Tris(trimethylsilyl)silane-Mediated Reductive Decyanation and Cyano Transfer Reactions of Malononitriles

Takuji Kawamoto, *[1] Yudai Shimaya, [1] Dennis P. Curran, [2] and Akio Kamimura[1]
[1] *Department of Applied Chemistry, Yamaguchi University, Ube, Yamaguchi 755-8611, Japan*
[2] *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

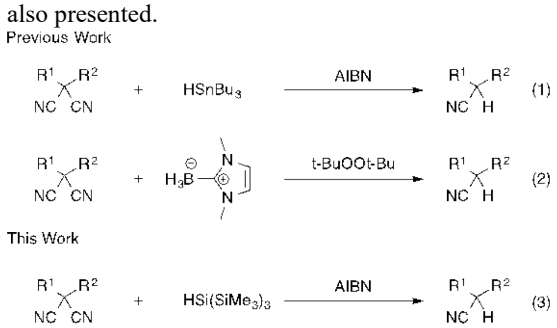
E-mail: tak102@yamaguchi-u.ac.jp

Reductive decyanation reactions of malononitriles were achieved with tris(trimethylsilyl)silane as a radical mediator. The reaction proceeds via a radical chain mechanism involving a silyl radical addition to the malononitrile to form an imidoyl radical followed by α-cleavage to give a silyl isocyanide and an α-cyano radical. The reaction of a 3-butenyl-substituted malononitrile afforded a decyano/cyanosilylation product in good yield through 1,4-cyano transfer.

Keywords: Radical, Malononitriles, Decyanation

Nitriles can be found in a wide variety of pharmaceuticals, agrochemicals, and optoelectronic materials. [1] They also serve as versatile synthetic intermediates for carboxylic acids, esters, amides, and amines. [2] Accordingly, the development of novel and efficient synthetic methods for nitriles has been a major topic in synthetic organic chemistry.

Malononitrile is the simplest geminal dinitrile. It has a highly acidic proton, thus it is easy to functionalize.[3] Once the dinitrile has served its purpose in the course of a synthesis, it often becomes necessary to replace one of the cyano groups with a hydrogen atom.[4] However, thus far, decyanation reactions of malononitriles are rarely reported. [5, 6, 7] Tributyltin hydride-mediated reductive decyanation of malononitriles were reported in 1991 (Scheme 1, eq. 1),[8] but the use of tin hydride is declining due to tin toxicity. Recently, we reported reductive decyanation of malononitriles with *N*-heterocyclic carbene boranes (eq. 2). [9] Other groups reported reductive decyanation of malononitriles via one electron reduction.[5c-e] Here we report radical decyanations of malononitriles with tris(trimethylsilyl)silane (TTMSS). [10] Related decyano/cyanosilylation and decyano/allylation reactions are also presented.



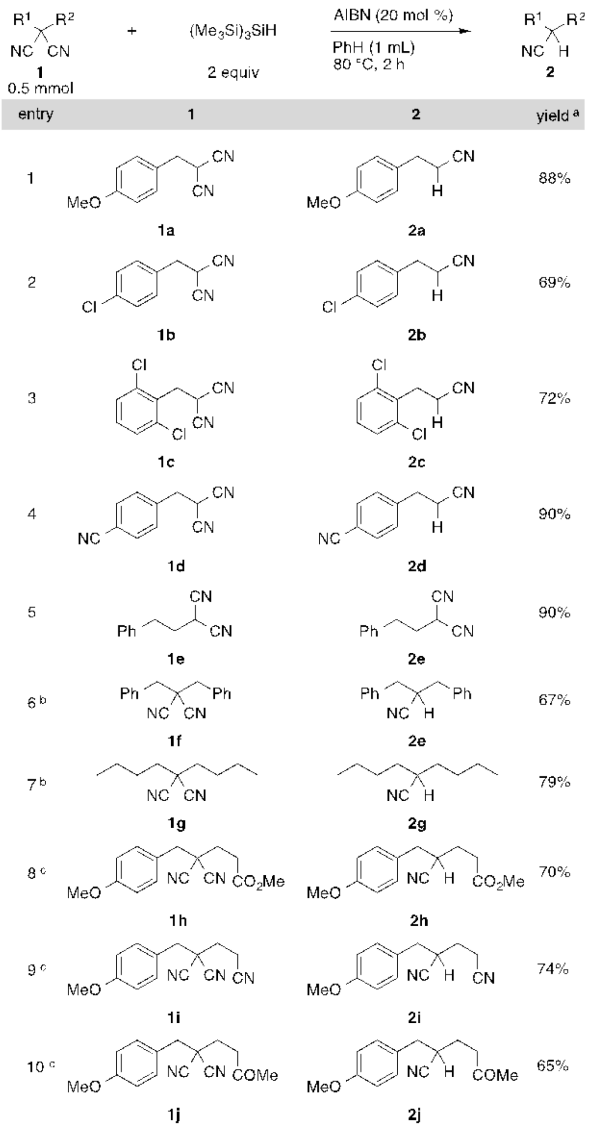
Scheme 1. Radical reductive decyanation of malononitriles

Initially, the reductive decyanation reaction was examined with 2-(4-methoxybenzyl)malononitrile (**1a**) as a model substrates in the presence of tris(trimethylsilyl)silane (TTMSS, 2 equiv) as reductant and azobisisobutyronitrile (AIBN, 20 mol%) as initiator (Table 1, entry 1). The reaction was conducted in benzene with heating at 80 ˚C. After purification by flash chromatography, the target decyanation product **2a** was obtained in 88% yield.[11]

Table 1 shows the results of other malononitriles that were reductively decyanated by the same procedure. Substrates having chlorine (**1b** and **1c**) or cyanide (**1d**) substituents on the benzene ring afforded the corresponding decyanation products **2b**–**2d** in 69–90% yields (entries 2–4). The reaction of 2-phenethylmalononitrile (**1e**) also worked well (entry 5). The reaction of bis-substituted malononitrile **1f** and **1g** gave decyanation product **2f** and **2g** in 67% and 79% yield with slightly harsh conditions, respectively (entries 6 and 7). Substrates **1h**–**1j**, which are easily prepared by Michael reactions of **1a**, [12] gave the corresponding decyanation products **2h**–**2j** in 65–74% yields (entries 8–10).

Radical probe experiments were then carried out to offer insights into the reaction mechanism. In the prior tin hydride decyanations, we speculated that the tin radical probably adds to the nitrile nitrogen to give an imidoyl radical, followed by α-fragmentation.[8] To support this speculation, we conducted reactions of 2-phenylcyclopropane-1,1-dicarbonitrile (**1k**) with TTMSS or Bu_3SnH, respectively. The reaction with TTMSS under that standard conditions for 16 h afforded the ring-opening product **1e** in 51% yield (Scheme 2). In the absence of AIBN, starting material **1k** was recovered. The corresponding reaction with Bu_3SnH also gave dinitrile **1e** in 42% yield along with mononitrile **2e** in 39% yield. Mononitrile **2e** is a secondary product that forms by reductive decyanation of **1e**.

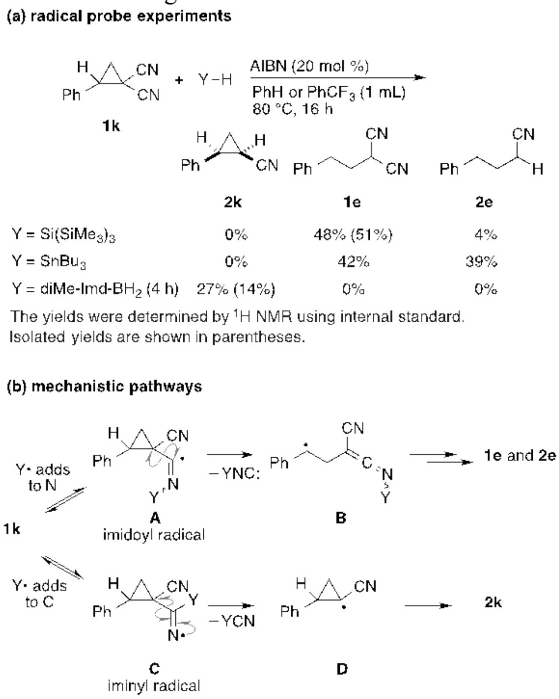
Table 1. TTMSS-mediated Reductive Decyanation Reactions



[a] Isolated yield after silica gel column chromatography. [b] *t*-BuOO*t*-Bu (1 equiv) was used instead of AIBN and the reaction performed at 120 °C for 4 h. [c] AIBN (40 mol %) was used.

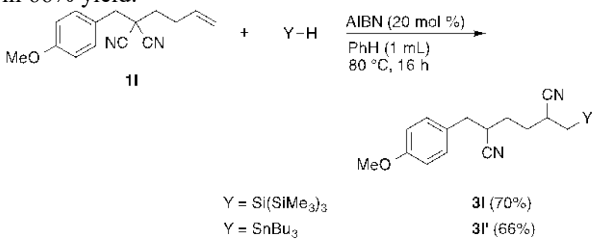
Next we conducted the reaction of **1k** with diMeImd-BH_3 and this gave decyanation product **2k**.

These results show that silyl- and tin-mediated decyanation reactions proceed via an imidoyl radical intermediate such as **A** (Y = $Si(SiMe_3)_3$ or $SnBu_3$), which usually undergoes an α-fragmentation to give an α-cyano radical and isocyanide (:CNSi$(SiMe_3)_3$ or :CNSnBu_3). However, with the radical probe **1k**, scission of the cyclopropane ring to give **B** is more rapid. This leads to product **1e** (and eventually **2e**) by H-transfer reaction and protodesilylation or protodestannylation of the resulting ketene imine. The generating Y• (Y = $Si(SiMe_3)_3$ or $SnBu_3$) adds to nitrile, thus keeping radical chain. In contrast, the NHC-borane radical-mediated decyanation reaction proceeds via an iminyl radical intermediate **C** (Y = diMe-Imd-BH_2). This undergoes a β-fragmentation to form NHC-BH_2CN and **D**, which in turn abstracts a hydrogen atom from the borane to give **2k**.



Scheme 2. Reactions of 2-Phenylcyclopropane-1,1-dicarbonitrile

Having learned that imidoyl radicals are intermediates in both silyl- and tin-mediated transformations, we wondered whether such intermediates could be trapped by other radical reactions besides cyclopropane cleavage. To address this question, we examined the behavior of 3-butenyl substituted malononitrile **1l**, which has an alkene poised to undergo 5-*exo* cyclization with an imidoyl radical (Scheme 3). However, the reaction of **1l** with $(Me_3Si)_3SiH$ did not give a cyclized product but instead gave decyano/cyanosilylation product **3l** in 70% yield. A reaction with Bu_3SnH gave the corresponding stannylated product **3l'** in 66% yield.[13]

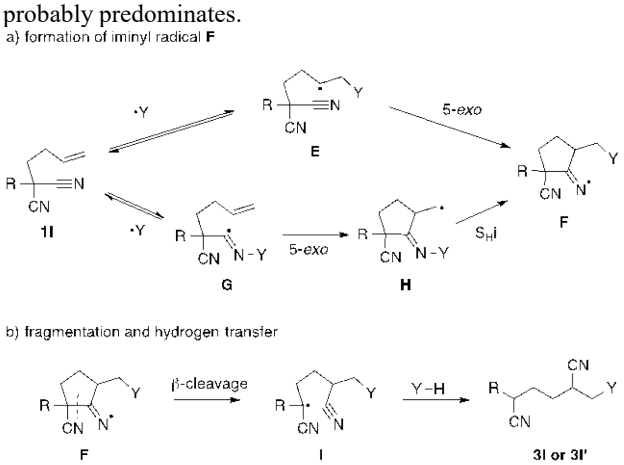


Scheme 3. Reaction of 3-Butenyl Substituted Malononitrile **1l**

Scheme 4 shows possible mechanisms for the cyanosilylation or cyanostannylation reactions of **1l**. A key intermediate is iminyl radical **F**, which can form by two routes (Scheme 4a). In the first route, a silyl (Y = $Si(SiMe_3)_3$) or stannyl (Y = $SnBu_3$) radical adds to the terminal alkene of **1l** to give **E**, followed by *5-exo* cyclization to give iminyl radical **F**.[14] β-Cleavage of **F** to

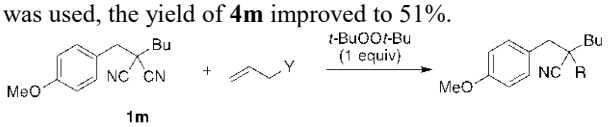
give α-cyano radical **I** is followed by hydrogen atom transfer to afford **3l** (Scheme 4b). In a second route to **F** (Scheme 4a), the silyl or stannyl radical adds to a nitrile to give an imidoyl radical **G**, which undergoes *5-exo* cyclization to afford **H**. Then **H** undergoes intramolecular homolytic substitution (S_Hi)[15] to give the iminyl radical **F**.

Differentiating the two possible paths to **F** is difficult because additions to both the alkene[9] and the nitrile may be reversible and because the rates of addition (and fragmentation) may be different for tris(trimethylsilyl) and tributylstannyl radicals. However, while intramolecular S_Hi reactions are well known for both silicon and tin,[15] most migration examples involve 1,5- or 1,6-group transfer. The conversion of **H** to **F** is a 1,4-migration, and S_Hi reactions in such settings usually occur not by migration but by displacement of one of the other groups on silicon or tin ($SiMe_3$ or Bu) to give a silacycle or a stannacycle. Such products are not observed, so the alkene addition pathway probably predominates.



Scheme 4. Plausible Mechanisms for Formation of **3l**: R = $CH_2C_6H_4$-4-OMe, Y = $Si(SiMe_3)_3$ or $SnBu_3$

To close the study, we examined a decyano/allylation reaction leading to an α-allylated quaternary nitrile (Scheme 5). When a mixture of disubstituted malononitrile **1m** and di-*tert*-butyl peroxide (*t*-BuOO*t*-Bu) was heated at 140 ºC in the presence of allyl tris(trimethylsilyl)silane,[16] the allylated product **4m** was obtained in 21% yield, along with decyanation product **2m** in 34% yield. When allylstannane was used, the yield of **4m** improved to 51%.



		4m (R = allyl)	**2m** (R = H)
$Y = Si(SiMe_3)_3$	140 °C, 2 h	21%	34%
$Y = SnBu_3$	120 °C, 16 h, MS 4Å (10 wt%)	51%	21%

Scheme 5. Decyano/Allylation reaction

In conclusion, we have developed reductive decyanation reactions of malononitriles with tris(trimethylsilyl)silane. A 3-butenyl substituted malononitrile gave silylcyano/decyanation product and a reaction with allyl tris(trimethylsilyl)silane gave an allylated product. Mechanistic experiments revealed that both the new silane reaction and the known tin reaction proceed via imidoyl radical intermediates.

This work was partially supported by a JSPS Grant-in-Aid for Young Scientists (B) (16K17869), Tokuyama Science Foundation, The Naito Foundation, Yamaguchi University, and Yamaguchi University Foundation. US support came from the National Science Foundation.

Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

References and Notes

1 (a) S. T. Murphy, H. L. Case, E. Ellsworth, S. Hagen, M. Huband, T. Joannides, C. Limberakis, K. R. Marotti, A. M. Ottolini, M. Rauckhorst, J. Starr, M. Stier, C.Taylor, T. Zhu, A. Blaser, W. A. Denny,; G.-L. Lu, J. B. Smaill, F. Rivault, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2150. (b) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902.

2 R. C. Larock, Comprehensive Organic Transformations; VCH: New York, 1989.

3 F. Freeman, 2001. Malononitrile. e-EROS Encyclopedia of Reagents for Organic Synthesis.

4 Chiba *et al*. reported a synthesis of bicyclic lactones through Bu_3SnH-mediated decyanation reaction, see Scheme 3 in; B. M. K. Tong, H. Chen, S. Y. Chong, Y. L. Heng, S. Chiba, *Org. Lett.* **2012**, *14*, 2826.

5 (a) H. Y. Kang, W. S. Hong, Y. S. Cho, H. Y. Koh, *Tetrahedron Lett.* **1995**, *36*, 7661. (b) U. Gerlach, *Tetrahedron Lett*. **1995**, *36*, 5159. (c) E. Doni, J. A. Murphy, *Org. Chem. Front.* **2014**, *1*, 1072. (d) S. S. Hanson, E. Doni, K. T. Traboulsee, G. Coulthard, J. A. Murphy, C. A. Dyker, *Angew. Chem., Int. Ed.* **2015**, *54*, 11236. (e) E. Hasegawa, N. Izumiya, T. Fukuda, K. Nemoto, H. Iwamoto, S.-Y. Takizawa, S. Murata, *Tetrahedron* **2016**, *72*, 7805.

6 For a review of decyanation reactions, see: a) J.-M. Mattalia, C. Marchi-Delapierre, H. Hazimeh, M. Chanon, *ARKIVOC* **2006**, 90. b) J.-M. R. Mattalia, *Beilstein J. Org. Chem.* **2017**, *13*, 267.

7 For a recent example of decyanation, see: P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem., Int. Ed.* **2016**, *55*, 3719.

8 D. P. Curran, C. M. Seong, *Synlett* **1991**, 107.

9 (a) T. Kawamoto, S. J. Geib, D. P. Curran, *J. Am. Chem. Soc.* **2015**, *137*, 8617. (b) D. A. Bolt, D. P. Curran, *J. Org. Chem.* **2017**, *82*, 13746.

10 For a review of TTMSS mediated radical reaction, see: C. Chatgilialoglu, *Chem. Eur. J.* **2008**, *14*, 2310.

11 The reaction of **1a** with 1.5 equiv of TTMSS gave **2a** in 90% yield. When the TTMSS loading was decreased to 1.2 equiv, **1a** remained.

12 A. G. Campaña, N. Fuentes, E. Gómez-Bengoa, C. Mateo, J. E. Oltra, A. M. Echavarren, J. M. Cuerva, *J. Org. Chem.* **2007**, *72*, 8127.

13 Bu_3SnH-mediated cyano transfer reaction have been reported, see: (a) D. P. Curran, C. M. Seong, *Tetrahedron* **1992**, *48*, 2175. (b) W. R. Bowman, B. C. F, P. Brookes, *Tetrahedron Lett.* **2000**, *41*, 8989. (c) K. Vervisch, M. D'hooghe, K. W. Törnroos, N. De Kimpe, *Org. Biomol. Chem.* **2012**, *10*, 3308. (d) X. Feng, Z. Zhou, X. Yin, R. Li, Y.-C. Chen, *Eur. J. Org. Chem.* **2014**, 5906.

14 For recent examples on C-CN bond cleavage reactions via iminyl radical intermediates, see: (a) S. Kamijo, S. Yokosaka, M. Inoue, *Tetrahedron Lett.* **2012**, *53*, 4324. (b) Z. Wu, R. Ren, C. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 10821. (c) N. Wang, L. Li, Z.-L. Li, N.-Y. Yang, Z. Guo, H.-X. Zhang, X.-Y. Liu, *Org. Lett.* **2016**,

18, 6026. (d) M. Ji, Z. Wu, J. Yu, X. Wan, C. Zhu, *Adv. Synth. Catal.* **2017**, *359*, 1959. (e) R. Ren, Z. Wu, L. Huan, C. Zhu, *Adv. Synth. Catal.* **2017**, *359*, 3052.

15 For a review of S_Hi reactions, see: S. H. Kyne, C. H. Schiesser, in *Encyclopedia of Radicals in Chemsitry, Biology and Materials.* C. Chatgilialoglu, A. Studer, Eds, John Wiley & Sons, Chichester, 2012, vol. 2, 629.

16 (a) M. Kosugi, H. Kurata, K.-I. Kawata, T. Migita, *Chem. Lett.* **1991**, *20*, 1327. (b) C. Chatgilialoglu, C. Ferreri, M. Ballestri, D. P. Curran, *Tetrahedron Lett.* **1996**, *37*, 6387.

NOTE *The diagram is acceptable in a colored form. Publication of the colored G.A. is free of charge.*
For publication, electronic data of the colored G.A. should be submitted. Preferred data format is EPS, PS, CDX, PPT, and TIFF.
If the data of your G.A. is "bit-mapped image" data (not "vector data"), note that its print-resolution should be 300 dpi.
You are requested to put a brief abstract (50-60words, one paragraph style) with the graphical abstract you provided, so that readers can easily understand what the graphic shows.

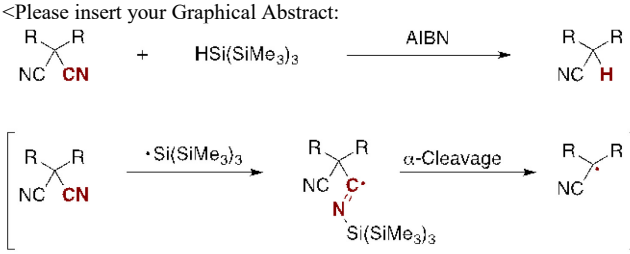
Graphical Abstract

Textual Information

A brief abstract (required)	Reductive decyanation reactions of malononitriles were achieved with tris(trimethylsilyl)silane as a radical mediator. The reaction proceeds via a radical chain mechanism involving a silyl radical addition to the malononitrile to form an imidoyl radical followed by α-cleavage to give a silyl isocyanide and an α-cyano radical. The reaction of a 3-butenyl-substituted malononitrile afforded a decyano/cyanosilylation product in good yield through 1,4-cyano transfer.
Title(required)	Tris(trimethylsilyl)silane-Mediated Reductive Decyanation and Cyano Transfer Reactions of Malononitriles
Authors' Names(required)	Takuji Kawamoto, *[1] Yudai Shimaya, [1] Dennis P. Curran, [2] and Akio Kamimura[1]

Graphical Information

<Please insert your Graphical Abstract:



The size is limited within 100 mm width and 30 mm height, or 48 mm square>(required)

References and Notes

1 (a) S. T. Murphy, H. L. Case, E. Ellsworth, S. Hagen, M. Huband, T. Joannides, C. Limberakis, K. R. Marotti, A. M. Ottolini, M. Rauckhorst, J. Starr, M. Stier, C.Taylor, T. Zhu, A. Blaser, W. A. Denny,; G.-L. Lu, J. B. Smaill, F. Rivault, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2150. (b) F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902.

2 R. C. Larock, Comprehensive Organic Transformations; VCH: New York, 1989.

3 F.Freeman, 2001. Malononitrile. e-EROS Encyclopedia of Reagents for Organic Synthesis.

4 Chiba *et al*. reported synthesis of bicyclic lactone through Bu_3SnH-mediate decyanation reaction, see; B. M. K. Tong, H. Chen, S. Y. Chong, Y. L. Heng, S. Chiba, *Org. Lett.* **2012**, *14*, 2826.

5 (a) H. Y. Kang, W. S. Hong, Y. S. Cho, H. Y. Koh, *Tetrahedron Lett.* **1995**, *36*, 7661. (b) U. Gerlach, *Tetrahedron Lett*. **1995**, *36*, 5159. (c) E. Doni, J. A. Murphy, *Org. Chem. Front.* **2014**, *1*, 1072. (d) S. S. Hanson, E. Doni, K. T. Traboulsee, G. Coulthard, J. A. Murphy, C. A. Dyker, *Angew. Chem., Int. Ed.* **2015**, *54*, 11236. (e) E. Hasegawa, N. Izumiya, T. Fukuda, K. Nemoto, H. Iwamoto, S.-Y. Takizawa, S. Murata, *Tetrahedron* **2016**, *72*, 7805.

6 For a review on decyanation reaction, see: a) J.-M. Mattalia, C. Marchi-Delapierre, H. Hazimeh, M. Chanon, *ARKIVOC* **2006**, 90. b) J.-M. R. Mattalia, *Beilstein J. Org. Chem.* **2017**, *13*, 267.

7 For a recent example of decyanation reaction, see: P. C. Too, G. H. Chan, Y. L. Tnay, H. Hirao, S. Chiba, *Angew. Chem., Int. Ed.* **2016**, *55*, 3719.

8 D. P. Curran, C. M. Seong, *Synlett* **1991**, 107.

9 (a) T. Kawamoto, S. J. Geib, D. P. Curran, *J. Am. Chem. Soc.* **2015**, *137*, 8617. (b) D. A. Bolt, D. P. Curran, *J. Org. Chem.* **2017**, *82*, 13746.

10 For a review of TTMSS mediated radical reaction, see: C. Chatgilialoglu, *Chem. Eur. J.* **2008**, *14*, 2310.

11 The reaction of **1a** with 1.5 equiv of TTMSS gave **2a** in 90% yield. Decreasing the TTMSS loading to 1.2 equiv, **1a** remained.

12 A. G. Campaña, N. Fuentes, E. Gómez-Bengoa, C. Mateo, J. E. Oltra, A. M. Echavarren, J. M. Cuerva, *J. Org. Chem.* **2007**, *72*, 8127.

13 Bu_3SnH-mediated cyano transfer reaction was reported, see: (a) D. P. Curran, C. M. Seong, *Tetrahedron* **1992**, *48*, 2175. (b) W. R. Bowman, B. C. F, P. Brookes, *Tetrahedron Lett.* **2000**, *41*, 8989. (c) K. Vervisch, M. D'hooghe, K. W. Törnroos, N. De Kimpe, *Org. Biomol. Chem.* **2012**, *10*, 3308. (d) X. Feng, Z. Zhou, X. Yin, R. Li, Y.-C. Chen, *Eur. J. Org. Chem.* **2014**, 5906.

14 For recent examples on C-CN bond cleavage reactions via iminyl radical intermediates, see: (a) S. Kamijo, S. Yokosaka, M. Inoue, *Tetrahedron Lett.* **2012**, *53*, 4324. (b) Z. Wu, R. Ren, C. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 10821. (c) N. Wang, L. Li, Z.-L. Li, N.-Y. Yang, Z. Guo, H.-X. Zhang, X.-Y. Liu, *Org. Lett.* **2016**, *18*, 6026. (d) M. Ji, Z. Wu, J. Yu, X. Wan, C. Zhu, *Adv. Synth. Catal.* **2017**, *359*, 1959. (e) R. Ren, Z. Wu, L. Huan, C. Zhu, *Adv. Synth. Catal.* **2017**, *359*, 3052.

15 For a review of S_Hi reactions, see: S. H. Kyne, C. H. Schiesser, in *Encyclopedia of Radicals in Chemsitry, Biology and Materials.* C. Chatgilialoglu, A. Studer, Eds, John Wiley & Sons, Chichester, 2012, vol. 2, 629.

16 (a) M. Kosugi, H. Kurata, K.-I. Kawata, T. Migita, *Chem. Lett.* **1991**, *20*, 1327. (b) C. Chatgilialoglu, C. Ferreri, M. Ballestri, D. P. Curran, *Tetrahedron Lett.* **1996**, *37*, 6387.