2004**, *126*, 11778–11779. (f) Creech, G. S.; Kwon, O. *J. Am. Chem. Soc.* **2010**, *132*, 8876–8877. (g) Itami, K.; Higashi, S.; Mineno, M.; Yoshida, J.-i. *Org. Lett.* **2005**, *7*, 1219–1222. (h) Russell, G. A.; Tashtoush, H.; Ngoviwatchai, P. *J. Am. Chem. Soc.* **1984**, *106*, 4622–4623.

(4) (a) Kuz'mina, N. V.; Lipina, E. S.; Kropotova, T. Y.; Berkova, G. A.; Pavlova, Z. F. *Russ. J. Org. Chem.* **2003**, *39*, 82–86. (b) Huang, Z.-T.; Gan, W.-X.; Li, L.-P. *J. Prakt. Chem.* **1990**, *332*, 1035–1040. (c) Sreedevi, N. K.; Mathews, A.; Devaky, K. S.; Anabha, E. R. *J. Heterocycl. Chem.* **2014**, *51*, 562–565. (d) Schirok, H.; Alonso-Alija, C.; Benet-Buchholz, J.; Göller, A. H.; Grosser, R.; Michels, M.; Paulsen, H. *J. Org. Chem.* **2005**, *70*, 9463–9469.

(5) (a) Julia, M.; Righini, A.; Uguen, D. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1646–1651. (b) Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D. *Tetrahedron* **1985**, *41*, 1401–1408.

(6) Fugami, K.; Hibino, J.-i.; Nakatsukasa, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1988**, *44*, 4277–4292.

(7) The basicity of thiyl radicals is less than corresponding thiyl anions, and the leaving ability is inversely proportional to the basicity of leaving groups. (a) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 58–102. (b) Grossman, R. B. *The Art of Writing Reasonable Organic Reaction Mechanisms*, 2nd ed.; Springer-Verlag Press; New York, 2003.

(8) Selected reports on the applications of Olefinic Compounds with *β*-Heteroatom Substituted Patterns: (a) Li, Q.; Dong, T.; Liu, X.; Lei, X. *J. Am. Chem. Soc.* **2013**, *135*, 4996–4999. (b) Hope, E. G.; Levason, W. *Coord. Chem. Rev.* **1993**, *122*, 109–170. (c) Giambattista, M. D.; Chinali, G.; Cocito, C. *J. Antimicrob. Chemother.* **1989**, *24*, 485–507. (d) Woo, S. Y.; Kim, J. H.; Moon, M. K.; Han, S.-H.; Yeon, S. K.; Choi, J. W.; Jang, B. K.; Song, H. J.; Kang, Y. G.; Kim, J. W.; Lee, J.; Kim, D. J.; Hwang, O.; Park, K. D. *J. Med. Chem.* **2014**, *57*, 1473–1487. (e) Zhang, L.; Hang, Z.; Liu, Z.-Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 236–239. (f) Kollár, L.; Keglevich, G. *Chem. Rev.* **2010**, *110*, 4257–4302.

(9) Roberts, B. P. *Chem. Soc. Rev.* **1999**, *28*, 25–35.

(10) (a) Challinor, A. J.; Calin, M.; Nichol, G. S.; Carter, N. B.; Thomas, S. P. *Adv. Synth. Catal.* **2016**, *358*, 2404–2409. (b) Banerjee, S.; Das, J.; Santra, S. *Tetrahedron Lett.* **2009**, *50*, 124–127. (c) Gao, R.; Pahls, D. R.; Cundari, T. R.; Yi, C. S. *Organometallics* **2014**, *33*, 6937–6944. (d) Nakata, N.; Sakashita, M.; Komatsubara, C.; Ishii, A. *Eur. J. Inorg. Chem.* **2010**, *2010*, 447–453. (e) Sridevi, V. S.; Fan, W. Y.; Leong, W. K. *Organometallics* **2007**, *26*, 1157–1160.

(11) (a) Noshi, M. N.; El-awa, A.; Torres, E.; Fuchs, P. L. *J. Am. Chem. Soc.* **2007**, *129*, 11242–11247. (b) Desrosiers, J.-N.; Charette, A. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 5955–5957. (c) Uttamchandani, M.; Liu, K.; Panicker, R. C.; Yao, S. Q. *Chem. Commun.* **2007**, 1518–1520. (d) Woo, S. Y.; Kim, J. H.; Moon, M. K.; Han, S.-H.; Yeon, S. K.; Choi, J. W.; Jang, B. K.; Song, H. J.; Kang, Y. G.; Kim, J. W.; Lee, J.; Kim, D. J.; Hwang, O.; Park, K. D. *J. Med. Chem.* **2014**, *57*, 1473–1487.

(12) (a) Eberhardt, M. K.; Colina, R. *J. Org. Chem.* **1988**, *53*, 1071–1074. (b) Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.* **1989**, *54*, 5224–5227. (c) Fontana, F.; Minisci, F.; Vismara, E. *Tetrahedron Lett.* **1988**, *29*, 1975–1978. (d) Jiang, Y.; Loh, T.-P. *Chem. Sci.* **2014**, *5*, 4939–4943.

(13) Silicon radicals may be also generated from the corresponding disilanes by homolysis.

(14) If the reaction has a fast addition step but a slow electron-transfer step, the chain does not propagate well, which is mentioned in ref 7a.

(15) (a) Xu, Y.; Tang, X.; Hu, W.; Wu, W.; Jiang, H. *Green Chem.* **2014**, *16*, 3720–3723. (b) Liang, Y.-F.; Li, X.; Wang, X.; Yan, Y.; Feng, P.; Jiao, N. *ACS Catal.* **2015**, *5*, 1956–1963. (c) Zhou, M.; Zhou, Y.; Song, Q. *Chem. - Eur. J.* **2015**, *21*, 10654–10659. (d) Wang, H.; Lu, Q.; Qian, C.; Liu, C.; Liu, W.; Chen, K.; Lei, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 1094–1097. (e) Moad, G.; Rizzardo, E.; Thang, S. H. *Polymer* **2008**, *49*, 1079–1131.