



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



Naoki Endo, Mao Kanaura, Tetsuo Iwasawa*

Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University, Otsu, Shiga 520-2194, Japan

ARTICLE INFO

Article history:

Received 23 November 2015

Revised 11 December 2015

Accepted 15 December 2015

Available online 17 December 2015

Keywords:

Alkene geometry

Reaction mechanism

Stereoselectivity

Tetrasubstituted olefin

β -Halogen elimination

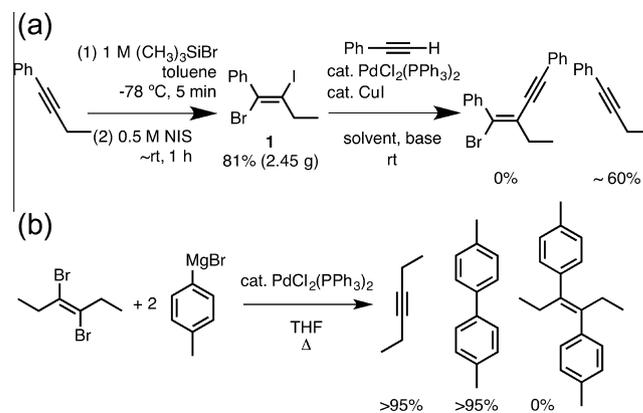
ABSTRACT

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.

© 2015 Elsevier Ltd. All rights reserved.

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*-I–Br 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

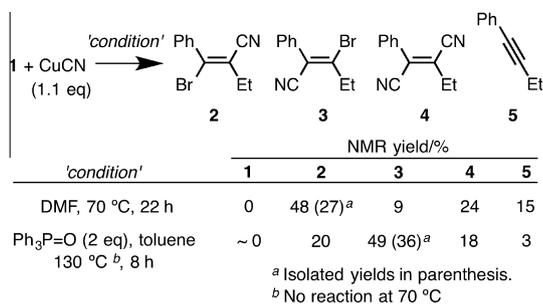


Scheme 1. (a) Regio- and stereoselective iodobromination of 1-phenyl-1-butyne, and the following attempt at reacting on iodide-site of **1**; (b) Rathore's report in 2002.

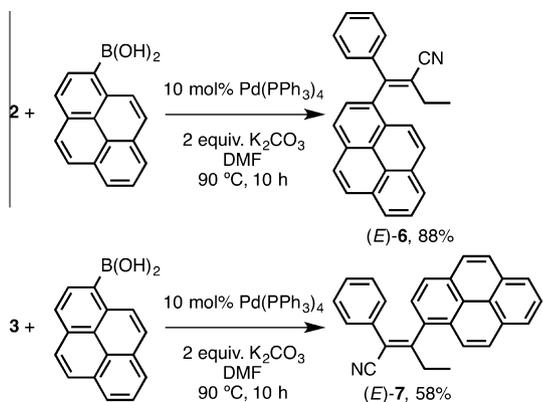
(Scheme 1b):¹⁵ oxidative addition of palladium into the first carbon–bromine bond would form the organopalladium intermediate that could then undergo subsequent β -halogen elimination to produce 3-hexyne.¹⁶ In both Scheme 1a and b, the eliminations were too fast to pursue the process with NMR technique; 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.

* Corresponding author. Tel.: +81 77 543 7461; fax: +81 77 543 7483.

E-mail address: iwasawa@rins.ryukoku.ac.jp (T. Iwasawa).



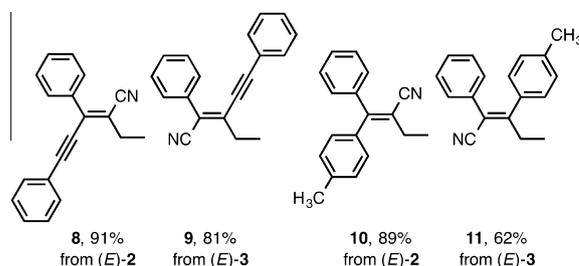
Scheme 2. Vinylic Rosenmund–von Braun reactions of **1**.



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.

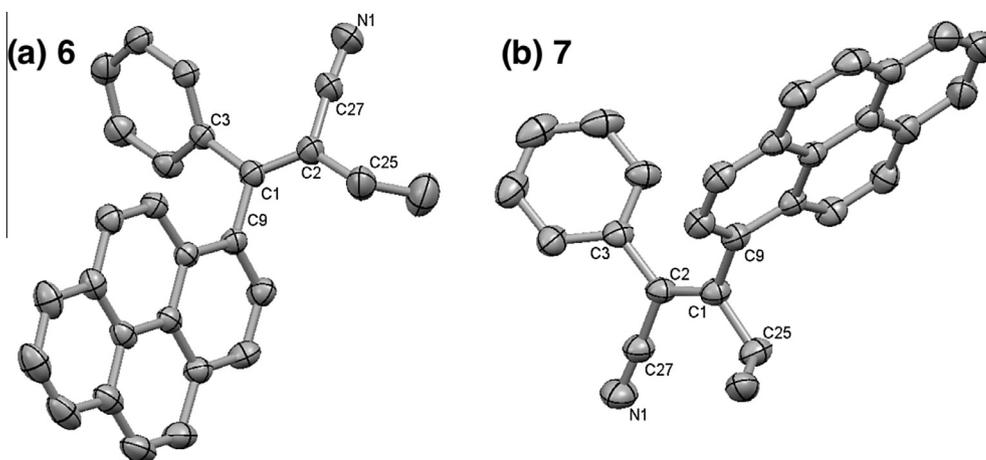
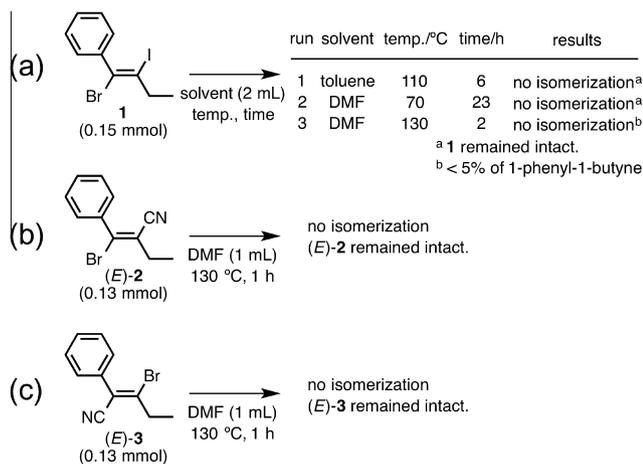


Figure 1. ORTEP drawings of **6** and **7** with thermal ellipsoids at the 30% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] for (*E*)-**6** (a): C1–C2 1.348, C1–C3 1.484, C1–C9 1.496, C2–C25 1.515, C2–C27 1.450; for (*E*)-**7** (b): C1–C2 1.348, C1–C9 1.494, C1–C25 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 condition³

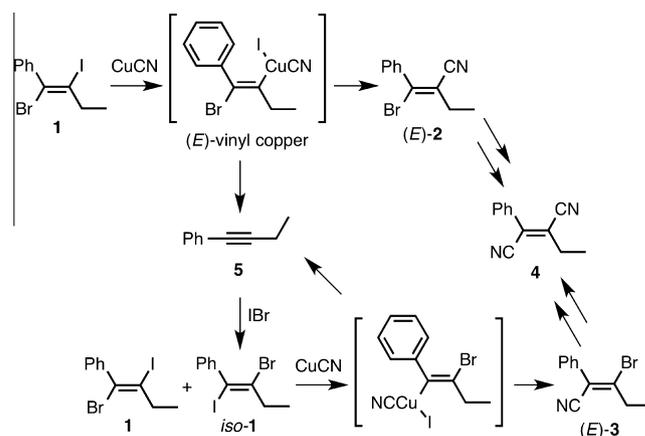
Entry	Temp (°C)	Time (h)	NMR yield (%)				
			1	(<i>E</i>)- 2	(<i>E</i>)- 3	4	5
1	rt	74	82	2	0	0	2
2	50	22	74	9	0	0	7
3	70	22	0	48	9	24	15
4	90	5	0	40	18	26	16
5	130	1	0	32	26	24	5

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

Table 2
Evaluation of reactivities of (*E*)-**2** and (*E*)-**3** on cyanation³

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.

Acknowledgments

Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research (C), Grant Number 24550066, supported this work. The authors thank Dr. Seiji Watase, Dr. Toshiyuki Iwai and Dr. Takatoshi Ito at OMTRI for assistance with measurement of X-ray diffraction and scattering and HRMS. Prof. Dr. Kingo Uchida at RU is gratefully thanked for help with measurement of UV–vis absorption.

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>.

References and notes

- Flynn, A. B.; Ogilvie, W. W. *Chem. Rev.* **2007**, *107*, 4698.
- a) Prasit, P.; Wang, Z.; Brideau, C.; Chan, C. C.; Charleson, S.; Cromlish, W.; Ethier, D.; Evans, J. F.; Ford-Hutchinson, A. W.; Gauthier, J. Y. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1773; b) Takahashi, A.; Kirio, Y.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 643; c) Arnone, A.; Brambilla, U.; Nasini, G.; Vajana de Pava, O. *Tetrahedron* **1995**, *51*, 13357.
- a) Williams, R. B.; Norris, A.; Slebodnick, C.; Merola, J.; Miller, J. S.; Andriantsiferana, R.; Rasamison, V. E.; Kingston, D. G. *J. Nat. Prod.* **2005**, *68*, 1371; b) Cerda-García-Rojas, C. M.; de Lampasona, M. E. P.; Catalan, C. A. N.; Joseph-Nathan, P. *J. Nat. Prod.* **2005**, *68*, 659; c) Clark, B.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H.; Bulheller, B.; Bringmann, G. *J. Nat. Prod.* **2005**, *68*, 1226.
- Browne, W. R.; Pollard, M. M.; de Lange, B.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 12412.
- a) Vicario, J.; Walko, M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 5127; b) Jager, W. F.; de Jong, J. C.; de Lange, B.; Huck, N. P. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 348; c) Feringa, B. L.; Jager, W. F.; de Lange, B. *Tetrahedron* **1993**, *49*, 8267.
- a) Calvin, J. R.; Frederick, M. O.; Laird, D. L. T.; Remacle, J. R.; May, S. J. *Org. Lett.* **2012**, *14*, 1038; b) Varela, J. A.; Pena, D.; Goldfuss, B.; Denisenko, D.; Kulhanek, J.; Polborn, K.; Knochel, P. *Chem. Eur. J.* **2004**, *10*, 4252; c) Oliver, S. F.; Hogenauer, K.; Simic, O.; Antonella, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996; c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105; d) Varela, J. A.; Pena, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* **2001**, *3*, 2395; e) de Meijere, A.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, 3809.
- For reviews of alkyne carbometalation, see: a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841; b) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899; c) Negishi, E.-I.; Wang, G.; Rao, H.; Xu, Z. *J. Org. Chem.* **2010**, *75*, 3151.
- a) Jenny, L.; Borschberg, H.-J. *Helv. Chim. Acta* **1995**, *78*, 715; b) Mandai, T.; Kaihara, Y.; Tsujii, J. *J. Org. Chem.* **1994**, *59*, 5847; c) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763; d) Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97.
- a) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543; b) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *Tetrahedron Lett.* **1997**, *38*, 1271; c) Johnson, E. P.; Volhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 381; d) Semmelhack, M. F.; Tomoda, S.; Hurst, K. M. *J. Am. Chem. Soc.* **1980**, *102*, 7567.
- a) Conrad, J. C.; Parnass, H. H.; Snelgrove, J. L.; Fogg, D. E. *J. Am. Chem. Soc.* **2005**, *127*, 11882; b) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.
- a) Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K.; Lee, B. Y. *J. Org. Chem.* **2006**, *71*, 91; b) Villalva-Serrvin, N. P.; Laurent, A.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 227; c) Laurent, A.; Villalva-Serrvin, N. P.; Forgione, P.; Wilson, P. D.; Smil, D. V.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 215; d) Villalva-Serrvin, N. P.; Laurent, A.; Yap, G.; Fallis, A. G. *Synlett* **2003**, 1263; e) Trost, B. M.; Macpherson, D. T. *J. Am. Chem. Soc.* **1987**, *109*, 3483.
- a) Begue, J.-P.; Bonnet-Delpon, D.; Bouvet, D.; Rock, M. H. *J. Org. Chem.* **1996**, *61*, 9111; b) Itami, K.; Mineno, M.; Muraoka, N.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11778; c) Lemay, A. B.; Vulic, K. S.; Ogilvie, W. W. *J. Org. Chem.* **2006**, *71*, 3615.
- a) Barczak, N. T.; Rooke, D. A.; Menard, Z. A.; Ferreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7579; b) Suero, M. G.; Bayle, E. D.; Collins, B. S. L.; Gaunt, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 5332.
- Ide, M.; Yauchi, Y.; Shioyai, R.; Iwasawa, T. *Tetrahedron* **2014**, *70*, 8532.
- Rathore, R.; Deselnicu, M. I.; Burns, C. L. *J. Am. Chem. Soc.* **2002**, *124*, 14832.
- a) Rossi, R.; Bellina, F.; Carpita, A.; Mazzarella, F. *Tetrahedron* **1996**, *52*, 4095; b) Organ, M. G.; Ghasemi, H.; Valente, C. *Tetrahedron* **2004**, *60*, 9453; c) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.
- 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**.
- 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, $\alpha = 90^\circ$, $\beta = 105^\circ$, $\gamma = 90^\circ$, *V* = 1950.28(12) Å³, *Z* = 4, *T* = 296 K, *d*_{calcd} = 1.217 g cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.070 \text{ mm}^{-1}$, *R*₁ = 0.0542, *wR*₂ = 0.2069, GOF = 1.074.
- 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, $\alpha = 90^\circ$, $\beta = 109^\circ$, $\gamma = 90^\circ$, *V* = 1926.61(10) Å³, *Z* = 4, *T* = 296 K, *d*_{calcd} = 1.232 g cm⁻³, $\mu(\text{Mo-K}\alpha) = 0.071 \text{ mm}^{-1}$, *R*₁ = 0.0470, *wR*₂ = 0.1352, GOF = 1.043.
- 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).
- 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**.
- Fitzgerald, J.; Taylor, W.; Owen, H. *Synthesis* **1991**, 686.
- Buchwald group reported the catalytic amounts of CuI and KI achieved the Rosenmund-von Braun cyanation of aryl bromides in mild conditions, see; Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 2890.
- Pradal, A.; Evano, G. *Chem. Commun.* **2014**, *50*, 11907–11910.
- 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.
- 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 (1.1 equiv), and CuCN (1.1 equiv), (see, entry 8 in Table 1S).