



Elucidation of reaction process through β -halogen elimination in CuCN-mediated cyanation of (*E*)-1-bromo-2-iodoalkene



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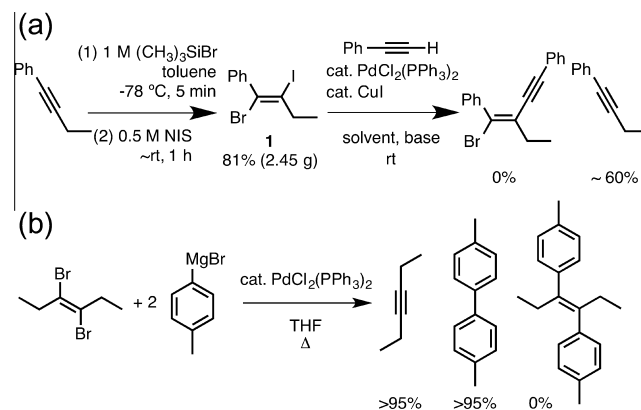
ABSTRACT

The previously unknown reaction process involved with metal-mediated β -halogen elimination is described, including a description of a vinylic Rosenmund–von Braun reaction of (*E*)-(1-bromo-2-iodobut-1-en-1-yl)benzene. We investigated the product structures on the basis of crystallographic analyses and revealed that copper cyanide would form bifurcated paths to deliver the isomeric mixtures.

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The efficient regio- and stereoselective synthesis of differentially all-carbon tetrasubstituted olefins remains a challenge,¹ although the significance of such olefins lies in medicinal chemistry,^{2,3} material science,^{4,5} and synthetic chemistry.⁶ Particularly, formation of the aliphatic and acyclic olefins bearing four different carbon-linked groups often faces selectivity problems, giving isomeric mixtures. Even monumental protocols for forming a carbon–carbon double bond, such as carbometalation of alkynes,⁷ carbonyl olefination,⁸ elimination reaction,⁹ olefin metathesis,¹⁰ and cycloaddition,¹¹ are powerless to produce such an aliphatic and acyclic olefin as a single isomer, because they encounter troubles of low stereochemical control and have limited utilities. These limitations have created the expectation of synthesizing single isomers on differentially substituted olefin templates¹² and continuous efforts have aimed to refine the diverse scaffold strategy.¹³

Recently, we have reported regio- and stereoselective iodobromination of unsymmetrically internal alkynes; for example, as illustrated in Scheme 1a, 1-phenyl-1-butyne reacted with in situ generated IBr to yield *anti*-IBr adduct **1** predominantly.¹⁴ To establish **1** as a stereo-defined alkenyl template for the synthesis of tetrasubstituted olefins, **1** was subjected to conventional transformations using palladium-catalyzed reactions; however, the reaction put back **1** to 1-phenyl-1-butyne and didn't afford any desired product. Actually, similar observation on (*E*)-3,4-dibromohex-3-ene was reported by the Rathore group in 2002

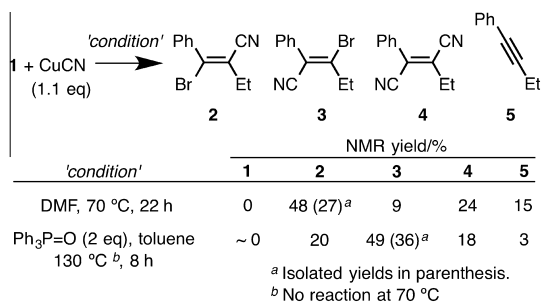
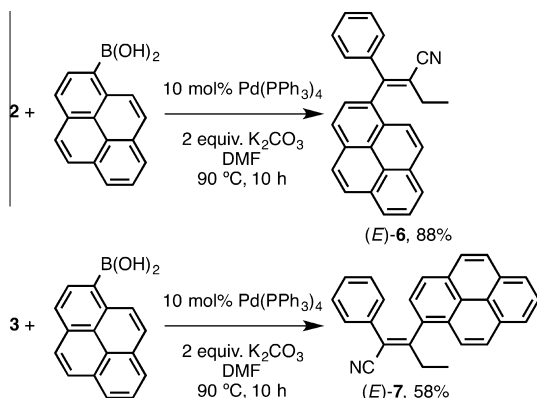


Scheme 1. (a) Regio- and stereoselective iodobromination of 1-phenyl-1-butyne, and the following attempt at reacting on iodide-site of **1**; (b) Rathore's report in 2002.

(Scheme 1b);¹⁵ oxidative addition of palladium into the first carbon–bromine bond would form the organopalladium intermediate that could then undergo subsequent β -halogen elimination to produce 3-hexyne.¹⁶ In both Scheme 1a and b, the eliminations were too fast to pursue the process with NMR technique; thus, the mechanistic aspect is not yet fully understood. Hence we chemists don't make good use of these vicinal dihaloalkenes for the synthesis of tetrasubstituted olefins.

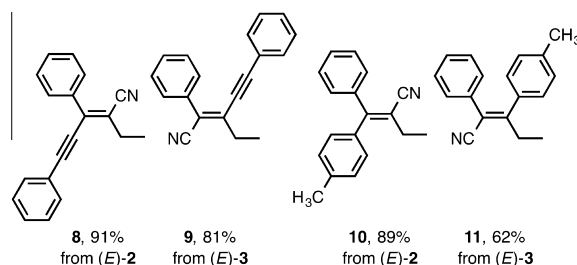
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Scheme 2. Vinylic Rosenmund–von Braun reactions of **1**.Scheme 3. Pd-catalyzed synthesis of **(E)-6** from **2**, and **(E)-7** from **3**.

It appeared to us that understanding this intrinsic problem would expand the importance and possibility of a vicinal dihaloalkene as a diverse scaffold for tetrasubstituted olefin synthesis. Herein we report previously unexplained reaction-paths involved with β-halogen elimination on the basis of a vinylic Rosenmund–von Braun reaction of *(E)*-(1-bromo-2-iodobut-1-en-1-yl)benzene. Cyanation gave some products, and the structural identification of them revealed that bifurcation from *(E)*-vinyl copper species causes one route to undergo desired reductive-elimination and another unpleasant β-halogen elimination.

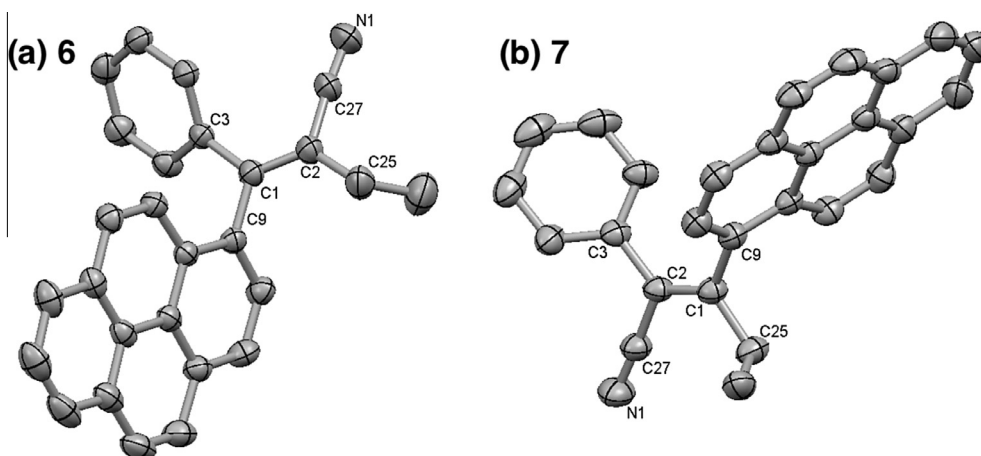
The reaction of **1** with CuCN under DMF solvent at 70 °C was performed to give mixtures of four compounds (Scheme 2). The analytical data of NMR and MS suggested they consisted of a set

Scheme 4. Stereo-retained synthesis of **8** and **10** from **(E)-2**, and **9** and **11** from **(E)-3**. Reaction conditions for **8** and **9**, ethynylbenzene, 10 mol % PdCl₂(PPh₃)₂, 20 mol % PPh₃, 20 mol % CuI, toluene, Et₃N, 70 °C, 2 h; for **10** and **11**, *p*-tolylboronic acid, 10 mol % Pd(PPh₃)₄, 2 equiv K₂CO₃, DMF, 90 °C, 22 h.

of vinyl bromides **2** (48% NMR yield) and **3** (9% NMR yield), and bis-nitriles **4**, and 1-phenyl-1-butyne **5**. Further investigations were demonstrated,¹⁷ and the system of Ph₃P=O/CuCN in toluene at 130 °C formed **3** predominantly (49% NMR yield). Employment of a large amount of silica gel gave separate fractions of single isomers of **2** and **3** in 27% and 36% yield, respectively.

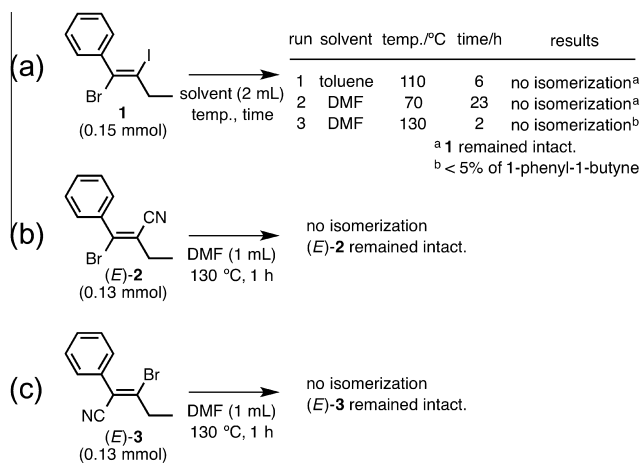
The stereochemistry of **2** and **3** was concluded from crystallographic analyses of **6** and **7** that are derived from palladium-catalyzed transformation of **2** and **3** (Scheme 3, and Fig. 1). As depicted in Scheme 3, cross-coupling on **2** and **3** yielded differentially all-carbon tetrasubstituted acrylonitriles **6** in 88% and **7** in 58%, respectively.²⁰ Crystallographic analyses of **6** and **7** determined the molecular structure as shown in Figure 1, which disclosed **6** as *(E)* and **7** as *(E)* stereochemistry.^{18,19} Thus, we rationally described **2** as *(E)*- and **3** as *(E)*-form, and illustrated both vinyl bromides with the array of four substituents attached to a double bond as shown in the Scheme 2. Actually, to our surprise, the structure of *(E)-3* was beyond what we expected. The bromine atom of **1** finally migrated from the original sp²-carbon to the adjacent sp²-carbon, giving another *(E)*-isomer.

Both structures of *(E)-2* and *(E)-3* were unveiled, and some syntheses of differentially all-carbon tetra-substituted acrylonitrile were performed through conventional palladium-catalyzed cross-coupling techniques (Scheme 4). The protocols readily accomplished stereo-defined preparation of olefins **8–11**. The important thing here is that *(E)-2* or *(E)-3* never isomerize to another during the metal-catalyzed reactions.²¹ Thus, the unpleasant isomerization reaction would be just triggered in the cyanation step of **1** with CuCN.

Figure 1. ORTEP drawings of **6** and **7** with thermal ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] for *(E)-6* (a): C1–C2 1.348, C1–C3 1.484, C1–C9 1.496, C2–C25 1.515, C2–C27 1.450; for *(E)-7* (b): C1–C2 1.348, C1–C9 1.494, C1–C25 1.508, C2–C3 1.486, C2–C27 1.443.

What kind of reaction process causes isomerization of the stereo-defined **1** to give two isomers of (*E*)-**2** and (*E*)-**3**? Does heating make them tautomerize? Experiments with just heating in solvents were tested on **1**, (*E*)-**2**, and (*E*)-**3** (Scheme 5). For **1**, three conditions of toluene/110 °C, DMF/70 °C, and DMF/130 °C didn't affect the tautomerization while DMF/130 °C slightly put **1** back to 1-phenyl-1-butyne **5** (Scheme 5a, run 3). On the other hand, (*E*)-**2** and (*E*)-**3** remained intact even in the harsh condition of DMF/130 °C (Scheme 5b and c). This result suggests that tautomerization by heating is unlikely.

Taking into account that a tautomerization occurs, we evaluated the reactivity of **1** as reaction temperature rising (Table 1). The cyanation at room temperature and 50 °C sparingly proceeded, and most of the starting **1** remained intact but (*E*)-**2** and alkyne **5** were formed (entries 1 and 2). At 70 °C overnight reaction consumed all the starting **1** to afford (*E*)-**2** as a main product (entry 3). When the temperature went up to higher 90 °C and 130 °C (entries 4 and 5), the cyanation of **1** occurred faster; both decrease in (*E*)-**2** and increase in (*E*)-**3** were observed. This clearly shows that CuCN mediates the isomerization paths, and that heating accelerates the stream from **1** to (*E*)-**3**. In addition, we set the CuCN-mediated cyanation of (*E*)-**2** and (*E*)-**3** under DMF solvent, respectively (Table 2). No reactions at 70 °C were observed (entries 1 and 3), while the reactions at 120 °C proceeded to yield single product of **4**²² in 64% from (*E*)-**2** and 45% from (*E*)-**3** (entries 2 and 4). Thus, interestingly, the bis-nitrile **4** was formed at 70 °C in Table 1, but not in Table 2.²³ Any inter-conversion between (*E*)-**2** and (*E*)-**3** was not observed.



Scheme 5. No tautomerization of **1**, (*E*)-**2**, and (*E*)-**3** by heating conditions.

Table 1
Temperature-dependent reactivity of **1** under the CuCN/DMF condition^a

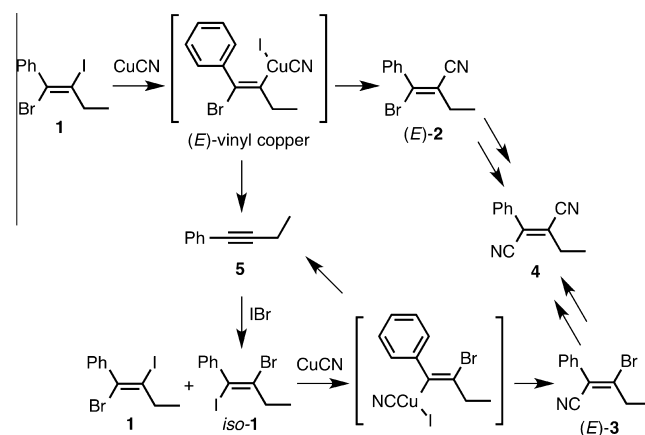
Entry	Temp (°C)	Time (h)	NMR yield (%)				
			1	(<i>E</i>)- 2	(<i>E</i>)- 3	4	5
1	rt	74	82	2	0	0	2
2	50	22	74	9	0	0	7
3	70	22	0	48	9	24	15
4	90	5	0	40	18	26	16
5	130	1	0	32	26	24	5

^a All reactions were performed on 0.5 mmol of **1**.

Table 2
Evaluation of reactivities of (*E*)-**2** and (*E*)-**3** on cyanation^a

Entry	Substrate	Temp (°C)	Time (h)	% yield	
				4	Recovered (<i>E</i>)- 2 or (<i>E</i>)- 3
1	(<i>E</i>)- 2	70	2	0	~100
2	(<i>E</i>)- 2	120	4	64	19
3	(<i>E</i>)- 2	120	16	0 ^a	0 ^a
4	(<i>E</i>)- 3	70	2	0	~100
5	(<i>E</i>)- 3	120	8	45	34
6	(<i>E</i>)- 3	120	16	0 ^a	0 ^a

^a (*E*)-**2** and (*E*)-**3** and **4** were totally decomposed, and ¹H NMR of crude states were messy.



Scheme 6. Plausible reaction paths.

From a view of these situations, we might draw plausible reaction paths as depicted in the Scheme 6. First, the CuCN activated a bond of carbon–iodine selectively.²⁴ Then, the resultant (*E*)-vinyl copper would bifurcate to afford (*E*)-**2** by reductive elimination and the alkyne **5** by β -halogen elimination: finally, **5** formally reacted with the concomitant IBr to give **1** and *iso*-**1**,²⁵ and *iso*-**1** provoked the following cyanation to give (*E*)-**3**. Seemingly, from Table 1, the rise in reaction-temperature presses to form **5** and (*E*)-**3**.²⁶

In summary, crystallographic analysis revealed the stereochemistry of (*E*)-**2** and (*E*)-**3**, and several experiments found which step triggers product isomerization. These results give a suggestion of reaction paths previously unexploited: the oxidative addition of CuCN to **1** generated the (*E*)-vinyl copper, then it would be disassembled into reductive elimination and β -halogen elimination, and the former affords desired (*E*)-**2** and the later unpleasant **5**. The alkyne **5** would be converted to (*E*)-**3** through second oxidative addition of CuCN to *iso*-**1**. Further synthetic development of the (*E*)-1-bromo-2-iodoalkene on the basis of these reaction routes is ongoing and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.12.063>.

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17. Many experiments were tested under varied conditions for producing **2** (or **3**) predominantly, and decreasing both **4** and **5**; however, products were always given as pesky mixtures. These results were summarized as Table 1S in Supporting Information. In addition, we examined many vicinal-dihaloalkenes on this cyanation, and almost all the substrates formed messy mixtures. For example, the reactivity and selectivity of (*E*)-(1-bromo-2-iodobut-1-en-1-yl) pyrene were similar to those of **1**.
18. CCDC-1430461 (for (*E*)-**6**) 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* = 15.0762(5) Å, *b* = 8.0948(3) Å, *c* = 16.5104(6) Å, α = 90°, β = 105°, γ = 90°, *V* = 1950.28(12) Å³, *Z* = 4, *T* = 296 K, *d*_{calc} = 1.217 g cm⁻³, μ (Mo-K α) = 0.070 mm⁻¹, *R*₁ = 0.0542, *wR*₂ = 0.2069, GOF = 1.074.
19. CCDC-1430878 (for (*E*)-**7**) 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/n, colorless, *a* = 16.5524(5) Å, *b* = 6.9513(2) Å, *c* = 17.7179(6) Å, α = 90°, β = 109°, γ = 90°, *V* = 1926.61(10) Å³, *Z* = 4, *T* = 296 K, *d*_{calc} = 1.232 g cm⁻³, μ (Mo-K α) = 0.071 mm⁻¹, *R*₁ = 0.0470, *wR*₂ = 0.1352, GOF = 1.043.
20. With viable pyrene-derivatives in hand, UV-vis absorption of (*E*)-**6** and (*E*)-**7** were checked; however, any significant difference between them was not observed (Fig. 1S in Supporting Information).
21. The usage of (*E*)-**3** in the cross-coupling reactions tends to decrease the chemical yields compared to that of (*E*)-**2**, presumably due to difference in steric congestion toward reactive C–Br sites between ethyl of (*E*)-**2** and phenyl of (*E*)-**3**.
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25. In this reaction system, a slight amount of *iso*-**1** was often observed; however, it was difficult to isolate it from other products, and occasionally obscures to discriminate between *iso*-**1** and others on ¹H NMR spectra. As **5** reacted with neat IBr under copper-free condition, the ratios of **1**:*iso*-**1** ranged from 92:8 to 74:21; see Ref. 14.
26. Not only temperature-up but also external ligands would enhance the halogen elimination. For example, the highest NMR yield of (*E*)-**3** was given in 53% under the condition of toluene (solvent), 110 °C, DMF (11 equiv), and CuCN (1.1 equiv), (see, entry 8 in Table 1S).