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Regio-selective cyanation of (*Z*)-(1,2-dibromo-2-arylvinyl) triisopropylsilane with suppression of halogen elimination



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ABSTRACT

Highly regio-selective cyanation of vicinal (*Z*)-dibromoalkenyl silanes was achieved by a vinylic Rosenmund-von Braun reaction, significantly suppressing side-production of alkyne. The alkyne was generated by a halogen elimination side-reaction that is an intrinsic problem in metal-activation of vicinal dihaloalkenes. We have studied to overcome the problem, and finally found the combination of CuCN and O = PPh₃ in toluene solvent effectively controlled the production of byproducts. The resultant single isomer has significance in potentially application as a multi-tunable synthetic scaffold.

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Vinyl halides are valuable intermediates in organic synthesis, because of their ability to serve as convenient substrates in transition metal-catalyzed cross-coupling reactions.^{1–3} From a synthetic point of view, the vicinal dihaloalkenes such as 1,2-dibromoalkene and 2-chloro-1-bromoalkene are versatile variants of vinyl halides; they have been possible to construct multifunctional and dissymmetrical compounds in the past decades.⁴ Thus, they are attracting much more attention as a template for stereo-defined synthesis of tetra-substituted olefins bearing four different carbon-linked groups.^{5,6}

Recently, we have reported regio- and stereoselective bis-halogenation of silyl ethynylarenes; the alkynyl silanes reacted with *in situ* BrCl to yield *syn*-BrCl adduct, like **1**, as a single isomer.⁷ To establish **1** as a stereo-defined alkenyl template for a synthesis of differentially all-carbon tetrasubstituted olefins, **1** was subjected to conventional transformations using copper mediated-cyanation (Scheme 1); however, the reaction didn't proceed at the Br site in selective manner, yielding mixture of an expected vinyl chloride in 48% and an unexpected vinyl bromide in 20%.⁸ In addition, the reaction put back **1** to the original alkynyl silane in 32% yield with dehalogenation of BrCl. For this halogen elimination, similar observations were reported on (*E*)-3,4-dibromohex-3-ene by the Rathore group, and on ethyl (*E*)-3-chloro-2-iodobut-2-enoate by the Ogilvie group⁹: both vicinal dihaloalkenes undertook halogen elimination through palladium catalyzed-reactions, whatever

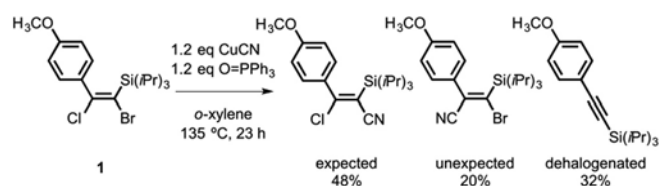
mechanism the substrates follow.¹⁰ This unpleasant side-reaction provides chemists a continuing challenge toward stereo-controlled synthesis of tetrasubstituted olefins.¹¹

Herein we present the successful suppression of beta-halogen elimination, the result of a regio-selective cyanation of vicinal (*Z*)-1,2-dibromoalkenylsilane like a full-substituted **2**. The substitution reaction allowed us to make stereo-defined tetrasubstituted acrylonitriles. We anticipated that the copper reagent would not only recognize difference in reactivity between two vinylic bromine-atoms of **2**, but also accelerate the corresponding reductive elimination rather than the beta-halogen elimination.¹²

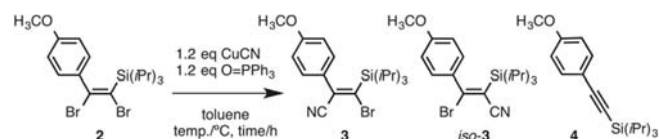
We started investigation with a vinylic Rosenmund-von Braun reaction of **2** undertaken as shown in Scheme 2.^{13,14} The preliminary research after several tests of standard conditions¹⁵ reached initial criterion of entry 1 in Table 1: the combination of CuCN with O = PPh₃ in *ortho*-xylene solvent yielded 62% of **3** and 38% of byproduct **4** derived from beta-halogen elimination. To our surprise, the formation of *iso*-**3** and a double cyanated product was not observed at all. This strongly suggests that the dibromide-**2** undergoes the highly regio-selective cyanation. For entries 2 and 3, the temperature-down to 80 °C in toluene solvent increased the yield of desired **3** to 90%, and decreased that of embarrassing **4** to 8%; thus, it significantly suppressed the beta-halogen elimination reaction. Rf values of **2**, **3**, and **4** were 0.63, 0.25, and 0.65 on TLC monitoring eluted with hexane/CH₂Cl₂ = 2/1, respectively; thus, separation of **3** from **2** and **4** was not laborious at all. This selective reaction protocol was readily amenable to scale-up synthesis (entry 4); finally, 10 mmol of **2** afforded 3.5 g of **3** in 88% yield (entry 5). The

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Scheme 1. A vinylic Rosenmund-von Braun cyanation of **1**.



Scheme 2. The regio-selective cyanation of **2** to give **3**.

molecular structure of **3** was determined by crystallographic analysis (Fig. 1), which disclosed that retention of the stereochemistry during the reaction course was accomplished.¹⁶

Evaluation of this cyanation protocol was demonstrated on other five kinds of (*Z*)-1,2-dibromoalkenylsilanes (Scheme 3). For part a of Scheme 3, the simple phenyl **5** showed less reactivity at 80 °C compared to **2**, while a high-yielding transformation into the desired **5a** at 110 °C was cleanly achieved. In part b, the 2-thienyl **6** undertook the smooth cyanation to selectively yield 86% of **6a** in 15 h at 80 °C without producing any isomers and alkyne **6b**. At 110 °C, the reaction completed in just 3 h with highest yield 91% of **6a**. To our surprise, in these two substrates, we hardly find side-products of alkyne **5b** and **6b**. For the starting naphthyl **7** in part c, the cyanation didn't proceed at 80 °C and the starting **7** remained intact. When the reaction temperature went up, **7** underwent the desired cyanation, giving **7a** in moderate 46 ~ 54% yields: however, the significant amounts of side-product **7b** were observed. Fortunately, **7a** was readily separated from **7b** with silica-gel column chromatography. For part d, *ortho*-methoxy **8** required the reaction temperature 110 °C for consuming the starting **8**. At 110 °C the desired **8a** was obtained in 69% yield, although dehalogenated **8b** was produced in 21%. For part e, the starting *meta*-xylyl **9** was not subject to the cyanation at all, even under *ortho*-xylene refluxing condition (144 °C), and was converted to alkyne **9b** in >99% yield. These results clearly suggest that this reactivity provides two salient features. One, electron-donating aromatic group enhances this selective cyanation with suppression of the beta-halogen elimination. Two, the sterically hindered aromatic group affects the cyanation adversely, and causes the beta-halogen elimination to give significant amounts of alkyne byproducts. Particularly, for the second point of steric factor, the two *ortho*-substituents could prevent the appropriate coordination of

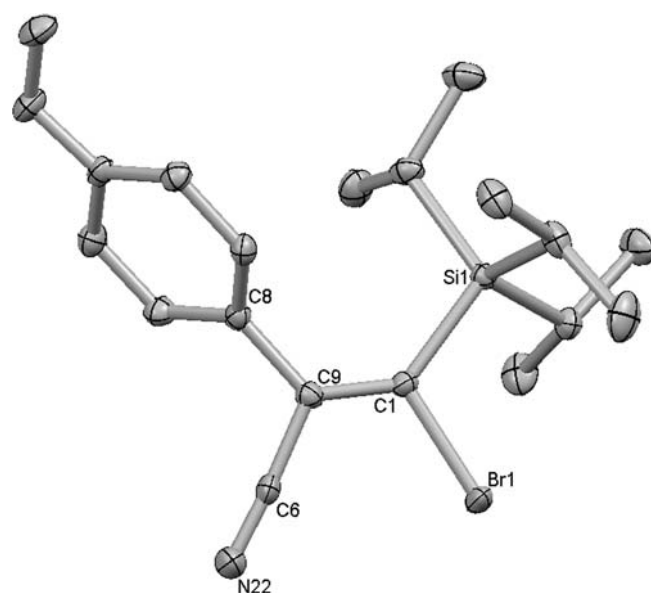


Fig. 1. ORTEP drawing of **3** with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] for **3**: C1–C9 1.354, C1–Br 1.923, C9–C6 1.446, C1–Si 1.920, C9–C8 1.490.

O = PPh₃ to the central Cu from giving the desired reductive elimination route.

We tested a different pattern of vicinal (*Z*)-dichloride **10** in the vinylic Rosenmund-von Braun reaction, and summarized the results of various reaction temperatures in Scheme 4.^{17,18} Although no reaction proceeded at 80 °C, the temperature-up to 110 °C put the reaction forward in 65% yield of **10a** for 15 h along with 22% of starting **10**. The reaction at 135 °C successfully afforded **10a** in the highest isolated-yield of 78%, but still left 10% of **10** unreacted. Further harsh condition at 155 °C under a solvent of 1,3,5-mesitylene was attempted: however, the starting **10** was still remained in 7%, and the product **10a** was contaminated with inseparable pesky impurities. On the other hand, the production of side-product **4** was suppressed in just trace amount. These results mean that vicinal (*Z*)-dichloride would also undertake the selectively vinylic Rosenmund-von Braun reaction at 2-positioned chlorine atom to give corresponding vinyl chloride molecules.¹⁹ Indeed, from the viewpoint of the result in Scheme 1, the reactivity of 2-positioned Cl atom of the substrate **1** gets closer to that of 1-positioned Br atom.

The mechanism resulting high stereochemical control to produce single isomer and to suppress side-reactions is not yet fully known.^{12,20} The preliminary investigation as illustrated in Scheme 5 was performed: a vinyl trimethylsilane in which **2**

Table 1
Evaluation of the reactivity of **2** conducted via Scheme 2.

Entry	Scale of 2 /mmol (g)	Temp/°C	Time/h	%Yields ^[b]			
				3	<i>iso</i> - 3	4	2
1	0.5 (0.23)	135 ^[a]	1.5	62	trace	38	0
2	0.5 (0.23)	60	1.5	0	0	0	99
3	0.5 (0.23)	80	19	90	0	8	2
4	3.0 (1.3)	80	23	86	0	7	1
5 ^{[c][d][e]}	10 (4.5)	80	23	88	0	6	1

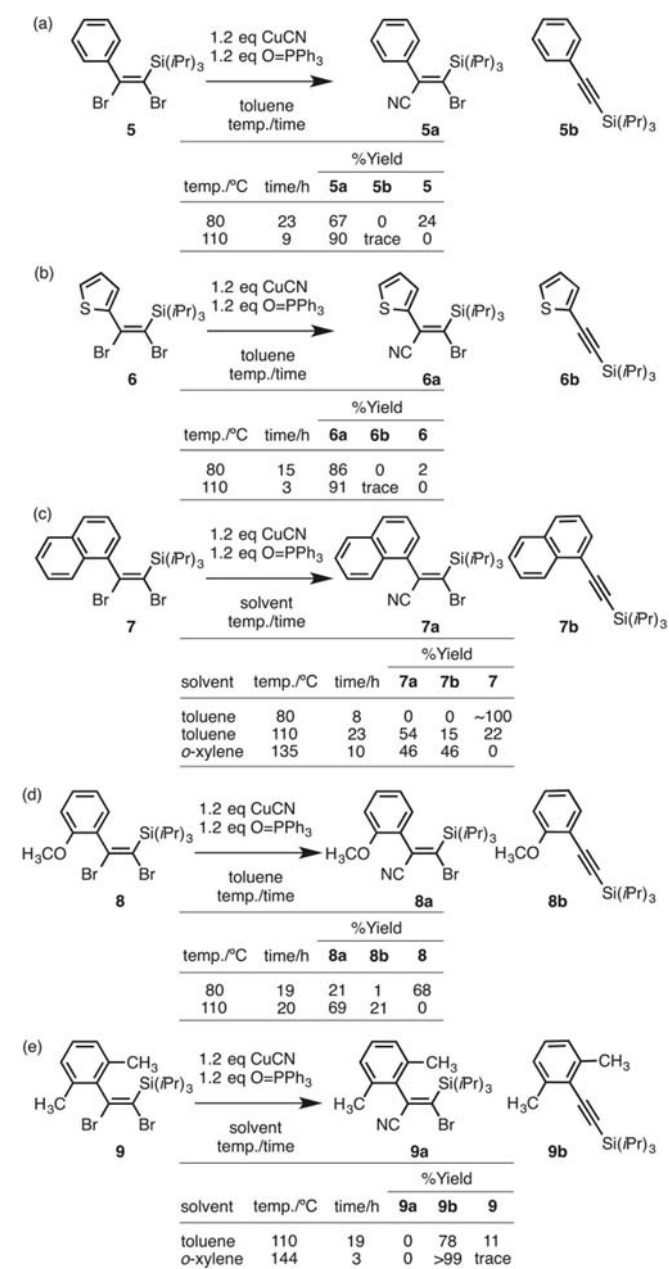
^a *o*-Xylene was used as a solvent.

^b Isolated yields.

^c 3.5 g of **3** was obtained.

^d 64 mL of toluene was used as a solvent.

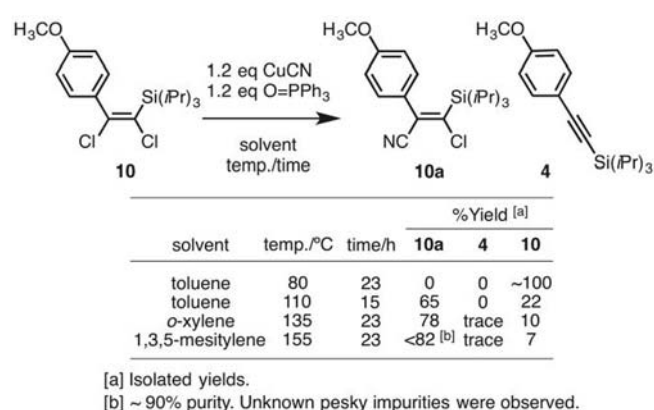
^e Any double cyanated product was not observed.



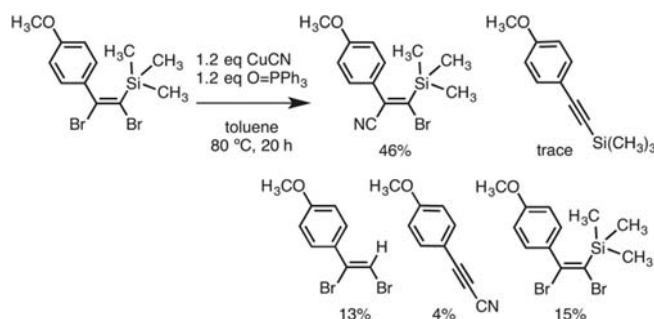
Scheme 3. Evaluation of the regio-selective cyanation reaction on (Z)-1,2-dibromoalkenylsilanes: (a) **5**, (b) **6**, (c) **7**, (d) **8**, (e) **9**. The stereochemistry of **5a–8a** was inferred from evidence of the ORTEP drawing in Fig. 1. The reactions were conducted with 0.5 mmol of starting dibromide in 4 mL of solvents according to the representative procedure as stated in Experimental Section. %Yield was isolated one.

replaced TIPS (triisopropylsilyl) with TMS (trimethylsilyl) was used as a starting dibromide. The cyanation proceeded selectively, suppressing the side-product of alkyne like as entries 3–5 of Table 1; however, a desilylated dibromide in 13%, an alkynyl nitrile in 4%, and the unreacted starting dibromide in 15% were observed. So, TIPS group of **2** firmly serves as a protecting group against side-reactions, and trialkyl substituents on the Si atom don't seem to influence the regio-selectivity.

In summary, we found that (Z)-(1,2-dibromo-2-arylvinyl)triisopropylsilane underwent a CuCN-mediated regio-selective cyanation of one side of two vinylic Br atoms to singly construct a moiety of poly-substituted acrylonitrile.²¹ The stereochemistry was ensured by crystallographic analysis. For starting substrates bearing electron-rich and unhindered aromatic groups, the reac-



Scheme 4. Evaluation of the regio-selective cyanation reaction on (Z)-(1,2-dichloro-2-arylvinyl)triisopropylsilane **10**. The stereochemistry of **10a** was inferred from evidence of the ORTEP drawing in Fig. 1.



Scheme 5. Evaluation of the cyanation on a substrate of (Z)-(1,2-dibromo-2-arylvinyl)trimethylsilane.

tion system significantly suppressed a side-reaction of beta-halogen elimination that was hard to control so far. The selective method was applicable to a vicinal (Z)-dichloroalkene, and the corresponding vinyl chloride was successfully isolated. This method is primitive but potentially useful as it gives single isomers and therefore avoids problematic olefin isomer separation. The regio-selective reaction could find its potential utility for making differentially all-carbon tetrasubstituted olefins that is one of the grand challenges in organic synthesis field.²² Development of installation of varied carbon groups at the 2-positioned Br atom is ongoing and will be reported in due course.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2017.03.082>.

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15. Use of polar solvents like DMF or DMSO consumed 2, giving 4 as a major product. The condition without O = PPh₃ in Scheme 2 didn't drive the reaction; which explains that O = PPh₃ might play a role of activator.
16. CCDC-1530949 (for 3) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Monoclinic, space group P 2₁/c, colorless, a = 8.46601(8) Å, b = 20.6087(2) Å, c = 11.5556(1) Å, α = 90° β = 99.0707(8)° γ = 90° V = 1990.93(3) Å³, Z = 4, T = 116 K, D_{calc} = 1.316 g cm⁻³, μ(Mo-Kα) = 3.410 mm⁻¹, R₁ = 0.0326, wR₂ = 0.0914, GOF = 1.074.
17. The dichloride 10 is prepared by addition of TMSCl (3.6 eq) and NCS (3.6 eq) to 4. On the other hand, (Z)-(1,2-diiodo-2-arylvinyl)triisopropylsilane is too labile to isolate in pure form, see ref 7a.
18. The reactions were conducted with 0.5 mmol of starting dichloride in 4 mL of solvents according to the representative procedure as stated in Experimental Section.
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21. Representative procedure for synthesis of (Z)-3-bromo-2-(4-methoxyphenyl)-3-(triisopropylsilyl)acrylonitrile 3 (Table 1, entry 5): Under an argon atmosphere, to a solution of 2 (4.48 g, 10 mmol) and O = PPh₃ (3.34 g, 12 mmol) in 64 mL of dry toluene was added CuCN (1.07 g, 12 mmol). The mixture was heated to 80 °C, and stirred for 23 h, and allowed to cool to room temperature. The reaction was quenched with 3 M aqueous NH₃ (108 mL). After stirred for 15 min, the mixture was transferred into a 300 mL separatory funnel. The separated organic layer was washed with brine (100 mL x 3), and dried over Na₂SO₄, and filtered, and concentrated *in vacuo* to give a crude product. The crude was dissolved in CH₂Cl₂, and then purified with short-plugged column chromatography (SiO₂, eluted with hexane/CH₂Cl₂=3/1, height: 4 cm, glass-apparatus: IWAKI model#17G-3) to afford 3.47 g of 3 as whitish yellow solid materials in 88% yield. ¹H NMR (400 MHz, CDCl₃) 7.27 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 3.93 (s, 3H), 1.13–1.00 (m, 21H) ppm. ¹³C NMR (100 MHz, CDCl₃) 161.1, 147.8, 130.9, 130.8, 127.4, 118.6, 114.1, 55.7, 19.0, 13.0 ppm. MS (DART-TOF) m/z: 411 [M(Br79)+NH₄]⁺. IR (neat): 2946, 2868, 2207, 1602, 1504, 1468, 1444, 1297, 1253, 1241, 1185, 1176 cm⁻¹. HRMS (DART-TOF) calcd for C₁₉H₃₂Br(79)N₂O₂Si: 411.1467 [M(79)+NH₄]⁺, Found 411.1449. Anal. Calcd for C₁₉H₂₈BrN₂O₂Si: C, 57.86; H, 7.16; N, 3.55. Found: C, 57.96; H, 7.02; N, 3.81.
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