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2-(3-Cyanopropyldimethylsilyl)ethyl as a Polar Sulfur Protecting Group

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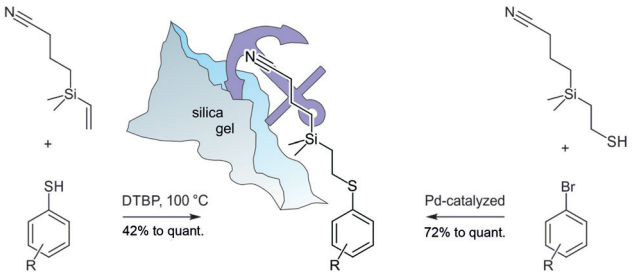

Received: 19.06.2019
Accepted after revision: 02.08.2019
Published online: 03.09.2019
DOI: 10.1055/s-0039-1690184; Art ID: ss-2019-t0337-op

Abstract Organosulfur compounds are ubiquitous in synthetic chemistry, biology and materials chemistry. The reactivity of free sulfhydryls requires their masking in many synthetic strategies. To facilitate the isolation of protected thiols by chromatography, we propose 2-(3-cyanopropyldimethylsilyl)ethyl as a polar protecting group analogue of 2-(trimethylsilyl)ethyl. The masked thiophenol is obtained in two synthetically complementing ways. Either an existing thiophenol is protected, or the protected thiol group is introduced by a cross-coupling reaction. In both cases the required reagents are readily available from inexpensive starting materials. Thiol protection and thiol introduction both tolerate a large variety of functional groups and substitution patterns, and the protected thiophenols are stable toward a broad range of reaction conditions. The stability of the protected derivatives in cross-coupling reactions and the mild reaction conditions for the release of the protecting group further emphasizes the potential of the methodology.

Key words thiols, protecting groups, cross-coupling, easy to purify, polarity

Thiol (sulfhydryl) groups are ubiquitous as important functional groups, e.g., in biology, materials chemistry and molecular devices. Due to their rich and unique chemistry, they are often involved in highly functional areas of proteins. An example is the formation of disulfides under rather mild conditions. The formation of disulfide bonds between thiols exposed by the amino acid cysteine contributes crucially to the stability of the tertiary structure of folded proteins.[1] The importance of sulfur-containing scaffolds for biological activity is also reflected in their frequent appearance in natural products,[2] medicinal chemistry[3] and sulfur-comprising proteins.[4]

The importance of sulfhydryl groups arises from the unique chemistry of sulfur (e.g., nucleophilicity, affinity to metals, rich redox chemistry),[5] reflected in a broad range of reactivity. While nature profits extensively from the rich diversity of reactivity of sulfur, this becomes challenging in many reaction strategies in synthetic organic chemistry. Examples are the tendency of free thiols to form disulfides and other oxidation products under more oxidative conditions.[6,7] Another issue is the strong affinity of thiols to metals and metal ions, being responsible for the poisoning of various catalytic systems.[8]

Our own interest in masking the thiol group is related to its role as an anchor group immobilizing molecules on noble-metal surfaces. We have also developed numerous single-molecule devices integrated in physical experiments with thiol–metal bonds. While the thiol–gold bond might have intrinsic challenges due to the variety of atomistic realizations on Au(111) surfaces, it remains the workhorse in single-molecule electronics.[9] In particular, the combination of reliable electronic contact and mechanical stability with enough mobility enabling, for example, the formation of self-assembled monolayers makes the thiol anchor group very appealing for this purpose. The examples of single-molecule experiments range from terminally thiol-functionalized rigid rods[10–15] and shape-persistent macrocycles[16,17] over mechano-sensitive structures[18,19] to three-dimensional objects, spatially oriented by three parallel immobilizing thiol–gold bonds.[20–25] In many cases, the syntheses of these functional molecules require the protection of the sulfhydryl groups.

So far, known protected aryl thiols can be categorized into five main groups: *S*-aryl thioates (e.g., acetyl),[26–31] arylalkylsulfides and arylheteroalkylsulfides,[32–36] *S*-aryl carbonothioates and *S*-aryl carbamothioates,[37–39] arylbenzylsulfides,[40–42] and silicon-comprising[43–46] aryl sulfides. Particularly appealing is the ethyl silane sulfur protecting group (PG)[43,47–49] due to its wide range of tolerated reaction conditions. On the other hand, trialkyl arylthiosilanes are considerably less stable than their oxygen analogues and are thus synthetically less useful.

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Ideal protecting groups are on the one hand stable under a wide range of reaction conditions, but on the other hand they remain removable under mild conditions, allowing a large variety of functional groups to be present. In addition, the protected and deprotected compounds should provide polarity features enabling their separation by chromatography.

Herein we report 2-(3-cyanopropyldimethylsilyl)ethyl (Figure 1, c) as a promising polar protecting group of arylthiols. The objective of the study is an analogue of the popular 2-(trimethylsilyl)ethyl protecting group (Figure 1, b),[43] but with optimized polarity features to facilitate separation by chromatography. The concept to enhance the polarity of a silyl protecting group with an exposed nitrile group is borrowed from Höger and Bonrad, who reported the potential of 3-cyanopropyldimethylsilyl as a protecting group for alkynes in 2000.[50] The peripheral nitrile group facilitates separation of the protected derivatives by flash column chromatography, while the trialkyl-silyl core structure provides similar stability features and deprotection conditions as the classical analogues. As displayed in Figure 1, the polarity of the 2-(3-cyanopropyldimethylsilyl)ethyl-protected thiophenol is increased considerably compared to the 2-(trimethylsilyl)ethyl analogue.

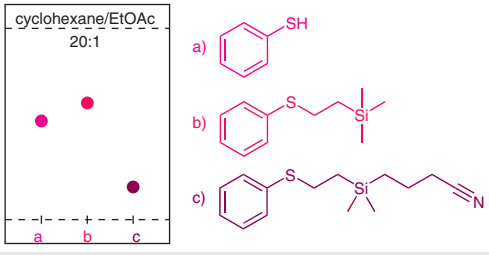
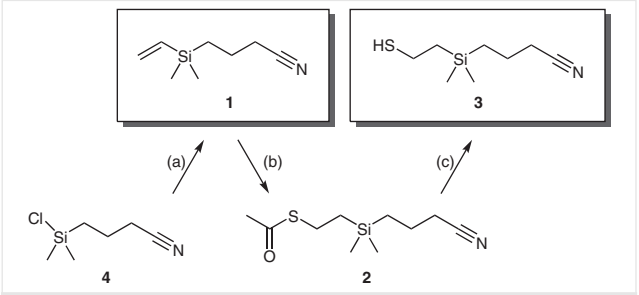


Figure 1 Thin-layer chromatography (TLC) of (a) benzenethiol (R_f = 0.52), (b) 2-(trimethylsilyl)ethyl thiophenol (R_f = 0.61), and (c) 2-(3-cyanopropyldimethylsilyl)ethyl thiophenol (R_f = 0.17), showing the enhanced polarity of the protecting group reported herein, which facilitates isolation of the protected compound by flash column chromatography

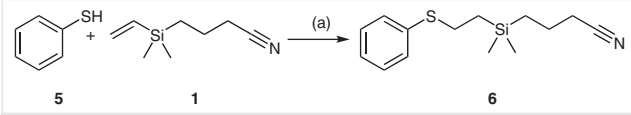
An appealing aspect of this protecting group is that it can be introduced with both 3-cyanopropyldimethyl vinylsilane (**1**) to mask an exposed aryl or alkyl thiol, and with 2-(3-cyanopropyldimethylsilyl)ethanethiol (**3**) in a masked-thiol-introducing cross-coupling reaction, substituting a suitable leaving group. As displayed in Scheme 1, the required reagent **3** is obtained via *S*-[2-(3-cyanopropyldimethylsilyl)ethyl] ethanethioate (**2**).

The protection of the thiols was investigated first. The reagent **1** for introducing the protecting group was prepared via a similar protocol to that reported for the synthesis of vinyl trimethylsilane[51,52] (Scheme 1). However, according to gas chromatography–mass spectrometry (GC-MS), the reaction was complete after the addition of vinylmagnesium chloride at 10 °C to a solution of chloro-(3-cyanopropyl)dimethylsilane (CPDMS-Cl) (**4**) in THF, and subsequent heating was not required. Product **1** was obtained as a colorless oil in 78% yield after vacuum distillation.



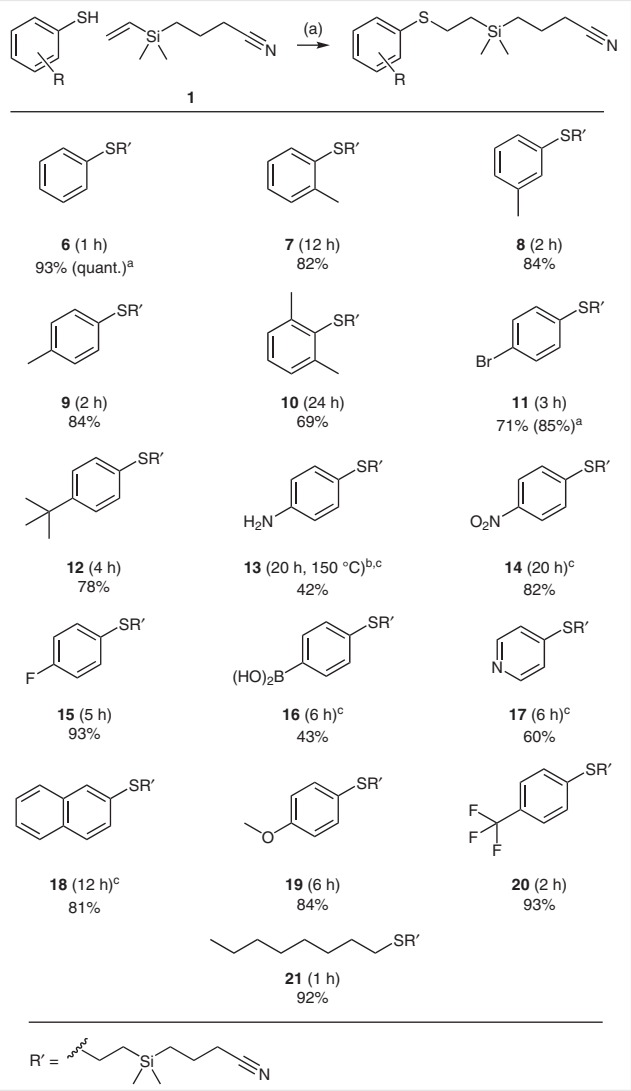
Scheme 1 Preparation of reagents **1** and **3**. (a) Vinylmagnesium chloride, THF, 10 °C, 30 min, 78%; (b) thioacetic acid, AIBN, 60 °C, 2 h, 91%; (c) K_2CO_3, MeOH, H_2O, Et_2O, room temperature, 2 h, then citric acid, 75%.

The thiol-ene addition between vinylsilanes and thiophenols with 2,2′-azobis(isobutyronitrile) (AIBN) as a radical initiator is well known,[43] and the protected thiophenols are usually obtained in excellent yields. Here, in our case, di-*tert*-butyl peroxide (DTBP) was favored as a radical initiator, because it is liquid at room temperature and thus it is better suited for the selected neat reaction conditions.[53–55] The radical reaction between **1** and the parent thiophenol **5** (Scheme 2) provided protected thiophenol **6** in a very good 93% yield on a half-gram scale, and in an even better 99% isolated yield on a 5 g scale.



Scheme 2 Protection of benzenethiol (**5**) with protecting group precursor **1**. (a) DTBP, neat, 100 °C, 1 h, 93% (0.5 g), 99% (5.0 g).

The reaction conditions for introducing the protecting group tolerate a variety of functional groups (Scheme 3). There are however general trends. Liquid thiophenols (e.g., **6**, **20**, and **21**) react faster and the masked derivatives are obtained in higher yields than for solid thiophenols (e.g., **13**, **14**, **16**, **17** and **18**). Steric hindrance in the investigated thiophenols requires extended reaction periods (e.g., **7** and **10** vs **6**, **8** and **9**). Strongly polarizing substituents tend to slow the reaction down (e.g., **13**, **14**, **15**, **16**, **17** or **19**). Aniline **13** required 150 °C as the reaction temperature, otherwise the reaction was extremely slow. The protocol also works in excellent yields with aliphatic thiols, as demonstrated with 1-octanethiol giving masked product **21** as a representative example.

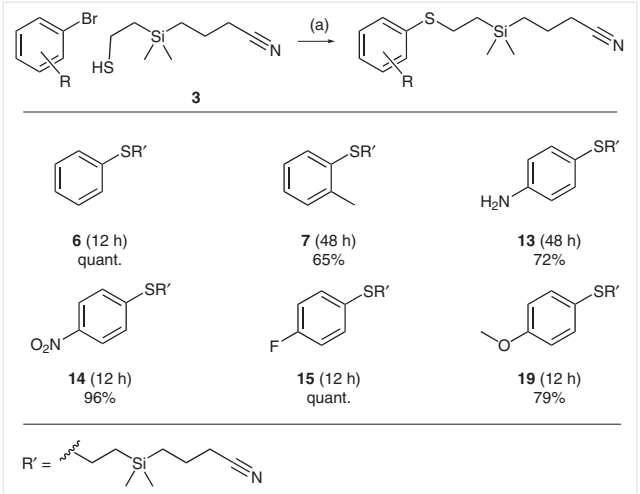


Scheme 3 Reaction scope of the protection of thioaryl derivatives (including a thioalkyl model compound) with the reagent **1**. (a) **1** (1.2 equiv), DTBP, 100 °C, 1–20 h. [a] Reaction on 5 g scale. [b] Reaction was extremely slow at 100 °C. [c] Reagent **1** (2.4 equiv) was used for reactions of solid compounds.

As an alternative approach to protected thiophenol derivatives, a cross-coupling protocol for the introduction of the masked thiol was considered. For the synthesis of 2-(3-cyanopropyldimethylsilyl)ethanthiol (**3**), the route developed by Schwan et al.[48] was used (Scheme 1). Freshly distilled thioacetic acid was stirred with **1** and AIBN as a radical initiator at 60 °C for 2 hours. Compound **2** was obtained as a light yellow oil in 91% yield after vacuum distillation. Thioacetate **2** was hydrolyzed with K_2CO_3 in a solvent mixture of MeOH, H_2O and Et_2O. After addition of citric acid to protonate the thiolate, 2-(3-cyanopropyldimethylsilyl)ethanethiol (**3**) was isolated by fractional vacuum distillation in 75% yield as a colorless oil.

The reaction protocol of Itoh and Mase[34] was adapted to substitute aryl bromides with thiol **3**. The reported procedure uses $Pd_2(dba)_3$ (2.5 mol%) as a pre-catalyst and Xantphos (5 mol%) as the ligand. The similar polarities of dba and compound **6** motivated the search for an alternative palladium source. By using $(Ph_3P)_4Pd$ or $(Ph_3P)_2PdCl_2$ as catalysts the same yields were obtained without purification issues. For the cross-coupling protocol $(Ph_3P)_2PdCl_2$ was chosen as the pre-catalyst due to its lower price and larger tolerance to oxygen impurities compared to $(Ph_3P)_4Pd$.

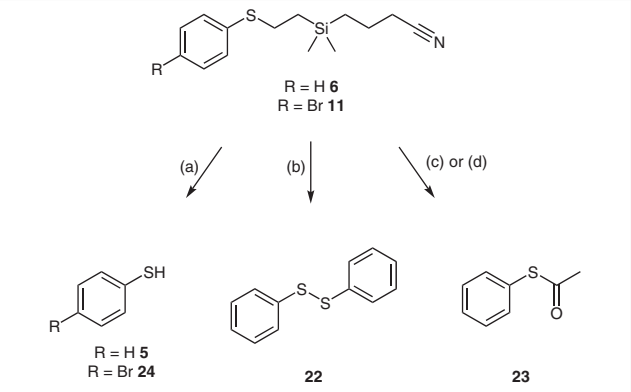
The protected thioaryls **6**, **14**, **15**, and **19** were all obtained in good to excellent yields with this protocol within a reaction time of 12 hours (Scheme 4). The syntheses of **7** and **13** required repeated addition of $(Ph_3P)_2PdCl_2$ and Xantphos until complete disappearance of the starting material was observed by GC-MS after 48 hours. The steric hindrance of the neighboring methyl group in compound **7** and the electron-donating amine group in **13** were not only reflected in reduced reaction rates, but also in lower isolated yields. While model compound **7** was obtained in a better yield by the radical reaction between 2-methylbenzenethiol and **1** (82% vs 65%), the cross-coupling reaction appears to be the better strategy for aniline **13** (72% vs 42%).



Scheme 4 Reaction scope of the masked thiol introduction by a cross-coupling protocol with reagent **3**. (a) **3** (1.2 equiv), $(Ph_3P)_2PdCl_2$ (2.5 mol%), Xantphos (5 mol%), iPr_2NEt, dioxane, 110 °C.

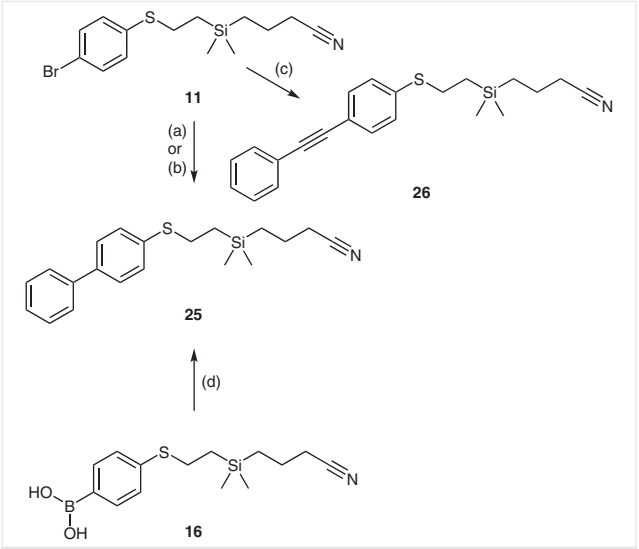
To remove the PG four different procedures were investigated, using **6** as a model compound (Scheme 5). In the first approach, benzenethiol (**5**) was obtained from **6** by deprotection with TBAF in THF at room temperature. Unfortunately, benzenethiol (**5**) is not suited as a model compound due to its challenging isolation features. While the deprotection reaction proceeded quantitatively according to reaction monitoring by gas chromatography, purification of **5** by column chromatography, acid–base extraction, and distillation resulted only in fractions comprising impurities. Finally, a pure fraction of **5** was isolated in a poor 42% yield

by extraction in Et_2O with $NaHCO_3$. As a more representative example, derivative **11** was exposed to the same reaction conditions and the corresponding less volatile thiophenol derivative **24** was isolated in 90% yield. However, thiol **24** was also quickly oxidized to the corresponding disulfide in the presence of oxygen. To facilitate isolation of the released thiophenols, their in situ transformation into the corresponding disulfides or acetyl-protected derivatives was investigated. Both derivatives are appealing due to their potential as precursors of self-assembled monolayers. To favor disulfide formation, iodine and pyridine were added to the TBAF deprotection reaction mixture and indeed, 1,1′-disulfanediyldibenzene (**22**) was isolated in an excellent 95% yield. Also, the capture of the thiophenol as *S*-phenyl ethanethioate (**23**) by addition of acetyl chloride to the deprotection reaction mixture was successful (83%). In an alternative protocol, **6** was treated with $AgBF_4$ and AcCl in CH_2Cl_2 at room temperature for 12 hours, providing ethanethioate **23** in 89% yield.



Scheme 5 Release of the PG demonstrated with compound **6**, providing benzenethiol (**5**), 1,1′-disulfanediyldibenzene (**22**), and *S*-phenyl ethanethioate (**23**). Procedure (a) was further studied with **11** yielding 4-bromobenzenethiol (**24**). (a) TBAF, THF, room temperature, 4 h, 42% (**5**), 90% (**24**); (b) TBAF, THF, room temperature, 4 h, then pyridine, I_2, 30 min, 95%; (c) TBAF, THF, room temperature, 4 h, then AcCl, 8 h, 83%; (d) $AgBF_4$, AcCl, CH_2Cl_2, room temperature, 12 h, 89%.

With our research topic geared toward rigid structures exposing thiophenols as anchor groups, the stability of the protected thiophenols in cross-coupling reactions was of particular interest. In particular, Suzuki cross-coupling conditions are known to be troublesome for a variety of thiophenol PGs.[29] As displayed in Scheme 6, 2-(3-cyanopropyldimethylsilyl)ethyl-protected thiophenol derivatives have been engaged successfully in both Suzuki and Sonogashira reactions. To explore the limit of the PG stability, bromine-substituted thiophenol **11** was selected as the starting material, requiring considerably higher reaction temperatures than the corresponding iodine analogues. In the case of the Suzuki reaction the stability of the PG was studied as a subunit of both reaction partners, the halide and the boronic acid. Biphenyl **25** was assembled first, starting with compound **11** and, in a second approach, using boronic acid **16** as starting material. The reaction of compound **11** with phenylboronic acid was investigated with two catalytic systems, $(Ph_3P)_2PdCl_2$ and SPhos Pd G2 (2 mol% respectively), with the second one giving a slightly better yield (90% vs 92%). Consequently, the same catalyst (SPhos Pd G2, 2 mol%) was used to couple boronic acid **16** with iodobenzene, yielding again **25** in a good 87% isolated yield and demonstrating the suitability of iodoaryls as reaction partners in the presence of PG. Compound **11** was also engaged in a Sonogashira reaction with phenylacetylene, using a mixture of THF and piperidine as solvent, and the combination of CuI (6 mol%) and $(Ph_3P)_2PdCl_2$ (5 mol%) as catalytic system.[56] Also, under these cross-coupling conditions, the PG proved to be perfectly stable and the desired tolane **26** was isolated in 91% yield.



Scheme 6 Stability of the PG in cross-coupling reactions. Assembly of biphenyl **25** in a Suzuki reaction with either bromine **11** or boronic acid **16**, and the synthesis of tolane **26** in a Sonogashira reaction. (a) Phenylboronic acid, K_2CO_3, $(Ph_3P)_2PdCl_2$ (2 mol%), toluene, H_2O, 80 °C, 3 h, 90%; (b) phenylboronic acid, K_2CO_3, SPhos Pd G2 (2 mol%), toluene, H_2O, 80 °C, 3 h, 92%; (c) phenylacetylene, CuI (6 mol%), $(Ph_3P)_2PdCl_2$ (5 mol%), THF, piperidine, 80 °C, 3 h, 91%; (d) iodobenzene, K_2CO_3, SPhos Pd G2 (2 mol%), toluene, H_2O, 80 °C, 12 h, 87%.

Of particular interest, with respect to a new protecting group, is its behavior under typical reaction conditions. Without claiming to be comprehensive, a variety of 29 different reaction conditions were investigated and are summarized in Table 1. In particular, the stability of the PG in aqueous conditions, and in the presence of bases, nucleophiles, electrophiles and redox agents was investigated. In each test reaction compound **6** (50 mg) was dissolved in the solvent (5 mL) (water/EtOH, 4:1, THF, EtOH or CH_2Cl_2) and the mixture was stirred at −78 °C, room temperature or 100 °C. With respect to the color code used in Table 1, a dark green background signals stability for a period of

Table 1 Stability of the 2-(3-Cyanopropyldimethylsilyl)ethyl Thiophenol Protecting Group[a]

Aqueous:	pH = 1, 100 °C[b,c]	pH = 1, r.t.[d,e]	pH = 4, r.t.[d,e]	pH = 9, r.t.[d,e]	pH = 12, r.t.[d,e]	pH = 12, 100 °C[b,c]
Bases:	LDA[f,g]	pyridine[e,h]	*t*BuOK[g,h]	–	–	–
Nucleophiles:	*n*BuLi[f,i]	*i*PrMgCl[e,f]	Me_2CuLi[f,i]	NaOEt[e,j]	NH_3[e,h]	–
Electrophiles:	AcCl[e,k]	AcH[e,h]	MeI[e,h]	AcOH[e,k]	Ac_2O[e,k]	–
Reduction:	Raney Ni, H_2[e,j]	Pd/C, H_2[e,j,l]	Fe, HCl[e,j,m]	$LiAlH_4$[e,h]	$NaBH_4$[e,j]	$NaBH_3CN$[e,j]
Oxidation:	OsO_4[g,h]	MnO_2[e,k]	*m*CPBA[i,k]	Br_2[g,k]	–	–

[a] Conditions for the stability measurements were as follows: the masked thiophenol **6** (50 mg) and the reagent (1.0 equiv) in solvent (5.0 mL) were stirred at room temperature under argon; GC-MS measurements were made after 1 h, 10 h, 24 h, 3 d and 7 d.
[b] Water (4 mL) + EtOH (1 mL), 100 °C.
[c] Stable for less than 1 h.
[d] Water (4 mL) + EtOH (1 mL).
[e] Stable for at least 7 d.
[f] THF, −78 °C.
[g] Stable for at least 3 d.
[h] THF.
[i] Partially stable (*n*BuLi: ~35% dec. within the first hour increasing to ~50% dec. after 7 d; Me_2CuLi: ~15% dec. within the first hour then stable in that range; *m*CPBA: ~50% of the protected thiophenol is oxidized to the corresponding sulfone within the first hour then stable in that range).
[j] EtOH.
[k] CH_2Cl_2.
[l] Pd/C (0.1 equiv).
[m] Fe (10 equiv) + conc. HCl (0.5 mL).

seven days, a light green background indicates no signs of degradation within 3 days, while a dark red background expresses that the masked thiophenol did not survive the first hour. The pale red background indicates challenging stability features and individual details are given as footnotes in Table 1. In 20 cases, compound **6** was stable for at least 7 days under the conditions employed (dark green background), and in four cases (LDA, *t*BuOK, OsO_4 and Br_2) for at least 3 days (light green background). Under conditions using electrophiles and reducing agents the 2-(3-cyanopropyldimethylsilyl)ethane thiol protecting group seems to be especially stable, as under none of the tested conditions were decomposition or side reactions observed. Under strongly acidic or basic aqueous conditions at 100 °C, compound **6** was not stable at all. *n*BuLi and Me_2CuLi reacted partially with compound **6**, but full decomposition was not observed. *m*CPBA oxidized ~50% of the protected thiophenol to the corresponding sulfone. If 2.5 equivalents of *m*CPBA were used, full conversion into the sulfone was observed.

In summary, 2-(3-cyanopropyldimethylsilyl)ethyl has been investigated as a polar protecting group for thiophenols, whilst maintaining the reactivity features of the parent TMS-ethyl protecting group. The new PG can be introduced by simple protocols, either from the corresponding vinylsilane **1** masking a free thiophenol, or sulfur-introducing reagent **3** substituting a halide atom in a cross-coupling protocol. In both cases, the required reagent is available from inexpensive, commercially available starting materials in good yields. A variety of substituents and substitution patterns are tolerated and the protected thiophenols are stable toward a wide range of reaction conditions. Furthermore, the PG is suited for cross-coupling reactions, as typical Pd-catalyzed Suzuki and Sonogashira reactions were performed in good yields. The 2-(3-cyanopropyldimethylsilyl)ethyl protecting group is released by mild reaction conditions, comparable to those used for the deprotection of the parent TMS-ethyl. The increased polarity of the presented PG considerably facilitates isolation of protected thiophenol derivatives by chromatographic methods.

All chemicals were directly used for synthesis without further purification unless stated otherwise. Dry solvents were used with crown caps as purchased from Sigma-Aldrich. Column chromatography was performed using SILICYCLE SilicaFlash® P60 (particle size: 40–63 µm, 230–400 mesh). The NMR solvent (CD_2Cl_2) was obtained from CIL Cambridge Isotope Laboratories, Inc. (Andover, MA, USA). All NMR experiments were performed on Bruker Avance III or III HD, two or four-channel NMR spectrometers operating at 500.13 MHz proton frequency. The instrument was equipped with direct observe BBFO 5 mm probes, with self-shielded z-gradient. $C^{13}\{1H\}$ spectra were recorded using the zgpg30 pulse sequence with power gated decoupling, DEPT-135 spectra with the sequence deptsp135, using a Crp60-comp4 shaped pulse for inversion. In both experiments, relaxation delay d1 was set to 1.0 s, acquisition times were 1.5 s and a waltz16 proton decoupling was applied. The experiments were performed at 298 K. All chemical shifts (δ) are reported in ppm relative to the used solvent and coupling constants (*J*) are given in Hertz (Hz). Multiplicities are written as: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = doublet of doublets, m = multiplet. A Shimadzu GC–MS-QP2010 SE gas chromatograph system, with a ZB-5HT inferno column (30 m × 0.25 mm × 0.25 mm), at 1 mL/min He-flow rate (split = 20:1) with a Shimadzu mass detector (EI 70 eV) was used. High-resolution mass spectra (HRMS) were measured with a Bruker Maxis 4G ESI-TOF instrument or on a Waters Micromass AutoSpec Ultima (EI-Sector).

3-Cyanopropyldimethyl Vinylsilane (1)[57]

[CAS Reg. No. 954114-30-8]

A 2 L three-neck round-bottom flask was equipped with a dropping funnel, a reflux condenser and a thermometer, heated out and then flushed with argon. Chloro-(3-cyanopropyl)dimethylsilane (CPDMS-Cl) (**4**) (100 mL, 611 mmol, 1.0 equiv) was added to the flask and dissolved in dry THF (300 mL). A solution of vinylmagnesium chloride in THF (420 mL, 1.6 M, 672 mmol, 1.1 equiv) was added dropwise over 30 min at 5–10 °C. The reaction was finished after the addition according to GC-MS, and the cold mixture was diluted with TBME (450 mL). The mixture was poured into ice-cold water (250 mL) (slightly exothermic) and acidified with aq HCl (1 M, ~125 mL). The organic layer was separated and washed with H_2O (450 mL) and brine (450 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford a yellow oil. The crude mixture was purified by vacuum distillation (82–94 °C at 5×10^{-1} mbar). Compound **1** (72.9 g, 475 mmol, 78%) was obtained as a colorless liquid.

Density (24 °C): 0.839 g/mL.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 6.14 (dd, *J* = 20.3 Hz, 14.7 Hz, 1 H), 5.98 (dd, *J* = 14.7 Hz, 3.8 Hz, 1 H), 5.71 (dd, *J* = 20.3 Hz, 3.8 Hz, 1 H), 2.34 (t, *J* = 7.0 Hz, 2 H), 1.70–1.61 (m, 2 H), 0.75–0.68 (m, 2 H), 0.09 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 138.7, 132.6, 120.4, 21.20, 21.15, 15.5, –3.4.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 138.7, 132.6, 21.20, 21.15, 15.5, –3.4.

HRMS (EI, 70 eV): *m*/*z* [M – CH_3]$^+$ calcd for $C_7H_{12}NSi$: 138.07335; found: 138.07332.

The spectroscopic data for this compound are identical to those reported in the literature.

S-[2-(3-Cyanopropyldimethylsilyl)ethyl] Ethanethioate (2)

Compound **1** (30.0 g, 196 mmol, 1.0 equiv) was added to an argon-flushed and dried one-neck round-bottom flask equipped with a reflux condenser. Freshly distilled thioacetic acid (17 mL, 235 mmol, 1.2 equiv) and AIBN (328 mg, 1.96 mmol, 0.01 equiv) were added and the mixture was heated at 60 °C for 2 h using a preheated oil bath. After full conversion according to GC-MS, the reaction mixture was cooled to room temperature and the reflux condenser was replaced with a short distillation bridge. Compound **2** (41.1 g, 179 mmol, 91%) was obtained after distillation (137–157 °C, 4–7 × 10^{-1} mbar) as a light yellow liquid.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 2.90–2.85 (m, 2 H), 2.36 (t, *J* = 7.0 Hz, 2 H), 2.28 (s, 3 H), 1.69–1.62 (m, 2 H), 0.92–0.86 (m, 2 H), 0.73–0.67 (m, 2 H), 0.05 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 196.3, 120.3, 31.0, 25.6, 21.3, 21.0, 16.5, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 31.0, 25.6, 21.3, 21.0, 16.5, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{19}NNaOSSi$: 252.0849; found: 252.0850.

2-(3-Cyanopropyldimethylsilyl)ethanethiol (3)

In an argon-flushed and dried one-neck round-bottom flask, a suspension of K_2CO_3 (27.2 g, 197 mmol, 1.1 equiv) in MeOH (170 mL) and H_2O (80 mL) was degassed with argon for 30 min. Compound **2** (41.0 g, 179 mmol, 1.0 equiv) in Et_2O (80 mL) was added and the reaction mixture was stirred for 2 h. After full conversion according to GC-MS, the reaction mixture was carefully quenched with citric acid (38.2 g, 197 mmol, 1.1 equiv) in small portions. TBME (250 mL) was added and the reaction mixture was transferred into a separating funnel. The separated organic layer was washed with aq citric acid solution (1%, 2 × 150 mL), dried over Na_2SO_4 and concentrated to give a yellow oil. Compound **3** (25.1 g, 134 mmol, 75%) was obtained as a colorless liquid after two consecutive fractional distillations (88–93 °C, 8.8 × 10^{-3} mbar).

Density (24 °C):0.932 g/mL

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 2.64–2.55 (m, 2 H), 2.35 (t, *J* = 7.0 Hz, 2 H), 1.68–1.60 (m, 2 H), 1.55 (t, *J* = 6.9 Hz, 1 H), 1.00–0.94 (m, 2 H), 0.71–0.65 (m, 2 H), 0.03 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 120.3, 22.0, 21.3, 21.1, 21.0, 15.3, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 22.0, 21.3, 21.1, 21.0, 15.3, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_8H_{17}NNaSSi$: 210.0743; found: 210.0743.

Protection of Free Thiols via a Radical Reaction; General Protocol 1

A microwave tube was charged with the thiol (500 mg, 1.0 equiv), compound **1** (1.2 equiv for liquid starting materials or 2.4 equiv for solid starting materials) and di-*tert*-butyl peroxide (0.15 equiv). The mixture was purged with argon, the tube was sealed and the contents stirred at 100 °C. After full conversion according to GC-MS, the reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL) and washed with aqueous NaOH solution (1 M, 50 mL). The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers washed with brine (50 mL) and dried over Na_2SO_4. The mixture was concentrated under reduced pressure and the residue subjected to column chromatography.

Palladium-Catalyzed Carbon–Sulfur Bond Formation; General Protocol 2

To a dry and argon-flushed Schlenk tube (25 mL) were added the corresponding bromide (500 mg, 1.0 equiv), *i*Pr_2NEt (2.0 equiv) and dioxane (6.0 mL), and the resulting solution was degassed by bubbling argon through the reaction mixture for 10 min. Compound **3** (1.2 equiv) was added and the mixture degassed for another 5 min. $(Ph_3P)_2PdCl_2$ (2.5 mol%) and Xantphos (5.0 mol%) were added together and the reaction mixture was stirred at 110 °C. After full conversion according to GC-MS, the reaction was cooled to room temperature, diluted with EtOAc (50 mL) and washed with H_2O (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure before subjecting the residue to column chromatography.

4-{Dimethyl[2-(phenylthio)ethyl]silyl}butanenitrile (6)

Protocol 1: 500 mg scale. Compound **6** (1.10 g, 4.18 mmol, 93%) was isolated as a light yellow liquid after purification by column chromatography [100 g SiO_2, cyclohexane/ethyl acetate (Cy/EtOAc) 99:1 → 90:10].

Protocol 1: 5.00 g scale. Compound **6** (11.9 g, 45.2 mmol, quant.) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 99:1 → 91:9).

Protocol 2: Compound **6** (829 mg, 3.15 mmol, quant.) was isolated as a light yellow liquid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 98:2 → 82:18).

R_f = 0.17 (Cy/EtOAc, 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.32–7.27 (m, 4 H), 7.20–7.15 (m, 1 H), 3.00–2.94 (m, 2 H), 2.34 (t, *J* = 7.0 Hz, 2 H), 1.67–1.60 (m, 2 H), 1.00–0.93 (m, 2 H), 0.73–0.67 (m, 2 H), 0.06 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 137.7, 129.4, 129.3, 126.2, 120.3, 29.7, 21.3, 21.1, 15.7, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 129.4, 129.3, 126.2, 29.7, 21.3, 21.1, 15.7, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{21}NNaSSi$: 286.1056; found: 286.1060.

4-{Dimethyl[2-(*o*-tolylthio)ethyl]silyl}butanenitrile (7)

Protocol 1: Compound **7** (891 mg, 3.21 mmol, 82%) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc 99:1, → 92:8).

Protocol 2: $(Ph_3P)_2PdCl_2$ (2.5 mol%) and Xantphos (5.0 mol%) were added 4 times over a reaction time of 48 h. Compound **7** (525 mg, 1.89 mmol, 65%) was isolated as a light yellow liquid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 99:1 → 90:10).

R_f = 0.18 (Cy/EtOAc, 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.26–7.22 (m, 1 H), 7.16 (m, 2 H), 7.10–7.05 (m, 1 H), 3.03–2.87 (m, 2 H), 2.40–2.30 (m, 5 H), 1.70–1.59 (m, 2 H), 1.03–0.94 (m, 2 H), 0.76–0.66 (m, 2 H), 0.07 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 137.7, 137.0, 130.5, 128.0, 126.9, 125.9, 120.3, 28.9, 21.3, 21.1, 20.6, 15.5, 15.3, –3.4.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 130.5, 127.9, 126.9, 125.9, 28.9, 21.3, 21.1, 20.6, 15.5, 15.3, –3.4.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{23}NNaSSi$: 300.1213; found: 300.1209.

4-{Dimethyl{2-(*m*-tolylthio)ethyl]silyl}butanenitrile (8)

Protocol 1: Compound **8** (938 mg, 3.38 mmol, 84%) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 100:0 → 92:8).

R_f = 0.17 (Cy/EtOAc, 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.18 (t, *J* = 7.6 Hz, 1 H), 7.13 (m, 1 H), 7.10 (m, 1 H), 6.99 (m, 1 H), 3.00–2.94 (m, 2 H), 2.37–2.31 (m, 5 H), 1.70–1.59 (m, 2 H), 0.99–0.92 (m, 2 H), 0.74–0.66 (m, 2 H), 0.07 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 139.3, 137.4, 129.9, 129.2, 127.1, 126.2, 120.3, 29.6, 21.6, 21.3, 21.1, 15.8, 15.3, –3.4.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 129.9, 129.2, 127.1, 126.2, 29.6, 21.6, 21.3, 21.1, 15.8, 15.3, –3.4.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{23}NNaSSi$: 300.1213; found: 300.1209.

4-{Dimethyl[2-(*p*-tolylthio)ethyl]silyl}butanenitrile (9)

Protocol 1: Compound **9** (947 mg, 3.41 mmol, 84%) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 99:1 → 90:10).

R_f = 0.18 (Cy/EtOAc, 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.24–7.19 (m, 2 H), 7.14–7.09 (m, 2 H), 2.97–2.88 (m, 2 H), 2.38–2.29 (m, 5 H), 1.68–1.58 (m, 2 H), 0.98–0.89 (m, 2 H), 0.73–0.64 (m, 2 H), 0.05 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 136.5, 133.8, 130.2, 130.1, 120.3, 30.4, 21.30, 21.25, 21.1, 15.9, 15.3, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 130.2, 130.1, 30.4, 21.30, 21.25, 21.1, 15.9, 15.3, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{23}NNaSSi$: 300.1213; found: 300.1209.

4-({2-[(2,6-Dimethylphenyl)thio]ethyl}dimethylsilyl)butanenitrile (10)

Protocol 1: Compound **10** (701 mg, 2.40 mmol, 69%) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 98:2 → 88:12).

R_f = 0.23 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.10 (s, 3 H), 2.71–2.65 (m, 2 H), 2.53 (s, 6 H), 2.32 (t, *J* = 7.0 Hz, 2 H), 1.64–1.55 (m, 2 H), 0.89–0.83 (m, 2 H), 0.68–0.61 (m, 2 H), 0.00 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 143.6, 134.3, 128.6, 128.5, 120.3, 31.2, 22.4, 21.3, 21.1, 16.5, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 128.6, 128.5, 31.2, 22.4, 21.3, 21.1, 16.5, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{25}NNaSSi$: 314.1369; found: 314.1369.

4-({2-[(4-Bromophenyl)thio]ethyl}dimethylsilyl)butanenitrile (11)

Protocol 1: 500 mg scale. Compound **11** (610 mg, 1.78 mmol, 71%) was isolated as a light yellow liquid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 98:2 → 81:19).

Protocol 1: 3.00 g scale. Compound **11** (4.39 g, 12.8 mmol, 85%) was isolated as a light yellow liquid after purification by column chromatography (680 g SiO_2, Cy/EtOAc, 98:2 → 82:18).

R_f = 0.29 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.45–7.37 (m, 2 H), 7.20–7.16 (m, 2 H), 3.00–2.90 (m, 2 H), 2.35 (t, *J* = 6.9 Hz, 2 H), 1.68–1.59 (m, 2 H), 0.98–0.90 (m, 2 H), 0.73–0.66 (m, 2 H), 0.06 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 137.1, 132.4, 130.9, 120.3, 119.8, 29.9, 21.3, 21.1, 15.7, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 132.4, 130.9, 29.9, 21.3, 21.1, 15.7, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}BrNNaSSi$: 364.0161; found: 364.0158.

4-({2-[(4-(*tert*-Butyl)phenyl]thio}ethyl)dimethylsilyl)butanenitrile (12)

Protocol 1: Compound **12** (723 mg, 2.26 mmol, 78%) was isolated as a colorless liquid after purification by column chromatography (50 g SiO_2, Cy/EtOAc, 98:2 → 82:18).

R_f = 0.29 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.36–7.29 (m, 2 H), 7.28–7.21 (m, 2H), 2.97–2.92 (m, 2 H), 2.34 (t, *J* = 7.0 Hz, 2 H), 1.67–1.60 (m, 2 H), 1.30 (s, 9 H), 0.98–0.93 (m, 2 H), 0.72–0.67 (m, 2 H), 0.06 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 149.7, 134.0, 129.5, 126.5, 120.3, 34.9, 31.6, 30.1, 21.3, 21.1, 15.9, 15.3, –3.4.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 129.5, 126.5, 31.6, 30.1, 21.3, 21.1, 15.9, 15.3, –3.4.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{29}NNaSSi$: 342.1682; found: 342.1680.

4-({2-[(4-Aminophenyl)thio]ethyl}dimethylsilyl)butanenitrile (13)

Protocol 1: Reaction temperature was 150 °C. Compound **13** (419 mg, 1.51 mmol, 42%) was isolated as a yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 90:10 → 0:100).

Protocol 2: $(Ph_3P)_2PdCl_2$ (2.5 mol%) and Xantphos (5.0 mol%) were added 4 times over a reaction time of 48 h. Compound **13** (586 mg, 2.10 mmol, 72%) was isolated as a yellow liquid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 90:10 → 0:100).

R_f = 0.21 (Cy/EtOAc, 1:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.22–7.17 (m, 2 H), 6.64–6.60 (m, 2 H), 3.77 (s, 2 H), 2.84–2.77 (m, 2 H), 2.32 (t, *J* = 7.0 Hz, 2 H), 1.65–1.54 (m, 2 H), 0.93–0.84 (m, 2 H), 0.69–0.61 (m, 2 H), 0.01 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 146.8, 134.3, 123.9, 120.3, 115.8, 32.5, 21.3, 21.1, 16.1, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 134.3, 115.8, 32.5, 21.3, 21.1, 16.1, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{23}N_2SSi$: 279.1346; found: 279.1343.

4-(Dimethyl{2-[(4-nitrophenyl)thio]ethyl}silyl)butanenitrile (14)

Protocol 1: Compound **14** (784 mg, 2.54 mmol, 82%) was isolated as a yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 98:2 → 82:18).

Protocol 2: Compound **14** (731 mg, 2.37 mmol, 96%) was isolated as a yellow liquid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 98:2 → 82:18).

R_f = 0.17 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.13–8.09 (m, 2 H), 7.34–7.30 (m, 2 H), 3.11–3.04 (m, 2 H), 2.37 (t, *J* = 6.9 Hz, 2 H), 1.71–1.62 (m, 2 H), 1.06–0.99 (m, 2 H), 0.78–0.71 (m, 2 H), 0.10 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 148.9, 145.4, 126.6, 124.4, 120.2, 28.3, 21.3, 21.0, 15.1, 15.0, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 126.6, 124.4, 28.3, 21.3, 21.0, 15.1, 15.0, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}N_2NaO_2SSi$: 331.0907; found: 331.0907.

4-({2-[(4-Fluorophenyl)thio]ethyl}dimethylsilyl)butanenitrile (15)

Protocol 1: Compound **15** (999 mg, 3.55 mmol, 93%) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 98:2 → 83:17).

Protocol 2: Compound **15** (796 mg, 2.83 mmol, quant.) was isolated as a light yellow liquid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 98:2 → 81:19).

R_f = 0.18 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.35–7.30 (m, 2 H), 7.04–6.99 (m, 2 H), 2.95–2.88 (m, 2 H), 2.34 (t, *J* = 6.9 Hz, 2 H), 1.66–1.58 (m, 2 H), 0.95–0.89 (m, 2 H), 0.71–0.65 (m, 2 H), 0.04 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 162.2 (d, J_{C-F} = 245.0 Hz), 132.5 (d, J_{C-F} = 7.9 Hz), 120.4, 116.4 (d, J_{C-F} = 21.8 Hz), 31.2, 21.4, 21.2, 16.0, 15.3, –3.4.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 132.5 (d, J_{C-F} = 7.9 Hz), 116.4 (d, J_{C-F} = 21.8 Hz), 31.2, 21.4, 21.2, 16.0, 15.3, –3.4.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{20}FNNaSSi$: 304.0962; found: 304.0960.

[4-({2-[(3-Cyanopropyl)dimethylsilyl]ethyl}thio)phenyl]boronic Acid (16)

Protocol 1: Compound **16** (388 mg, 1.26 mmol, 43%) was isolated as a white solid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 90:10 → 0:100).

R_f = 0.22 (Cy/EtOAc, 1:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.14–8.10 (m, 2 H), 7.40–7.35 (m, 2 H), 3.11–3.05 (m, 2 H), 2.37 (t, *J* = 7.0 Hz, 2 H), 1.71–1.62 (m, 2 H), 1.07–1.01 (m, 2 H), 0.78–0.71 (m, 2 H), 0.11 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 144.3, 136.4, 126.8, 120.3, 28.3, 21.3, 21.1, 15.5, 15.2, –3.4. The resonance of the aryl carbon atom with the boron substituent was not detectable in the ^{13}C NMR spectrum, probably because of line broadening due to the short relaxation time and the quadrupole moment of ^{11}B.[58]

DEPT-135 (126 MHz, CD_2Cl_2): δ = 136.4, 126.8, 28.3, 21.3, 21.1, 15.5, 15.24, –3.4.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{22}BNNaO_2SSi$: 330.1126; found: 330.1127.

4-{Dimethyl[2-(pyridin-4-ylthio)ethyl]silyl}butanenitrile (17)

Protocol 1: Compound **17** (321 mg, 1.21 mmol, 60%) was isolated as a yellow liquid after purification by column chromatography (340 g SiO_2, Cy 100%).

R_f = 0.07 (Cy 100%).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.38–8.33 (m, 2 H), 7.11–7.07 (m, 2 H), 3.06–2.99 (m, 2 H), 2.37 (t, *J* = 6.9 Hz, 2 H), 1.70–1.61 (m, 2 H), 1.04–0.98 (m, 2 H), 0.77–0.71 (m, 2 H), 0.10 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 150.0, 149.7, 121.1, 120.2, 27.0, 21.3, 21.1, 15.2, 15.0, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 149.7, 121.1, 27.0, 21.3, 21.1, 15.2, 15.0, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{21}N_2SSi$: 265.1189; found: 265.1189.

4-{Dimethyl[2-(naphthalen-2-ylthio)ethyl]silyl}butanenitrile (18)

Protocol 1: Compound **18** (780 mg, 2.49 mmol, 81%) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 99:1 → 90:10).

R_f = 0.15 (Cy/EtOAc, 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.81 (dq, *J* = 7.7 Hz, 0.8 Hz, 1 H), 7.77 (dd, *J* = 8.2 Hz, 0.8 Hz, 2 H), 7.72 (dd, *J* = 1.9 Hz, 0.8 Hz, 1 H), 7.48 (ddd, *J* = 8.1 Hz, 6.7 Hz, 1.4 Hz, 1 H), 7.46–7.43 (m, 1 H), 7.43–7.39 (m, 1 H), 3.13–3.06 (m, 2 H), 2.34 (t, *J* = 7.0 Hz, 2 H), 1.68–1.60 (m, 2 H), 1.05–0.99 (m, 2 H), 0.77–0.69 (m, 2 H), 0.09 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 135.4, 134.4, 132.1, 128.8, 128.2, 127.6, 127.4, 127.1, 126.6, 126.0, 120.3, 29.5, 21.3, 21.1, 15.7, 15.2, –3.4.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 128.8, 128.2, 127.6, 127.4, 127.1, 126.6, 126.0, 29.5, 21.3, 21.1, 15.7, 15.2, –3.4.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{23}NNaSSi$: 336.1213; found: 336.1210.

4-({2-[(4-Methoxyphenyl)thio]ethyl}dimethylsilyl)butanenitrile (19)

Protocol 1: Compound **19** (878 mg, 2.99 mmol, 84%) was isolated as a light yellow liquid after purification by column chromatography (340 g SiO_2, Cy/EtOAc, 98:2 → 84:16).

Protocol 2: Compound **19** (622 mg, 2.12 mmol, 79%) was isolated as a light yellow liquid (100 g SiO_2, Cy/EtOAc, 98:2 → 82:18).

R_f = 0.19 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.34–7.29 (m, 2 H), 6.87–6.83 (m, 2 H), 3.78 (s, 3 H), 2.90–2.83 (m, 2 H), 2.33 (t, *J* = 7.0 Hz, 2 H), 1.65–1.56 (m, 2 H), 0.94–0.85 (m, 2 H), 0.71–0.63 (m, 2 H), 0.03 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 159.4, 133.4, 127.5, 120.3, 115.0, 55.8, 31.9, 21.3, 21.1, 16.1, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 133.4, 115.0, 55.8, 31.9, 21.3, 21.1, 16.1, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{23}NNaOSSi$: 316.1162; found: 316.1163.

4-[Dimethyl(2-{[4-(trifluoromethyl)phenyl]thio}ethyl)silyl]butanenitrile (20)

Protocol 1: Compound **20** (836 mg, 2.52 mmol, 93%) was isolated as a light yellow liquid after purification by column chromatography (100 g SiO_2, Cy/EtOAc, 98:2 → 82:18).

R_f = 0.21 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.54–7.51 (m, 2 H), 7.37–7.34 (m, 2 H), 3.07–3.00 (m, 2 H), 2.36 (t, *J* = 6.9 Hz, 2 H), 1.70–1.61 (m, 2 H), 1.03–0.96 (m, 2 H), 0.76–0.70 (m, 2 H), 0.09 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 143.7 (q, J_{C-F} = 1,5 Hz), 127.7, 127.4 (q, J_{C-F} = 32 Hz), 126.1 (q, J_{C-F} = 3.8 Hz), 125.0 (q, J_{C-F} = 271 Hz), 120.3, 28.7, 21.3, 21.1, 15.4, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 127.7, 126.1 (q, J_{C-F} = 3.8 Hz), 28.7, 21.3, 21.1, 15.4, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{20}F_3NNaSSi$: 354.0930; found: 354.0934.

4-{Dimethyl[2-(octylthio)ethyl]silyl}butanenitrile (21)

Protocol 1: Compound **21** (932 mg, 3.11 mmol, 92%) was isolated as a light yellow liquid after purification by column chromatography (400 g SiO_2, Cy/EtOAc, 20:1).

R_f = 0.18 (Cy/EtOAc, 20:1), $KMnO_4$ dip.

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 2.56–2.52 (m, 2 H), 2.52–2.48 (m, 2 H), 2.37–2.33 (m, 2 H), 1.69–1.61 (m, 2 H), 1.60–1.52 (m, 2 H), 1.41–1.24 (m, 10 H), 0.91–0.85 (m, 5 H), 0.71–0.66 (m, 2 H), 0.04 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 120.3, 32.41, 32.38, 30.2, 29.79, 29.79, 29.5, 27.8, 23.2, 21.3, 21.2, 16.3, 15.3, 14.4, –3.4.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 32.41, 32.38, 30.2, 29.79, 29.79, 29.5, 27.8, 23.2, 21.3, 21.2, 16.3, 15.3, 14.4, –3.4.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{33}NNaSSi$: 322.1995; found: 322.1990.

Benzenethiol (5)

[CAS Reg. No. 108-98-5]

To a round-bottom flask equipped with a magnetic stir bar were added compound **6** (500 mg, 1.90 mmol, 1.0 equiv) and THF (25 mL). TBAF (3.8 mL, 3.80 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 4 h. After full conversion according to GC-MS, the reaction was quenched with TFA (292 µL, 3.80 mmol, 2.0 equiv). The reaction mixture was diluted with Et_2O (100 mL) and washed with aq citric acid solution (1%, 100 mL) and water (2 × 100 mL). The organic layer was then washed with aq sat. Na_2CO_3 solution (3 × 100 mL). The combined sat. Na_2CO_3 solutions were acidified with conc. HCl and extracted with Et_2O (3 × 100 mL) and the three combined organic layers (not the first) were dried over Na_2SO_4 and concentrated. Remaining Et_2O was removed from the product by distillation. Product **5** (88.1 mg, 800 µmol, 42%) was isolated as a light yellow liquid.

R_f = 0.52 (Cy/EtOAc, 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.30–7.27 (m, 2 H), 7.26–7.22 (m, 2 H), 7.18–7.14 (m, 1 H), 3.54 (s, 1 H).

The spectroscopic data of this compound are identical to those reported in the literature.[59]

1,2-Diphenyldisulfane (22)

[CAS Reg. No. 882-33-7]

To a round-bottom flask equipped with a magnetic stir bar were added compound **6** (500 mg, 1.90 mmol, 1.0 equiv) and THF (25 mL). TBAF (3.8 mL, 3.80 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 4 h. After full conversion according to GC-MS, pyridine (170 µL, 2.09 mmol, 1.1 equiv) was added followed by a solution of I_2 (290 mg, 1.14 mmol, 0.60 equiv) in THF (5.0 mL). The reaction mixture was stirred for 30 min and then diluted with EtOAc (100 mL). The mixture was washed with aq citric acid solution (1%, 100 mL), sat. $Na_2S_2O_3$ (100 mL) and brine (100 mL) and then dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue subjected to column chromatography (50 g SiO_2, Cy/EtOAc, 98:2 → 86:14) to afford product **22** (196 mg, 898 µmol, 95%) as a light yellow solid.

R_f = 0.57 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.55–7.50 (m, 4 H), 7.35–7.30 (m, 4 H), 7.27–7.23 (m, 2 H).

The spectroscopic data of this compound are identical to those reported in the literature.[60]

***S*-Phenyl Ethanethioate (23)**

[CAS Reg. No. 934-87-2]

Method 1: To a round-bottom flask equipped with a magnetic stir bar were added compound **6** (500 mg, 1.90 mmol, 1.0 equiv) and THF (25 mL). TBAF (3.8 mL, 3.80 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 4 h. After full conversion according to GC-MS, acetyl chloride (542 µL, 7.60 mmol, 4.0 equiv) was added and the mixture was stirred for 8 h. The reaction mixture was diluted with EtOAc (100 mL), washed with water (100 mL) and brine (100 mL), and then dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue subjected to column chromatography (50 g SiO_2, Cy/EtOAc, 98:2 → 90:10). Compound **23** (240 mg, 1.58 mmol, 83%) was isolated as a light yellow liquid.

Method 2: To a round-bottom flask equipped with a magnetic stir bar were added compound **6** (500 mg, 1.90 mmol, 1.0 equiv) and acetyl chloride (542 µL, 7.6 mmol, 4.0 equiv) in CH_2Cl_2 (25 mL). Then $AgBF_4$ (740 mg, 3.80 mmol, 2.0 equiv) was added and the resulting mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc (100 mL), washed with water (100 mL) and brine (100 mL), and then dried over Na_2SO_4. The organic layer was concen-

trated under reduced pressure and the residue subjected to column chromatography (50 g SiO_2, Cy/EtOAc, 98:2 → 90:10). Product **23** (256 mg, 1.68 mmol, 89%) was isolated as a light yellow liquid.

R_f = 0.41 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.43 (s, 5 H), 2.41 (s, 3 H).

The spectroscopic data of this compound are identical to those reported in the literature.[61]

4-Bromobenzenethiol (24)

[CAS Reg. No. 106-53-6]

To a round-bottom flask equipped with a magnetic stir bar were added compound **11** (500 mg, 1.46 mmol, 1.0 equiv) and THF (25 mL). TBAF (7.3 mL, 7.30 mmol, 5.0 equiv) was added and the reaction mixture was stirred at room temperature for 1 h. After full conversion according to GC-MS, the reaction was quenched with TFA (225 µL, 2.92 mmol, 2.0 equiv). The reaction mixture was diluted with EtOAc (100 mL), washed with aq citric acid solution (1%, 100 mL), water (100 mL) and brine (100 mL), and then dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue subjected to column chromatography (340 g SiO_2, Cy/EtOAc, 95:5 → 66:34). Product **24** (249 mg, 1.32 mmol, 90%) was isolated as a light yellow solid.

R_f = 0.13 (Cy/EtOAc, 4:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.39–7.34 (m, 2 H), 7.19–7.14 (m, 2 H), 3.56 (s, 1 H).

The spectroscopic data of this compound are identical to those reported in the literature.[62]

4-{[2-([1,1′-Biphenyl]-4-ylthio)ethyl]dimethylsilyl}butanenitrile (25)

Method 1: To a dry and argon-flushed Schlenk tube were added compound **11** (500 mg, 1.46 mmol, 1.0 equiv), phenylboronic acid (275 mg, 2.10 mmol, 1.5 equiv) and K_2CO_3 (611 mg, 4.38 mmol, 3.0 equiv) and the contents were placed under vacuum for 5 min. Then dry toluene (10 mL) and H_2O (2.5 mL) were added and the mixture degassed by passing argon through for 5 min. SPhos Pd G2 (21.0 mg, 29.2 µmol, 0.02 equiv) was added and the mixture was heated at 80 °C for 3 h. After full conversion according to GC-MS, the reaction mixture was diluted with CH_2Cl_2 (100 mL), washed with H_2O (100 mL) and brine (100 mL), and then dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue subjected to column chromatography (100 g SiO_2, Cy/EtOAc, 98:2 → 82:18). Product **25** (455 mg, 1.34 mmol, 92%) was isolated as a yellow liquid.

Method 2: An oven-dried and argon-flushed Schlenk tube was charged with compound **16** (240 mg, 781 µmol, 1.2 equiv), iodobenzene (136 mg, 651 µmol, 1.0 equiv) and K_2CO_3 (273 mg, 1.95 mmol, 3.0 equiv) and the contents were placed under vacuum for 5 min. Then dry toluene (5 mL) and H_2O (1.25 mL) were added and the mixture degassed by passing argon through for 5 min. SPhos Pd G2 (9.38 mg, 13.0 µmol, 0.02 equiv) was added and the mixture was heated at 80 °C for 12 h. The solution was diluted with CH_2Cl_2 (100 mL), washed with H_2O (100 mL) and brine (100 mL), and then dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue subjected to column chromatography (50 g SiO_2, Cy/EtOAc, 98:2 → 82:18). Product **25** (193 mg, 568 µmol, 87%) was isolated as a yellow liquid.

R_f = 0.24 (Cy/EtOAc, 10:1).

H NMR (500 MHz, CD_2Cl_2): δ = 7.62–7.58 (m, 2 H), 7.57–7.53 (m, 2 H), 7.46–7.42 (m, 2 H), 7.40–7.37 (m, 2 H), 7.35 (ddt, *J* = 8.6 Hz, 7.0 Hz, 1.0 Hz, 1 H), 3.06–2.99 (m, 2 H), 2.35 (t, *J* = 6.9 Hz, 2 H), 1.70–1.60 (m, 2 H), 1.05–0.98 (m, 2 H), 0.77–0.68 (m, 2 H), 0.08 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 140.3, 138.4, 136.4, 129.0, 128.8, 127.4, 127.3, 126.7, 119.7, 29.2, 20.8, 20.5, 15.2, 14.7, –4.0.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 129.0, 128.8, 127.4, 127.3, 126.7, 29.2, 20.8, 20.5, 15.2, 14.7, –4.0.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{25}NNaSSi$: 362.1369; found: 362.1366.

4-[Dimethyl(2-{[4-(phenylethynyl)phenyl]thio}ethyl)silyl]butanenitrile (26)

An oven-dried and argon-flushed Schlenk tube was charged with compound **11** (500 mg, 1.46 mmol, 1.0 equiv), dry THF (3 mL) and piperidine (1 mL) and the resulting yellow mixture was degassed with argon for 10 min. Then phenylacetylene (245 µL, 2.19 mmol, 1.5 equiv) was added and the reaction mixture was again bubbled with argon for 5 min. $(Ph_3P)_2PdCl_2$ (51.2 mg, 73.0 µmol, 0.05 equiv) and CuI (17.0 mg, 87.6 µmol, 0.06 equiv) were added and the resulting exothermic mixture degassed with argon for an additional 5 min. The yellow suspension was stirred at 80 °C for 3 h. After full conversion according to GC-MS, the reaction mixture was diluted with EtOAc (50 mL), washed with H_2O (50 mL) and brine (50 mL), and then dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue subjected to column chromatography (340 g SiO_2, Cy/EtOAc, 98:2 → 83:17). Product **26** (481 mg, 1.32 mmol, 91%) was isolated as a yellow liquid.

R_f = 0.21 (Cy/EtOAc, 10:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.54–7.51 (m, 2 H), 7.47–7.44 (m, 2 H), 7.38–7.34 (m, 3 H), 7.28–7.25 (m, 2 H), 3.05–2.97 (m, 2 H), 2.36 (t, *J* = 7.0 Hz, 2 H), 1.70–1.60 (m, 2 H), 1.02–0.96 (m, 2 H), 0.77–0.68 (m, 2 H), 0.08 (s, 6 H).

^{13}C NMR (126 MHz, CD_2Cl_2): δ = 139.0, 132.4, 132.0, 129.0, 128.9, 128.3, 123.8, 120.5, 120.3, 90.0, 89.6, 29.2, 21.3, 21.1, 15.6, 15.2, –3.5.

DEPT-135 (126 MHz, CD_2Cl_2): δ = 132.4, 132.0, 129.0, 128.9, 128.3, 29.2, 21.3, 21.1, 15.5, 15.2, –3.5.

HRMS (ESI, MeOH): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{25}NNaSSi$: 386.1369; found: 386.1369.

Trimethyl[2-(phenylthio)ethyl]silane (b)

[CAS Reg. No. 17988-59-9]

A microwave tube was charged with thiophenol (0.46 mL, 4.49 mmol, 1.00 equiv), vinyl trimethylsilane (0.81 mL, 5.39 mmol, 1.2 equiv) and di-*tert*-butyl peroxide (0.12 mL, 0.673 mmol, 0.15 equiv). The mixture was purged with argon and the tube was sealed and the contents stirred for 1 h at 100 °C. After full conversion according to GC-MS, the reaction mixture was cooled to room temperature, diluted with EtOAc (50 mL) and washed with aqueous NaOH solution (1 M, 50 mL). The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layers washed with brine (50 mL) and dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the residue subjected to column chromatography (100 g SiO_2, Cy/EtOAc, 100:0 → 85:15). Trimethyl[2-(phenylthio)ethyl]silane (**b**) (888 mg, 4.22 mmol, 94%) was isolated as a colorless liquid.

R_f = 0.61 (Cy/EtOAc, 20:1).

^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.33–7.26 (m, 4 H), 7.19–7.14 (m, 1 H), 3.02–2.94 (m, 2 H), 0.97–0.91 (m, 2 H), 0.06 (s, 9 H).

The spectroscopic data of this compound are identical to those reported in the literature.[43]

Funding Information

The authors thank Schweizerischer Nationalfonds zur Förderung der Wissenschaftlichen Forschung (Swiss National Science Foundation) (SNF) (Grant No. 200020-178808) for continuous and generous financial support. M.M. acknowledges support from the 111 project (Grant No. 90002-18011002).

Acknowledgment

We thank Loïc Le Pleux and Lukas Jundt for proofreading the manuscript.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690184.

Primary Data

for this article are available online at https://doi.org/10.1055/s-0039-1690184 and can be cited using the following DOI: 10.4125/pd0107th.

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