

Letter

Subscriber access provided by CAL STATE UNIV BAKERSFIELD

Pd-Catalyzed Allylic Isocyanation: Nucleophilic *N*-Terminus Substitution of Ambident Cyanide

Taiga Yurino, Ryutaro Tani, and Takeshi Ohkuma

ACS Catal., Just Accepted Manuscript • DOI: 10.1021/acscatal.9b00858 • Publication Date (Web): 15 Apr 2019

Downloaded from http://pubs.acs.org on April 15, 2019

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

7

8 9 10

11 12

13 14

15

16

17

18

23

24 25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60

Pd-Catalyzed Allylic Isocyanation: Nucleophilic N-Terminus Substitution of Ambident Cyanide

Taiga Yurino,* Ryutaro Tani and Takeshi Ohkuma*

Division of Applied Chemistry and Frontier Chemistry Center, Faculty of Engineering, Hokkaido University, Kita 13, Nishi 8, Sapporo, Hokkaido 060-8628, Japan

ABSTRACT: In the presence of catalytic amount of $Pd(OAc)_2$, allylic phosphates reacted with trimethylsilyl cyanide (TMSCN) to afford the corresponding allylic isonitriles exclusively. No allylic nitriles, which are selectively obtained in the traditional Pd(0)-catalyzed reaction, were observed. The use of phosphate as the leaving group was crucial to achieve complete regioselectivity of the ambident cyanide species as the *N*-terminus nucleophile. The reaction was applicable to a series of aromatic, hetero-aromatic, vinylic, and aliphatic substituted allylic phosphates. The mechanistic studies suggested that the allylic isocyanation was catalyzed by the Pd(II) species, and not by Pd(0).

Keywords: isonitrile, palladium, allylic substitution, ambident, Lewis acid catalysis, nucleophilic substitution

A nucleophilic substitution using an ambident reagent, which has two alternative reactive sites, affords at least two possible products. A reliable method for controlling the reactive site is indispensable in order to synthesize the desired products selectively.^{1,2} Cyanide is one of the most typical ambident nucleophiles and reacts with an electrophile (R-X: R = alkyl, allyl, etc.; X = leaving group) at the C- and Nterminus, vielding either the nitrile (R-CN) or the isonitrile (R-NC) (Scheme 1, equation 1).³ According to the traditional Kornblum's rule,⁴ which is applied for prediction of the regioselectivity of ambident nucleophiles, the N-terminus of cyanide preferentially reacts in the S_N1-type substitution. However, even in those reactions, the C-terminus of the cyanide reacts prior to the N-terminus, because the formation of the nitrile is both kinetically and thermodynamically more favorable in most cases.^{3,5–9} Therefore, development of a selective synthetic method of isonitrile by the nucleophilic substitution is highly desirable.¹⁰ Realizing such a method by the catalytic procedure is more challenging.

To date, only two types of catalytic systems have permitted the production of isonitrile by nucleophilic substitution. Gassman and coworkers demonstrated the ZnI₂-catalyzed ringopening isocyanation of epoxides and oxetanes with trimethylsilyl cyanide (TMSCN) (Scheme 1a).¹¹ Other metal salts, such as Pd(CN)₂, SnCl₂ and Me₃Ga, were also reported to show catalytic activity for the isocyanation.¹² A chiral BINOL–Ga(III) complex promoted a similar isocyanation with moderate enantioselectivity.¹³ Recently, Shenvi and coworkers reported the isocyanation of tertiary alcohol derivatives with TMSCN catalyzed by Sc(OTf)₃ (Scheme 1b).^{14,15} The reaction using trifluoroacetate as an electrophile gave the best result, forming the isonitrile with stereoinversion selectively.

Herein we describe the first successful example of a catalytic allylic isocyanation (Scheme 2a). An allylic phosphate reacts with TMSCN as the *N*-nucleophile in the

presence of Pd(II) catalyst, affording the linear isonitriles selectively. The

$$R-X + \stackrel{\bigcirc}{\longrightarrow} R-NC$$
 or $R-CN + \stackrel{\bigcirc}{\longrightarrow} X$ (eq. 1)
N-addition C-addition

C-addition is both kinetically and thermodynamically favorable.

Limited examples of catalytic nucleophilic isocyanation:



Scheme 1. Ambident Nucleophilic Properties of Cyanide and Examples of Catalytic Isocyanation

Pd(0)-catalyzed allylic substitution is known as the Tsuji– Trost-type reaction, which proceeds through the π -allyl–Pd(II) intermediate.¹⁶ Tsuji and coworkers applied this protocol to the allylic cyanation of an allyl acetate with TMSCN as the *C*nucleophile catalyzed by Pd(PPh₃)₄ (Scheme 2b).¹⁷ The complete reversal of regioselectivity between these two reactions was ascribed to the change of the Pd catalyst precursor and the leaving group of the allylic substrate, and it suggests that the Pd-catalyzed isocyanation proceeds without formation of the π -allyl–Pd(II) species.¹⁸

Our study commenced with optimization of the reaction conditions in catalytic allylic isocyanation (Table 1). Cinnamyl diethyl phosphate was employed as the model substrate for the optimization. In the presence of $Pd(OAc)_2$ (2 mol%), the substrate reacted smoothly with TMSCN (2.0 equiv) in toluene at 80 °C under an argon atmosphere in 3 h to

afford the linear allylic isonitrile **1a** in 96% yield (entry 1). The product was isolated with column chromatography in 82% (a) Pd(II)-catalyzed allylic isocyanation of the phosphate substrate (this work)



(b) Pd(0)-catalyzed allylic cyanation of the acetate substrate (previous work)

R	Pd(PPh ₃) ₄ (5 mol%) Me ₃ SiCN (2.0 equiv) THF, reflux	R
		up to 98% vield

Scheme 2. Pd-Catalyzed Allylic Isocyanation and Cyanation

yield. Notably, neither branched isomer 2a nor cinnamyl nitrile was observed at all. No substrate consumption was observed without Pd catalyst (entry 2). PdCl₂ was also a usable precursor, but the major linear product 1a was contaminated with a small amount of the branched isonitrile 2a (entry 3). $Pd(PPh_3)_4$ was far less reactive, and afforded a mixture of 1a and 2a in moderate yield (entry 4). Unexpectedly, no detectable amount of the nitrile compounds was produced. Toluene and THF were the preferable solvents (entries 1 and 5). The polar aprotic solvents MeCN and DMF, which are frequently used in the S_N2-type reactions, were not suitable for this reaction (entries 6 and 7). The reaction without solvent also resulted in poor yield of the product (entry 8). The isocyanation under atmospheric air proceeded smoothly to afford 1a in comparable yield to that under argon (entry 9). The catalyst loading could be decreased to 0.2 mol% and the reaction furnished the product in 81% yield with prolongation of the reaction time from 3 h to 25 h (entry 10).

Table 1. Optimization of the Reaction Conditions

Ì	[∼] OP($(O)(OEt)_{2} \xrightarrow{Pd(OAc)_{2} (2 \text{ mol%Pd})}_{toluene, 80 °C, Ar, 3 h}$	NC +	NC
			1a	2a
			Yield (%) ^a
	Entry	Deviation from the "Standard" Conditions	1a	2a
	1	None	96(82)	0
	2	No Pd cat. was used	0	0
	3	PdCl ₂ instead of Pd(OAc) ₂	85	8
	4	Pd(PPh ₃) ₄ instead of Pd(OAc) ₂	21	14
	5	THF instead of toluene	95	0
	6	MeCN instead of toluene	26	0
	7	DMF instead of toluene	34	7
	8	No solvent was used	39	5
	9	Reaction under air	95(83)	0
	10	0.2 mol% of catalyst was used ^b	81	0

^{a 1}H NMR yield. The isolated yield was given in parentheses. ^bThe reaction time was 25 h.

The $Pd(OAc)_2$ -catalyzed allylic isocyanation was remarkably affected by the nature of the leaving groups, as shown in Table 2. The phosphate was exceptionally wellsuited for the reaction, even in the case of the corresponding diphenyl ester. The imidate gave **1a** in synthetically usable yield accompanied by a small amount of the branched isomer **2a**. The trifluoroacetate, which was the appropriate leaving group in the Shenvi's $Sc(OTf)_3$ -catalyzed substitution, was not applicable to this reaction. Some leaving groups frequently used in the Tsuji–Trost-type allylic substitution, such as acetate, carbonate, and bromide, were not replaced with cyanide at all. Cinnamyl alcohol reacted with TMSCN to form the corresponding silylether under the typical conditions. No substitution product was observed.

Table 2. Leaving Group-Dependency on the Catalytic Allylic Isocyanation^a



We next investigated the scope of allylic phosphates for the isocyanation under the optimized reaction conditions (Table 3). The reactions were conducted under argon (black characters), but comparable results were obtained under atmospheric air (red characters). No evanation product was observed in all cases. Cinnamyl phosphates with a methyl group on the phenyl ring were converted into the linear allylic isonitriles, 1b-1d, in around 90% yield irrespective of the substituted position. The E/Z ratio of 1d was slightly increased compared to that of the substrate. The corresponding branched products were not detected. The reaction allowed the substitution of both electron-withdrawing Br and -donating MeO, affording the desired isonitriles, 1e and 1f, in high yield. Notably, the C-Br bond was left intact under the reaction conditions, suggesting that the active Pd(0) species was not included in the catalyst system. The thienyl- and indolylsubstituted allylic phosphates were also converted to the linear isonitriles. 1g and 1h. exclusively. The reaction of the conjugated 2,4-dienyl phosphate predominantly afforded the linear dienyl isonitrile 1i in 91% yield. No detectable amounts of the γ - and ϵ -substituted isomers were produced. An 8.8:1 E/Z mixture (18:1 under air)¹⁹ of γ -methyl cinnamyl isonitrile 1 was obtained in the reaction of the *E*-configured γ -methyl cinnamyl phosphate. This indicated the presence of the E/Zisomerization pathway, as discussed later. In contrast, the βmethyl cinnamyl phosphate reacted with TMSCN to give a 2.9:1 mixture of the *E*-configured linear β -methyl cinnamyl isonitrile (1k) and the branched isomer in 94% yield. The Z isomer of 1k was not observed. The relatively unstable branched isomer of 1k was decomposed through the isolation procedure, resulting in the linear-enriched product. The aliphatic substrates were applied to the substitution reaction. The cyclohexyl-substituted allylic phosphate was converted to 1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27 28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43 44

45

46

47

48

49

50

51

52

53

54

55

56

57

58 59

60

the linear product 11 in high yield. The reaction of 5-phenyl-2pentenyl phosphate, a primary alkyl-substituted compound, afforded a 3.4:1 mixture of the linear isonitrile 1m and the corresponding branched isomer. A 3.1:1 mixture of linear (1n)/branch isomers was obtained in the reaction of geranyl phosphate. The reaction of (Z)-cinnamyl phosphate under the typical conditions resulted in an approximately 2:1 E/Z(1a/1a') mixture of the isonitrile (Scheme 3).

Table 3. Substrate Scope of the Allylic Phosphate for the Isocyanation^{a,b}



^aThe results of reactions under argon and atmospheric air are indicated with in black and red characters respectively. ^b⁻¹H NMR yield. The isolated yield is given in parentheses. ^cThe *E*/*Z* ratio of the substrate was 13/1. ^dThe *E*/*Z* ratio of the product was >20/1 (>20/1). ^aThe *E*/*Z* ratio of the product was 8.8/1 (11/1). ^fThe *E*/*Z* ratio of the product was 18/1 (>20/1). ^gThe *l/b* ratio of the product was 2.9/1 (15/1). ^fThe *l/b* ratio of the product was 3.4/1. ^tsolated yield. ^The *l/b* ratio of the product was 3.4/1. ^kThe *l/b* ratio of the product was 3.1/1.





Scheme 3. Pd(II)-Catalyzed Allylic Isocyanation of (Z)-Cinnamyl Phosphate

The unusual isonitrile formation through the Pd-catalyzed allylic substitution prompted us to perform some mechanistic experiments. According to Tsuji's report, cinnamyl acetate and TMSCN reacted with a catalytic amount of Pd(PPh₃)₄ in THF at the reflux temperature to give cinnamyl nitrile in 98% yield (Scheme 4a).¹⁷ The use of cinnamyl phosphate completely reversed the cyanide regioselectivity under the same conditions, although the yield of the isonitrile **1a** was moderate. The remarkable influence of the leaving-group on the cyanide regioselectivity was noteworthy. The reaction of the isolated η^3 -cinnamyl–Pd(II) dimeric complex and TMSCN in toluene- d_8 monitored by ¹H NMR gave the cinnamyl nitrile

3a exclusively (Scheme 4b). When the π -allyl-Pd(II) phosphate prepared from the n³-cinnamyl-Pd(II) dimeric complex and silver phosphate was employed for the reaction with TMSCN, a complex mixture including 3a (approximately 3%) was obtained (Scheme 4c). There was no trace of isonitrile 1a in the mixture. These results indicated that the allylic isocyanation proceeded without forming the π -allyl-Pd(II) species, which was the key intermediate of the Pd(0)catalyzed allylic cyanation. The cinnamyl phosphate does not form the π -allyl-Pd(II) compound under the reaction conditions even with the $Pd(PPh_3)_4$, a typical Pd(0) catalyst. Indeed, Pd(CN)₂(PPh₃)₂ was obtained through the reaction between Pd(PPh₃)₄ and TMSCN (5 equiv) in 86% yield. The resulting Pd(II) complex was catalytically active for the allylic isocyanation (Scheme 4d). Again the formation of 3a was not observed.

(a) Pd-catalyzed allylic cyanation and isocyanation



(b) The reaction of the isolated n3-cinnamyI-Pd(II) chloride dimer and TMSCN



(c) The reaction of η3-cinnamyI-Pd(II) phosphate and TMSCN





(d) Pd(CN)₂(PPh₃)₂-catalyzed allylic isocyanation



Scheme 4. Investigation of the Potential Involvement of the π -Allyl–Pd(II) Intermediate in the Catalytic Isocyanation

We next examined the roles of the Pd species in the catalytic allylic isocyanation (Scheme 5). $Pd(OAc)_2$ exhibited the best catalyst performance, reacting with an excess amount of TMSCN in toluene to afford $Pd(CN)_2$ quantitatively (equation 1). The isolated $Pd(CN)_2$ catalyzed the allylic isocyanation of cinnamyl phosphate under the typical conditions for 3 h to give the linear cinnamyl isonitrile **1a** and the branched isomer **2a** in 75% and 9% yield, respectively (equation 2). $Pd(CN)_2$ exhibited a somewhat lower catalyst efficiency than $Pd(OAc)_2$, achieving 96% yield of **1a** under the same conditions (see Table 1, entry 1). The isolated $Pd(CN)_2$ was hardly soluble in toluene, and it may cause the slower reaction rate. A stoichiometric amount of $Pd(CN)_2$ without TMSCN did not react with the cinnamyl phosphate (equation

3). These results suggested that $Pd(CN)_2$ was formed in situ from $Pd(OAc)_2$ and TMSCN in the reaction mixture. $Pd(CN)_2$ was not the active nucleophile, but it behaved as the Pd(II) catalyst or the reservoir. In fact, $[Pd(CN)_3]^-$ and $[Pd(CN)_4]^{2-}$ were detected on the ESI-MS analysis (negative mode) of the mixture of Pd(CN)₂ and TMSCN, even though the corresponding signals were not detected on the measurement of the isolated $Pd(CN)_2$ (see the Supporting Information). TMS(OAc) showed some catalytic activity for the isocvanation in the absence of Pd species to afford a mixture of 1a and 2a in low yield (equation 4). The Lewis acidic TMS cation appeared to take part in the activation of the allylic phosphate. These observations are consistent with the following mechanistic hypothesis shown in Scheme 6: $Pd(OAc)_2$ is converted to an equilibrium mixture of the neutral $Pd(CN)_2$ and the ate-complexes of $(TMS)[Pd(CN)_3]$ and (TMS)₂[Pd(CN)₄] in the presence of an excess amount of TMSCN. Pd(CN)₂ is the most stable Pd species. Not only Pd(CN)₂ but also the TMS cation of the ate-complexes functions as a Lewis-acid catalyst to activate the allylic phosphate. [Pd(CN)₃]⁻ and [Pd(CN)₄]²⁻ as well as TMSCN react as N-terminus nucleophiles with the activated substrate to yield the allylic isonitrile. The high leaving ability of the phosphate in the presence of Lewis acid promotes the smooth reaction. Moreover, the dissociated phosphate anion rarely inhibits the catalytic performance. These chemical features probably make allylic phosphate as the suitable substrate for the isocyanation.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60



Scheme 5. Mechanistic Experiments on the Roles of Pd(II) Species

We also found that the rearrangement of the branched allylic isonitrile **2a** into the linear compound **1a** occurred under the appropriate conditions (equation 5 and Scheme 6): The reactions in the NMR tubes required longer time. No rearrangement was observed without Pd(II) species even in the presence of two equivalents of TMSCN. A catalytic amount of Pd(CN)₂ without TMSCN gradually converted **2a** into **1a**.²⁰ The rearrangement proceeded smoothly in the presence of both Pd(CN)₂ (2 mol%) and TMSCN (2 equiv) to afford **1a** in 93% yield in 15 h. In contrast, no isomerization was observed with 2 mol% of TMS(OAc), suggesting that the rearrangement also specifically occurs by Pd(II) catalyst. The *E/Z*

isomerization observed in the formation of 1j and 1a from the (Z)-cinnamyl phosphates seems to occur through this process (see Table 3 and Scheme 3). The E/Z ratio of the product through the isomerization is dependent on the thermodynamic stability. The direct linear isonitrile formation increases the ratio of the Z isomer. The rearrangement forming aliphatic 1m and 1n from the corresponding branched isomers is slow, and therefore the branched isomers were observed (see the Supporting Information).



Scheme 6. Plausible Reaction Pathway of the Allylic Isocyanation

In conclusion, we reported the first successful example of a catalytic allylic isocvanation. The allylic phosphate reacted with TMSCN in the presence of a catalytic amount of $Pd(OAc)_2$ to afford the allylic isonitrile in high yield. The use of phosphate as a leaving group was crucial for exclusive formation into the isonitrile. The corresponding allylic nitriles were not observed. The reaction could be conducted either under argon or atmospheric air. A series of aromatic, heteroaromatic, vinylic, and aliphatic substituted substrates was applicable to this reaction. Several mechanistic experiments suggested that the equilibrating system of $Pd(CN)_2$, (TMS)[Pd(CN)₃], and (TMS)₂[Pd(CN)₄] catalyzes the allylic isocyanation. The Lewis acidic Pd(CN)₂ and TMS cation activate the allylic phosphate, and TMSCN, [Pd(CN)₃], and $[Pd(CN)_4]^{2-}$ act as the *N*-terminus nucleophiles. Thus, the isocvanation proceeded without a π -allyl-Pd(II) species, which was a key intermediate of most allylic substitutions with Pd(0) catalysts. The Pd(II) species also catalyze the rearrangement of the branched isonitrile into the linear isomer. The dual roles of the Pd(II) catalytic system afford the linear allylic isonitriles in high yields. Further investigations on the reaction mechanism, especially on the specificity of the allylic phosphate, are underway in our laboratory.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

*E-mail: <u>tyurino@eng.hokudai.ac.jp</u> (T. Yurino) *E-mail: <u>ohkuma@eng.hokudai.ac.jp</u> (T. Ohkuma) 1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57 58 59

60

ORCID

Taiga Yurino: 0000	0-0002-4158-3463
Takeshi Ohkuma: (0000-0002-5467-3169

Notes

The authors declare no conflict of interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, details of experiment and spectral data (PDF)

ACKNOWLEDGMENT

This work was supported by Grants-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 15H03802 and No. 16K17900). T.Y. also acknowledges the support of the Sumitomo Foundation in the form of a Grant for Basic Science Research Projects (No. 171018) and support from the Feasibility Study Program of the Frontier Chemistry Center, Faculty of Engineering, Hokkaido University.

REFERENCES

- Fleming, I Molecular Orbitals and Organic Chemical Reactions; John Wiley & Sons Ltd. Chichester, 2009; pp 121– 134.
- (2) (a) Breugst, M.; Zipse, H.; Guthrie, J. P.; Mayr, H. Marcus Analysis of Ambident Reactivity. *Angew. Chem. Int. Ed.* **2010**, 49, 5165–5169. (b) Mayr, H.; Breugst, A. R.; Ofial, A. R. Farewell to the HSAB Treatment of Ambident Reactivity. *Angew. Chem. Int. Ed.* **2011**, 50, 6470–6505.
- (3) Tishkov, A. A.; Mayr, H. Ambident Reactivity of the Cyanide Ion: A Failure of the HSAB Principle. *Angew. Chem. Int. Ed.* 2005, 44, 142–145.
- (a) Kornblum, N.; Taub, B.; Ungnade, H. E. The Reaction of (4)Silver Nitrite with Primary Alkyl Halides. J. Am. Chem. Soc. 1954, 76, 3209-3211. (b) Kornblum, N.; Smiley, R. A. Ungnade H. E.; White, A. M.; Taub, B.; Herbert Jr., S. A. The Reaction of Silver Nitrite with Secondary and Tertiary Alkyl Halides. J. Am. Chem. Soc. 1955, 77, 5528-5533. (c) Kornblum, N.; Fishbein, L.; Smiley, R. A. The Stereochemistry of the Reaction of Alkyl Halides with Silver Nitrite. J. Am. Chem. Soc. 1955, 77, 6261-6266. (d) Kornblum, N.; Smiley, R. A.; Blackwood, R. K.; Iffland, D. C. The Mechanism of the Reaction of Silver Nitrite with Alkyl Halides. The Contrasting Reactions of Silver and Alkali Metal Salts with Alkyl Halides. The Alkylation of Ambident Anions. J. Am. Chem. Soc. 1955, 77, 6269-6280. (e) Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. A New Method for the Synthesis of Aliphatic Nitro Compounds. J. Am. Chem. Soc. 1956, 78, 1497–1501. (f) Kornblum, N. Synthesis of Aliphatic and Alicyclic Nitro Compounds. Org. React. 1962, 12, 101-156
- (5) (a) Mowry, D. T. The Preparation of Nitriles. *Chem. Rev.* 1948, 42, 189–283. (b) Romero–Hernández, L. L. Trimethylsilyl Cyanide (TMSCN). *Synlett*, 2015, 26, 563– 564.
- (6) (a) Rad, M. N. S.; Khalafi–Nezhad, A.; Berouz, S.; Faghihi, M. A. A Simple One-Pot Procedure for the Direct Conversion of Alcohols into Alkyl Nitriles Using TsIm. *Tetrahedron Lett.* 2007, *48*, 6779–6784. (b) Chen, G.; Wang, Z.; Wi, J.; Ding, K. Facile Preparation of α-Aryl Nitriles by Direct Cyanation of Alcohols with TMSCN Under the Catalysis of InX₃. *Org. Lett.* 2008, *10*, 4573–4576. (c) Rajagopal, G.; Kim, S. S. Synthesis of α-Aryl Nitriles through B(C₆F₅)₃-Catalyzed

Direct Cyanation of α -Aryl Alcohols and Thiols. *Tetrahedron* **2009**, *65*, 4351–4355. (d) Wang, J.; Masui, Y.; Onaka, M. Direct Synthesis of Nitriles from Alcohols with Trialkylsilyl Cyanide Using Brønsted Acid Montmorillonite Catalysts. *ACS Catal.* **2011**, *1*, 446–454. (e) Theerthagiri, P.; Lalitha, A. Zn(OTf)₂-Catalyzed Direct Cyanation of Benzylic Alcohols–A Novel Synthesis of α -Aryl Nitriles. *Tetrahedron Lett.* **2012**, *53*, 5535–5538. (f) Fan, X.; Guo, K.; Guan, Y.–H.; Fu, L.–A.; Cui, X.–M.; Lv, H.; Zhu, H.–B. Efficient Assembly of α -Aryl and α -Vinyl Nitriles via Iron-Catalyzed Ether Bond Activation. *Tetrahedron Lett.* **2014**, *55*, 1068–1071.

- (7)(a) Austad, T.; Songstad, J.; Stangeland, L. J. The Ambident Nature of Cyanide Ion. The Reaction between Trityl Chloride and Tetraphenylarsonium Cyanide in Acetonitrile. Acta Chem. Scand. 1971, 25, 2327-2336. (b) Reetz, M. T.; Chatziiosifidis, I.; Künzer, H.; Müller-Starke, H. Trimethylsilyl Cyanide Promoted Cyanation of Tertiary Alkyl Chloride and Other S_N1 Active Compounds. Tetrahedron 1983, 39, 961–965. (c) Zieger, H. E.; Wo, S. Titanium(IV) Chlodride-Catalyzed Cyanation of Benzylic Halides with Trimethylsilyl Cyanide. J. Org. Chem. 1994, 59, 3838-3840. (d) Mobele, B. I.; Venkatraman, S.; McNaughton-Smith, G.; Gibb, C.; Ulysse, L. G.; Lindmark, C. A.; Shaw, S.; Marron, B.; Spear, K.; Suto, M. J. Process Development and Optimization for Production of a Potassium Ion Channel Blocker, ICA-17043. Org. Proc. Res. Dev. 2012, 16, 1385-1392
- (8) (a) Chini, M.; Crotti, P.; Favero, L.; Macchia, F. Easy Direct Stereo- and Regioselective Formation of β-Hydroxy Nitriles by Reaction of 1,2-Epoxides with Potassium Cyanide in the Presence of Metal Salts. *Tetrahedron Lett.* **1991**, *32*, 4775–4778. (b) Shaus, S. E.; Jacobsen, E. N. Asymmetric Ring Opening of Meso Epoxides with TMSCN Cataylzed by (Pybox)lanthanide Complexes. *Org. Lett.* **2000**, *2*, 1001–1004. (c) Yamasaki, S.; Kanai, M.; Shibasaki, M. Novel Multiaction of Zr Catalyst: One-Pot Synthesis of β-Cyanohydrins from Olefins. *J. Am. Chem. Soc.* **2001**, *123*, 1256–1257. (d) Saha, B.; Lin, M.–H.; RajanBabu, T. V. Exceptionally Active Yttrium-Salen Complexes for the Catalyzed Ring Opening of Epoxides by TMSCN and TMSN₃. *J. Org. Chem.* **2007**, *72*, 8648–8655.
- (9) Yanagisawa, A.; Nezu, T.; Mohri, S.-i. Brønsted Acid-Promoted Hydrocyanation of Arylalkenes. Org. Lett. 2009, 11, 5286–5289.
- (10) For isocyanation through direct substitution of cyanide as an *N*-nucleophile by a stoichiometric amount of activator, see: (a) Songstad, J. Stangeland, L. J.; Austad, T. Isonitriles from Alkyl Halides and Onium Dicyanoargentates. Acta Chem. Scand. 1970, 24, 355-356. (b) Engemyr, L. B.; Martinesen, A.; Songstad, J. Isocyanides from Alkyl Halides and Onium Dicyanoargentates. Scope and Mechanism. Acta Chem. Scand. 1974, 28A, 255-266. (c) Boullanger, P.; Descotes, G. Synthesis of 1-Isocyano Sugars. Tetrahedron Lett. 1976, 3427-3430. (d) Sasaki, T.; Nakanishi, A.; Ohno, M. Synthesis of Adamantine Derivatives. 56. Reaction of 1-Adamantyl Chloride with Trimethylsilyl Pseudohalide. J. Org. Chem. 1981, 46, 5445-5447. (e) Corey, E. J.; Magriotis, P. A. Total Synthesis and Absolute Configuration of 7,20-Diisocyanoadociane. J. Am. Chem. Soc. 1987, 109, 287-289. (f) Kitano, Y.; Chiba, K.; Tada, M. A Direct conversion of Alcohols to Isocyanides. Tetrahedron Lett. 1998, 39, 1911-1912. (g) Kitano, Y.; Chiba, K.; Tada, M. A Direct Conversion of Alkenes to Isocyanides. Synlett 1999, 288-290. (h) Kitano, Y.; Chiba, K.; Tada, M. Highly Efficient Conversion of Alcohols to Isocyanides. Synthesis 2001, 437-443. (i) Li, D. R.; Xia, W. J.; Shi, L.; Tu, Y. Q. A General Approach from Eudesmane to Isodaucane Sesquiterpenes: Synthesis of 7-Epi-14-isocyano-isodauc-5-ene from α -(-)-Santonin. Synthesis 2003, 41-44. (j) Masutani, K.; Minowa, T.; Mukaiyama, T. Selective Synthesis of Isocyanides from

Secondary Alcohols by a New Type of Oxidation–Reduction Condensation. *Chem. Lett.* **2005**, *34*, 1124–1125. (k) Kitano, Y.; Manoda, T.; Miura, T.; Chiba, K.; Tada, M. A Convenient Method for the Preparation of Benzyl Isocyanides. *Synthesis* **2006**, 405–410. (l) Kaim, L. E.; Grimaud, L.; Schiltz, A. Isocyanide-Based Multicomponent Reaction 'without' Isocyanides. *Synlett* **2009**, 1401–1404. (m) Kaim, L. E.; Grimaud, L.; Schiltz, A. ''Isocyanide-Free'' Ugi Reactions. *Org. Biomol. Chem.* **2009**, *7*, 3024–3026. (n) Kaim, L. E.; Grimaud, L.; Schiltz, A. One-Pot Synthesis of Oxazoles Using Isocyanide Surrogates. *Tetrahedron Lett.* **2009**, *50*, 5235–5237. (o) Okada, I.; Kitano, Y. One-Pot Synthesis of Isocyanides from Alcohols. *Synthesis* **2011**, 3997–4002.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37 38 39

40 41

42

43

44

45

46

47

48

60

- (11) (a) Gassman, P. G.; Guggenheim, T. L. Opening of Epoxides with Trimethylsilyl Cyanide to Produce β-Hydroxy Isonitriles. A General Synthesis of Oxazolines and β-Amino Alcohols. J. Am. Chem. Soc. 1982, 104, 5849–5850. (b) Gassman, P. G.; Haberman, L. M. Regiospecific Opening of Oxetanes with Trimethylsilyl Cyanide–Zinc Iodide. A General Approach to γ-Amino Alcohols. Tetrahedron Lett, 1985, 26, 4971–4974. (c) Carr, S. A.; Weber, W. P. Zinc Iodide Catalyzed Reactions of Oxetanes With Trimethylsilyl Cyanide. Synth. Commun. 1985, 15, 775–781. (d) Gassman, P. G.; Haberman, L. M. Epoxide Opening with tert-Butyldimethylsilyl Cyanide-Zinc Iodide. Evidence for a Stepwise Process in the Opening of a Sterically Hindered Epoxide. J. Org. Chem. 1986, 51, 5010–5013.
 - (12) Imi, K.; Yanagihara, N.; Utimoto, K. Reaction of Cyanotrimethylsilane with Oxiranes. Effects of Catalysts or Mediators on Regioselectivity and Ambident Character. J. Org. Chem. 1987, 52, 1013–1016.
 - (13) Zhu, C.; Yuan, F.; Gu, W.; Pan, Y. The First Example of Enantioselective Isocyanosilylation of *meso* Epoxides with TMSCN Catalyzed by Novel Chiral Organogallium and Indium Complexes. *Chem. Commun.* **2003**, 692–693.
 - (14) Pronin, S. V.; Reiher, C. A.; Shenvi, R. A. Stereoinversion of Tertiary Alcohols to Tertiary-Alkyl Isonitriles and Amines. *Nature* 2013, 501, 195–199.
- (15) (a) Pronin, S. V.; Shenvi, R. A. Synthesis of a Potent Antimalarial Amphilectene. J. Am. Chem. Soc. 2012, 134, 19604–19606. (b) Daub, M. E.; Prudhomme, J.; Roch, K. L.; Vanderwal, C. D. Synthesis and Potent Antimalarial Activity of Kalihinol B. J. Am. Chem. Soc. 2015, 137, 4912–4915. (c) Lu, H.-H.; Pronin, S. V.; Antonova–Koch, Y.; Meister, S.; Winzeler, E. A.; Shenvi, R. A. Synthesis of (+)-7,20-

Diisocyanoadociane and Liver-Stage Antiplasmodial Activity of the Isocyanoterpene Class. J. Am. Chem. Soc. 2016, 138, 7268–7271. (d) Daub, M. E.; Prudhomme, J.; Mamoun, C. B.; Roch, K. G. L.; Vanderwal, C. D. Antimalarial Properties of Simplified Kalihinol Analogues. ACS Med. Chem. Lett. 2017, 8, 355–360. (e) Reiher, C. A.; Shenvi, R. A. Stereocontrolled Synthesis of Kalihinol C. J. Am. Chem. Soc. 2017, 139, 3647– 3650.

- (16) Tsuji, J. Palladium Reagents and Catalysts: New Perspectives for the 21st Century, John-Wiley & Sons Ltd. Chichester, 2004; pp 431–517.
- (17) (a) Tsuji, Y.; Yamada, N.; Tanaka, S. Cyanation of Allylic Carbonates and Acetates Using Trimethylsilyl Cyanide Catalyzed by Palladium Complex. J. Org. Chem. 1993, 58, 16–17. (b) Tsuji, Y.; Kusui, T.; Kojima, T.; Sugiura, Y.; Yamada, N.; Tanaka, S.; Ebihara, M.; Kawamura, T. Palladium-Complex-Catalyzed Cyanation of Allylic Carbonates and Acetates Using Trimethylsilyl Cyanide. Organometallics, 1998, 17, 4835–4841.
- (18) For recent chemo- and regioselective allylic substitution with the substrate bearing multiple nucleophilic sites, see (a) Miyabe, H.; Yoshida, K.; Yamauchi, M.; Takemoto, Y. Hydorxylamines as Oxygen Atom Nucleophiles in Transition-Metal-Catalyzed Allylic Substitution. J. Org. Chem. 2005, 70, 2148-2153. (b) Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. Selective Synthesis of Allylated Oxime Ethers and Nitrones Based on Palladium-Catalyzed Allylic Substitution of Oximes. J. Org. Chem. 2005, 70, 5630-5635. (c) Jung, B.; Hoveyda, A. H. Site- and Enantioselective Formation of Allene-Bearing Tertiary or Quaternary Carbon Stereogenic Centers through NHC-Cu-Catalyzed Allylic Substitution. J. Am. Chem. Soc. 2012, 134, 1490-1493. (d) Kumar, D.; Vemula, S. R.; Cook, G. R. Highly Chemo- and Regioselective Allylic Substitution with Tautomerizable Heteroarenes. Green Chem. 2015, 17, 4300-4306. (e) Jay, L. P.; Barker, T. J. Palladium-Catalyzed Synthesis of Allylic Ureas via an Isocyanate Intermediate. Eur. J. Org. Chem. 2016, 1829-1831.
- (19) The higher E/Z ratio of 1j in the isocyanation under air than that under argon atmosphere may be due to instability of the Z isomer under air.
- (20) $Pd(PPh_3)_4$ scarcely catalyzed the rearrangement under the same conditions.

