

The Cyanation of Vinyl Halides with Alkali Cyanides Catalyzed by Nickel(0)–Phosphine Complexes Generated In Situ: Synthetic and Stereochemical Aspects

Yasumasa Sakakibara, Hiroji Enami, Hiroshi Ogawa, Shinpei Fujimoto, Hiroyuki Kato, Katsumi Kunitake, Ken Sasaki,* and Mutsuji Sakai

Department of Polymer Science and Engineering, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606

(Received April 10, 1995)

The cyanation of β -bromostyrenes catalyzed by $\text{Ni}(\text{PPh}_3)_n$, which was generated in situ from $\text{NiBr}_2(\text{PPh}_3)_2\text{-Zn-PPh}_3$ ($\text{Ni}:\text{Zn}:\text{P}=1:3:2$ molar ratio), was at first examined with various MCN ($\text{M}=\text{K}, \text{Na}$)-dipolar aprotic solvent systems by several procedures. The presence of excess cyanide ion inhibited the reaction. However, when the KCN–DMF system with some intermediate cyanide solubility was used, the nitriles were obtained in high yields and high stereoselectivity at 50 °C by almost all of the procedures attempted. On the contrary, the KCN–HMPA and KCN–MeCN systems with low cyanide solubilities accelerated the coupling of the halides to inhibit the cyanation, and in general the NaCN–DMF and NaCN–HMPA systems with high cyanide solubilities needed to reduce Ni(II) before adding MCN in order to make the catalytic reaction start. Vinyl halides such as 1- and 2-halo (Cl, Br)-1-alkenes, 2-bromo-2-butenes, 3-bromo-3-hexenes, and 1-chlorocyclohexene were also cyanated using suitable procedures and MCN–solvent systems to give the corresponding nitriles in high yields and fair-to-good stereoselectivities. However, with (*Z*)-2-ethoxy-1-bromoethene the (*E*)-nitrile, though its selectivity markedly varied with the reaction temperature, was obtained as the main product. The cyanation of ethyl (*Z*)- β -bromoacrylate and ethyl α -bromoacrylate was unsuccessful due to polymerization.

Stereoselective cyanation of vinyl halides is of considerable importance in synthetic methodology. Some metal cyanides, such as CuCN ,^{1–3} $\text{NaCu}(\text{CN})_2$,^{3,4} $\text{K}_4\text{Ni}_2(\text{CN})_6$,^{5–7} and $(\text{Et}_3\text{MeN})_3\text{Co}(\text{CN})_5$,⁸ are known to be effective for the stoichiometric synthesis of cinnamonitriles from β -bromostyrenes. On the other hand, it has been reported that $\text{Pd}(\text{PPh}_3)_4$ -crown ether^{3,9} and $[\text{Co}(\text{CN})_4]^{3-}$, which is formed in an aqueous alkaline solution of $[\text{Co}(\text{CN})_5]^{3-}$ under a hydrogen atmosphere,^{10,11} catalyze the cyanation of vinyl halides with KCN. We reported, in preliminary form, on the cyanation of vinyl halides with KCN catalyzed by $\text{Ni}(\text{PPh}_3)_n$ ($n=3$ or 4), which was generated in situ from $\text{NiBr}_2(\text{PPh}_3)_2\text{-Zn-PPh}_3$ ¹² (Chart 1). We have more closely studied the cyanation of various vinyl halides in order to clarify the scope and limitations of this method. This paper deals with these results.

Experimental

Materials. All of the solvents were purified by ordinary methods. The KCN, NaCN, zinc dust, and triphenylphosphine (Nacalai) were commercially available. Dibromobis(triphenylphosphine)nickel was prepared by a literature

method.¹³

Pure (*E*)- β -bromostyrene was obtained by the purification of commercial β -bromostyrene,¹⁴ whereas pure (*Z*)- β -bromostyrene was prepared by a literature method.^{14,15} (*E*)-1-Chloro-1-hexene, (*E*)-1-bromo-1-hexene, and (*E*)-3-bromo-3-hexene were prepared by reactions of the corresponding alkenylpentafluorosilicates,^{16,17} derived from alkynes, with copper(II) halides.^{18,19} (*Z*)-1-Bromo-1-hexene and (*Z*)-3-bromo-3-hexene were prepared by a method of Brown et al.²⁰ 2-Bromo-1-hexene,^{21,22} and (*E*)- and (*Z*)-2-bromo-2-butenes²³ were prepared from 1-hexene and *trans*- and *cis*-2-butenes, respectively, via bromination–dehydrobromination. 1-Chloro-2-methyl-1-propene from Tokyo Kasei was used without further purification. 1-Chlorocyclohexene²⁴ and ethyl (*Z*)- β -bromoacrylate²⁵ were prepared by literature methods. (*Z*)-1-Bromo-2-ethoxyethene²⁶ and ethyl α -bromoacrylate^{27,28} were prepared from ethyl vinyl ether and ethyl acrylate, respectively, via bromination–dehydrobromination.

Procedures. Six procedures were attempted for cyanation. A typical example of each is described below.

Procedure A: A 30 ml flask was charged with $\text{NiBr}_2(\text{PPh}_3)_2$ (740 mg, 1.0 mmol), Zn dust (196 mg, 3.0 mmol), PPh_3 (520 mg, 2.0 mmol), and KCN (2.54 g, 39 mmol; fine powder). The mixture was degassed by evacua-

tion and flushed with nitrogen; a solution of (*E*)- β -bromostyrene (5.49 g, 30 mmol) and dibenzyl ether (about 0.3 g, GC internal standard) in DMF (8 ml) was then added by syringe while stirring. The reaction mixture was kept at 50 °C for 16 h. Small aliquots of the mixture were withdrawn and, after bubbling air, subjected to GC analysis (Run 6 in Table 1).

Procedure A': The catalyst components and MCN (M=K or Na) were placed in a flask. After replacing the air with nitrogen, a solvent was added by syringe while stirring. The mixture was heated at 40 °C for 40 min and, after adding a substrate, kept at a specified temperature during the reaction period.

Procedures B and B': Only the catalyst components were placed in a flask whose side arm was connected by means of a ground-glass joint to an MCN container. After replacing the air with nitrogen, a solvent was added by syringe. After the mixture was heated at 40 °C for 40 min with stirring, a substrate was added at the specified reaction

temperature. After continued heating for 30 min, MCN was added from the MCN container, and the reaction mixture was kept under the specified reaction conditions (Procedure B). With Procedure B', MCN was added immediately after adding the substrate.

Procedures C and C': These procedures were the same as Procedure B and B', respectively, except that the order of the addition of the substrate and MCN was reversed.

Analysis. Gas chromatographic analyses were made with He carrier gas (TCD detector) using a 5-m PEG-20M column for β -bromostyrenes, 1-halo-1-hexenes, 2-bromo-1-hexene, 2-bromo-2-butenes, 3-bromo-3-hexenes, and 1-chlorocyclohexene; a 3-m Silicone DC-200 column for 1-chloro-2-methyl-1-propene; and a 3-m EGS column for 1-bromo-2-ethoxyethene. The analyses for ethyl (*Z*)- β -bromoacrylate and ethyl α -bromoacrylate were made with N₂ carrier gas (FID detector) using a 3-m Silicone OV-3 and a 3-m Silicone XE-60, respectively. All products, except for 2-ethyl-2-

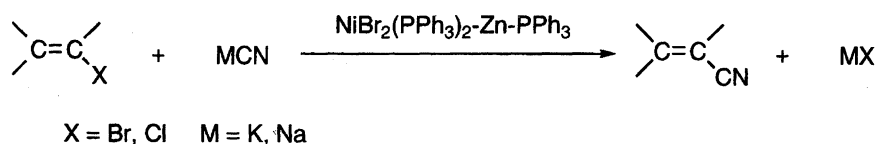


Chart 1.

Table 1. Cyanation of β -Bromostyrenes

Run	Solvent	MCN	Procedure ^{a)}	Temp	Conv.	Nitrile		Coupling	
				°C	%	Yield/%	E/Z	product/(% ^{b)})	
<i>(E)</i> -PhCH=CHBr									
1	HMPA	KCN	(1.5) ^{c)}	A	50	33	5	99/1	11
2	MeCN	KCN	(1.9)	A	50	37	4	99/1	16
3	DNF	KCN	(15.0)	A	40	55	48	97/3	0
4				A	50	2 ^{d)}	0		
5				A	50	68	66	96/4	0
6				A	50	100 ^{e)}	99	95/5	0
7				A	60	37	17	99/1	11
8				A'	50	100	94	95/5	0
9	DMF	NaCN	(127)	A	50	84	72	95/5	4
10				A'	50	17	7	89/11	-
11				B	50	41	21	90/10	7
12				C	50	97	95	94/6	0
13	DMSO	KCN	(131)	A	50	32	29	91/9	0
14	HMPA	NaCN	(467)	B	50	53	29	98/2	6
15				C	50	84	63	97/3	3
<i>(Z)</i> -PhCH=CHBr									
16	DMF	KCN	(15.0)	A	50	55 ^{f)}	43	7/93	3
17				A	50	96	82	12/88	4
18				A'	50	8	7	34/66	0
19				B	50	100	83	18/82	8
20				C	50	100	84	22/78	6
21	DMF	NaCN	(127)	A	50	5	4	39/61	1
22				B	50	14	11	52/48	2
23				C	50	19	13	45/55	0

- a) See Experimental section. NiBr₂(PPh₃)₂, 1 mmol (Ni:Zn:P=1:3:2 molar ratio); β -Bromostyrene, 30 mmol; MCN, 39 mmol; Solvent, 8 ml; Time, 8 h. b) Total yield of (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-1,4-diphenyl-1,3-butadienes. c) Solubility (mmol dm⁻³) of MCN at 60 °C. d) Carried out without catalyst. e) Reaction time, 16 h. f) Reaction time, 4 h.

pentenenitriles, were identified by comparisons with authentic samples which were commercially available or prepared by known methods.

Isolation of Nitriles. The isolation of four nitriles is exemplified.

(*E*)-2-Methyl-2-butenenitrile: (*E*)-2-Bromo-2-butene (4.05 g, 30 mmol) was allowed to react with NaCN (1.91 g, 39 mmol) in the presence of the Ni catalyst ($\text{NiBr}_2(\text{PPh}_3)_2$, 1 mmol; Ni:Zn:P=1:3:2 molar ratio) in HMPA (12 ml) at 30 °C for 8 h by Procedure C'. The reaction mixture was poured into water (30 ml), and then extracted twice with ether (30 ml). The combined extracts were washed with water (8 ml), dried (Na_2SO_4), and concentrated. The residue was distilled to give 1.61 g (66%) of 2-methyl-2-butenenitriles (*E*/*Z*=98/2). The pure *E* isomer was obtained by fractional distillation. Bp 72 °C/90 mmHg (1 mmHg=133.322 Pa); n_D^{20} 1.4341 (lit.²⁹) bp 73 °C/90 mmHg; n_D^{20} 1.4334; IR (CCl_4) 2220 cm^{-1} (CN); $^1\text{H NMR}$ (CCl_4) δ =1.80 (3H, d), 1.85 (3H, s), and 6.35 (1H, m); MS 81 (M^+).

(*E*)-2-Ethyl-2-pentenenitrile: (*E*)-3-Bromo-3-hexene (4.89 g, 30 mmol) was allowed to react with NaCN (1.91 g, 39 mmol) in the presence of the nickel catalyst (1 mmol) in DMF (12 ml) at 40 °C for 12 h by Procedure C'. The reaction mixture was worked up in a similar manner as above. Distillation gave 2.46 g (75%) of 2-ethyl-2-pentenenitriles (*E*/*Z*=98/2). The pure *E* isomer was obtained by fractional distillation. Bp 67–68 °C/15 mmHg; n_D^{21} 1.4390 (lit.³⁰) bp 88–89 °C/15 mmHg; n_D^{23} 1.4383; $^1\text{H NMR}$ (CCl_4) δ =1.04 (6H, m), 2.18 (4H, m), and 6.19 (1H, t); MS 109 (M^+).

(*Z*)-2-Ethyl-2-pentenenitrile: (*Z*)-3-Bromo-3-hexene (4.89 g, 30 mmol) was cyanated similarly to (*E*)-3-bromo-3-hexene but at 60 °C for 24 h. Distillation gave 2.66 g (81%) of 2-ethyl-2-pentenenitriles (*E*/*Z*=15/85). The pure *Z* isomer was obtained by fractional distillation. Bp 54–55 °C/20 mmHg; n_D^{22} 1.4310 (lit.³⁰) bp 155–156 °C; n_D^{23} 1.4305; $^1\text{H NMR}$ (CCl_4) δ =1.07 (6H, m), 2.26 (4H, m), and 6.05 (1H, t); MS 109 (M^+).

(*E*)-3-Ethoxyacryronitrile: (*Z*)-1-Bromo-2-ethoxyethene (4.53 g, 30 mmol) was allowed to react with KCN (2.54 g, 39 mmol) in the presence of the nickel catalyst (1 mmol) in DMF (12 ml) at 0 °C for 4 h by Procedure A. The reaction mixture was poured into a saturated aq NaCl (30 ml) and then extracted three times with ether (30 ml). The combined extracts were dried (Na_2SO_4) and concentrated. The residue was distilled to give 2.09 g (72%) of 3-ethoxyacryronitrile (*Z*/*E*=20/80). Pure *E* isomer was obtained by fractional distillation. Bp 77–78 °C/15 mmHg; n_D^{20} 1.4535 (lit.³¹) bp 76–78 °C/15 mmHg; n_D^{25} 1.4510; IR (CCl_4) 2212 cm^{-1} (CN); $^1\text{H NMR}$ δ =1.73 (3H, t), 3.91 (2H, q), 4.59 (1H, d, *J*=13 Hz) and 7.14 (1H, d, *J*=13 Hz); MS 97 (M^+).

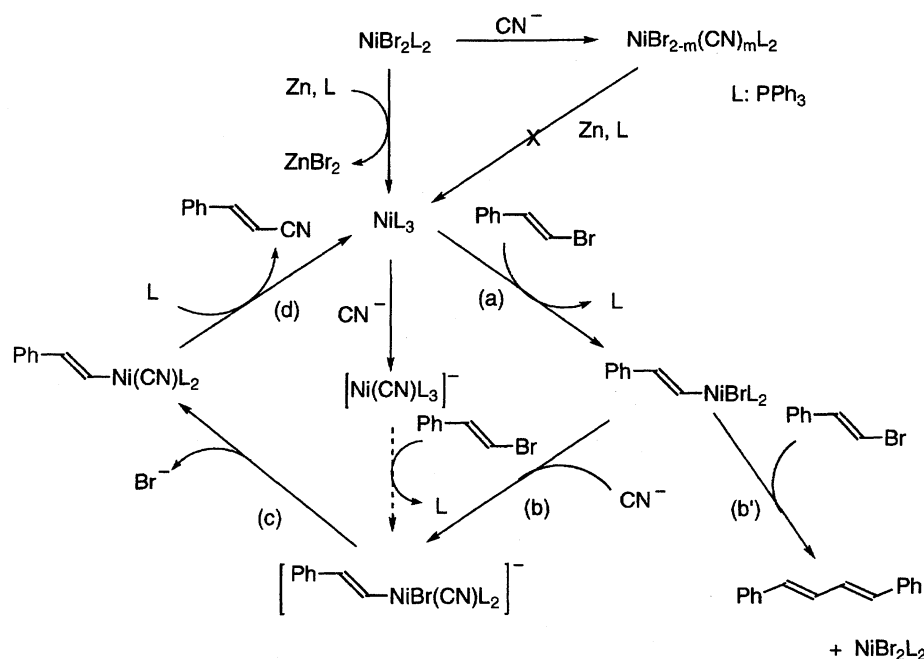
Results and Discussion

We presented, in preliminary form,¹²⁾ a new and convenient method for the stereoselective preparation of 2-alkenenitriles from vinyl halides and KCN by the use of a catalytic amount of $\text{Ni}(\text{PPh}_3)_n$ which is easily generated in situ from $\text{NiBr}_2(\text{PPh}_3)_2\text{-Zn-PPh}_3$. During the course of a further investigation of the catalytic cyanation, it was noticed that the presence of excess cyanide ion and the coupling reaction of vinyl halides, being

the main side reaction, inhibit cyanation, as observed by us³²⁾ in the Ni(0) catalyzed cyanation of chlorobenzene (vide infra). Accordingly, much attention should be paid to the selection of the MCN-solvent system and reaction procedure.

Cyanation of β -Bromostyrenes. Cyanation with MCN (*M*=K, Na) of β -bromostyrenes catalyzed by $\text{Ni}(\text{PPh}_3)_n$, which was generated in situ from $\text{NiBr}_2(\text{PPh}_3)_2\text{-Zn-PPh}_3$ (Ni:Zn:P=1:3:2 molar ratio), was examined with various MCN-dipolar aprotic solvent systems by means of four procedures: A (catalyst-reactant mixing without pretreatment), A' (catalyst reduction in the presence of MCN-halide addition), B (catalyst reduction-halide addition-cyanide addition), and C (catalyst reduction-cyanide addition-halide addition) (see Experimental section for further details). In the catalytic cyanation of chlorobenzene³²⁾ it was observed by us that the presence of excess cyanide ion inhibits the reaction. However, when certain MCN-dipolar aprotic solvent systems with low cyanide solubilities were used, the cyanation of chlorobenzene proceeded very well by Procedure A, which is most convenient, rather than by Procedures B and C. On the other hand, in the use of MCN-solvent systems with high cyanide solubilities, the cyanation proceeded only by Procedure B. Thus, the cyanation of β -bromostyrenes was attempted by the four procedures and various MCN-solvent systems in order to clarify the aspect of catalytic cyanation and to compare with the cyanation of chlorobenzene. The results are shown, together with the solubilities of MCN, in Table 1. The reaction proceeded catalytically under suitable conditions to give cinnamionitriles together with trace to small amounts of 1,4-diphenylbutadienes, which are coupling products of β -bromostyrene. The pathways for their formation are proposed by reference to the cyanation of aromatic halides reported by us³²⁾ and Cassar et al.,³³⁾ as shown in Scheme 1.

In contrast with chlorobenzene and bromobenzene,³²⁾ (*E*)- β -bromostyrene was not cyanated smoothly by the most convenient procedure A with the KCN-HMPA and KCN-MeCN systems (Runs 1 and 2). In both of these systems with low cyanide solubilities, the coupling reaction of (*E*)- β -bromostyrene, which accompanied the formation of an inactive Ni(II) complex, occurred in preference to its cyanation, and, therefore, the catalyst was deactivated during the early stage of reaction (step (b') in Scheme 1). However, the KCN-DMF system with a higher solubility gave much better results. For example, at 50 °C, which was a most favorable temperature, cinnamionitriles were obtained in 66% yield (97% selectivity) and *E*/*Z*=96/4 (Run 5), though not formed in the absence of the catalyst (Run 4). At a longer reaction time of 16 h, a best yield of 99% was obtained while maintaining a high stereoselectivity of *E*/*Z*=95/5 (Run 6). On the other hand, a higher reaction temperature of 60 °C was unfavorable on account of an acceleration of



Scheme 1.

the coupling reaction (Run 7). Interestingly, compared with Procedure A (Run 5), Procedure A' brought about a high reaction rate to give cinnamitriles in 94% yield ($E/Z=95/5$ at 8 h (Run 8).

With the NaCN-DMF system, which bears a much higher cyanide solubility, (E)- β -bromostyrene was favorably cyanated by Procedures A and C (Runs 9 and 12) in contrast with chlorobenzene. Especially, Procedure C gave cinnamitriles in a satisfactory yield of 95% ($E/Z=94/6$) without accompanying the coupling reaction. With the above system, the cyanation of chlorobenzene was presumed to be inhibited due to the formation of no reducible cyanonickel(II) complexes, $\text{NiBr}_{2-m}(\text{CN})_m(\text{PPh}_3)_2$, with Procedure A and the formation of a coordinatively less reactive cyanonickel(0) complex, $[\text{Ni}(\text{CN})(\text{PPh}_3)_3]^-$, with Procedure C (Scheme 1).³² This difference in reactivity between both halides may be caused by the fact that vinyl halides easily undergo the oxidative addition (step (a) in Scheme 1) to Ni(0) complexes compared with aryl halides.^{34,35} Generally, however, Procedures A and A' were unfavorable with MCN-solvent systems bearing high cyanide solubilities, as exemplified by Runs 13 and 10. With such systems, Procedures B and C, though being somewhat troublesome, may be expected to be preferable to Procedures A and A', because Ni(II) is reduced beforehand to Ni(0) without undergoing inhibition due to the cyanide ion. In fact, cyanation was started by Procedures B and C with the NaCN-DMF and NaCN-HMPA systems. However, Procedure B did not give satisfactory results (Runs 11 and 14) due to the coupling reaction accompanying the deactivation of the catalyst, while Procedure C gave good results despite inhibition due to the formation of $[\text{Ni}(\text{CN})(\text{PPh}_3)_3]^-$ (Runs 12 and 15). Such results by Procedure C are

presumed to be due to a strong coordination ability of (E)- β -bromostyrene.³⁶

In the cyanation of (Z)- β -bromostyrene, the KCN-DMF system (Runs 16–20) gave much better results than the NaCN-DMF system (Runs 21–23). With the former system, the cyanation proceeded smoothly by all procedures, except for Procedure A', which gave a good result for the (E)-bromide; Procedure A gave the best result of 82% yield and $E/Z=12/88$ (Run 17). Furthermore, with Procedure A and the KCN-DMF system the (Z)-bromide was cyanated more rapidly than the E -isomer (Runs 17 and 5), although it has been reported that the former has a low ability for the oxidative addition to Ni(0), compared with the latter.^{37,38} In general, however, the stereoselectivity was somewhat low compared with that of the E -isomer. With the NaCN-DMF system bearing a much higher cyanide solubility, the (Z)-bromide was hardly cyanated, even by Procedures B and C, in contrast to the E -isomer. This is presumed to be due to a low ability of the former for the coordination-oxidative addition (as described above).

Cyanation of Various Vinyl Halides. The results of the cyanation of β -bromostyrenes suggest that MCN-solvent systems, such as KCN-HMPA and KCN-MeCN, with low cyanide solubilities and high temperature make the coupling reaction rather rapid to deactivate the catalyst. The cyanation of several types of vinyl halides was examined by using the KCN-DMF, NaCN-DMF, and NaCN-HMPA systems with higher cyanide solubilities (See Table 1). A part of the results is listed in Table 2. Generally, most vinyl halides were cyanated at low temperature with the KCN-DMF system by Procedure A. With certain vinyl halides, however, better results in the yield and stereoselectivity

Table 2. Cyanation of Various Vinyl Halides

Run	Halide	MCN	Solvent	Procedure ^{a)}	Temp	Time	Conv.	Nitrile	
					°C	h	%	Yield/%	E/Z
1	(<i>E</i>)-BuCH=CHCl ^{b)}	KCN ^{c)}	DMF ^{d)}	A	50	8	71	50	100/0
2	(<i>E</i>)-BuCH=CHBr	KCN ^{c)}	DMF ^{d)}	A'	50	8	77	69	98/2
3	(<i>Z</i>)-BuCH=CHBr	KCN ^{c)}	DMF ^{d)}	A'	50	8	83	80	14/86
4	BuC(Br)=CH ₂	KCN ^{c)}	DMF ^{d)}	A'	50	8	67	62	
						16	100	90	
5	Me ₂ C=CHCl	KCN	DMF	A	50	8	85	68	
6		NaCN	DMF	B	50	8	98	71	
7				B'	50	8	97	87	
8	(<i>E</i>)-MeCH=CMeBr	KCN	DMF	A	50	4	93	69	91/9
9		NaCN	HMPA	B'	30	8	100	73	92/8
10				C'	30	8	100	81	97/3
11	(<i>Z</i>)-MeCH=CMeBr	KCN	DMF	C'	30	8	99	94	26/74
12		NaCN	DMF	C'	30	8	50	45	18/82
13					40	8	100	96	11/89
14					50	8	99	91	19/81
15		NaCN	HMPA	C'	40	8	32	27	23/77
16					50	8	99	84	27/73
17	(<i>E</i>)-EtCH=CEtBr	NaCN	DMF	C'	40	8	67	61	98/2
						20	100	97	98/2
18	(<i>Z</i>)-EtCH=CEtBr	NaCN	DMF	C'	60	40	98	92	13/87
19	1-Cl-C ₆ H ₉ ^{e)}	KCN ^{c)}	DMF ^{d)}	A	50	16	99	92	
20	(<i>Z</i>)-EtOCH=CHBr	KCN	DMF	C'	-10	4	100	87	84/16
21					10	4	100	90	75/25
22					30	4	62	33	54/46
23	(<i>Z</i>)-EtO ₂ CCH=CHBr	KCN	DMF	C'	50	2	52	11	48/52
24	CH ₂ =CBrCO ₂ Et	KCN	MeCN	C'	20	6	80	0	

a) See Experimental section. NiBr₂(PPh₃)₂, 0.5 mmol (Ni:Zn:P=1:3:2 molar ratio); Halide, 15 mmol; MCN/halide=1.3 molar ratio; Solvent, 6 ml. b) Halide, 10 mmol. c) MCN/halide=1.1 molar ratio. d) Solvent, 4 ml. e) 1-Chlorocyclohexene.

were obtained by using the NaCN–DMF system with high cyanide solubilities by Procedure C'; this was probably due to a suppression of the coupling reaction due to the high cyanide concentration.

First, the cyanation of 1- and 2-halo-1-alkenes bearing a terminal double bond was examined by Procedures A and A' with the KCN–DMF. With 1- and 2-bromo-1-hexenes (Runs 2–4), the reaction did not go to completion at 50 °C and 8 h; however, they were converted into the corresponding nitriles in high selectivity (> 90% based on the bromides consumed). At a longer reaction time of 16 h, 2-bromo-1-hexene reacted completely to give the nitrile in a high yield of 90%. 1-Chloro-1-hexene, though being only slightly reactive compared with the corresponding bromide, was also cyanated under such mild conditions (Run 1). Concerning the stereoselectivity, although (*E*)-1-chloro- and (*E*)-bromo-1-hexenes showed high values (*E*>98%), (*Z*)-1-bromo-1-hexene was not as good as the *E*-isomer (*E*/*Z*=14/86). 1-Chloro-2-methyl-1-propene, which bears two alkyl groups at the 2-position, was also smoothly cyanated by any of Procedure A with the KCN–DMF system and Procedures B and B' with the NaCN–DMF system (Runs 5–7). Especially, with the NaCN–DMF system, Procedure B', in which NaCN is introduced immediately after adding the halide, suppressed the formation

of the coupling product compared with Procedure B, and gave a good result of 87% yield at 97% conversion.

Next, the cyanation of 2-bromo-2-butenes and 3-bromo-3-hexenes, bearing an internal double bond, was examined in some detail because 3-halo-3-hexenes were unsatisfactorily cyanated by Procedure A with the KCN–DMF system, as exemplified in a preliminary communication.¹²⁾ With (*E*)-2-bromo-2-butene, the reaction proceeded smoothly compared with 1-bromo-1-hexenes by Procedure A and the KCN–DMF system; however, 2-methyl-2-butenenitriles were not obtained in satisfactory yield and stereoselectivity (69% yield at 93% conversion; *E*/*Z*=91/9) (Run 8). Thereupon, cyanation was attempted by Procedure C' in addition to Procedure B' using the NaCN–HMPA system with a high cyanide solubility. Procedure C' may be expected to diminish both the inhibitory action of cyanide ion and the formation of a coupling product by introducing the halide immediately after adding NaCN to the Ni(0) complex generated in situ. As a result, it was found that the halide was smoothly cyanated without undergoing inhibition due to the cyanide ion at a low temperature of 30 °C by both of the procedures, and that Procedure C' gave a better result (81% yield; *E*/*Z*=97/3) than that of Procedure B' (73% yield; *E*/*Z*=92/8) (Runs 10 and 9). In the cyanation of (*Z*)-2-bromo-2-butene by

Procedure C' the NaCN-DMF system was most suitable among three systems (KCN-DMF, NaCN-DMF, and NaCN-HMPA (Runs 11–16)) giving 2-methyl-2-butenenitriles in a high yield of 96% and a fairly high stereoselectivity of $E/Z=11/89$ at 40 °C, which was a most suitable temperature (Run 13). It is noteworthy that the reaction rate in NaCN-DMF at 40 °C was much more rapid than that in NaCN-HMPA (Run 15). With the NaCN-HMPA system, however, 3-bromo-3-hexenes were not satisfactorily cyanated by Procedure C'. This was probably due to an increase in inhibition of the cyanide ion with a decreasing coordination ability of the halides to Ni(0): 2-bromo-2-butenes > 3-bromo-3-hexenes. However, both (*E*)- and (*Z*)-3-bromo-3-hexenes were cyanated by Procedure C' using the NaCN-DMF system with a low cyanide solubility compared with NaCN-HMPA. With (*E*)-3-bromo-3-hexene, a good result of 97% yield of 2-ethyl-2-pentenitriles and $E/Z=98/2$ was obtained at 40 °C and 20 h (Run 17). (*Z*)-3-bromo-3-hexene, though being less reactive, was cyanated at 60 °C and 40 h to give the nitriles in 92% yield and $E/Z=13/87$ (Run 18). In order to see if the stereoselectivity in the cyanation of the (*Z*)-bromide changes through the reaction period, the variations in the yield of the nitrile and the selectivity of the (*Z*)-nitrile with the reaction time were also examined (Fig. 1). The selectivities of the (*Z*)-nitrile, being somewhat low at an early stage of the reaction, were 66, 82, and 85% at 1 h (7% yield), 4 h (23%), and 8 h (35%), respectively, and, after that, almost constant at 87%. Furthermore, this synthetic method was applicable to 1-chlorocyclohexene. The chloride was cyanated in a

high yield of 92% by Procedure A with the KCN-DMF system (Run 19).

The cyanation was applied to vinyl halides bearing a functional group at the carbon in the α or β position. In the presence of the catalyst (*Z*)-1-bromo-2-ethoxybutene was cyanated by Procedures A and C' with the KCN-DMF system, while not by Procedure C' with the NaCN-DMF system. In this connection, it has been reported by Prochazka and Siroky³⁾ that the halide was not cyanated with KCN in benzene at 80 °C under a catalysis with $\text{Pd}(\text{PPh}_3)_4$ and 18-crown-6-ether. By Procedure C' with KCN-DMF the cyanation proceeded rapidly, even at a low temperature of –10 °C to give 3-ethoxy-2-propenenitriles in good yield (87%) (Run 20). Interestingly, the (*E*)-nitrile was formed as a major product ($E/Z=84/16$). The selectivity of the (*Z*)-isomer increased with increasing temperature from 16% at –10 °C to 46% at 30 °C (Runs 20–22). However, the selectivity at each temperature attempted was almost constant over the reaction period, e.g., being about 25% at 10 °C (Fig. 2). This suggests that the (*Z*)-nitrile does not isomerize to the *E*-isomer during the course of the reaction and that the formation of the *E*-isomer is mainly caused by the isomerization of the vinylnickel complex formed by the oxidative addition of 1-bromo-2-ethoxyethene to Ni(0). With ethyl (*Z*)- β -bromoacrylate a favorable result was not obtained because of a rapid polymerization of both the bromide and the nitrile formed. For example, the bromide reacted at 50 °C by Procedure C' with the KCN-DMF system; the yield of ethyl β -cyanoacrylate, however, was 11% ($Z/E=48/52$) at 52% conversion (Run 23) and

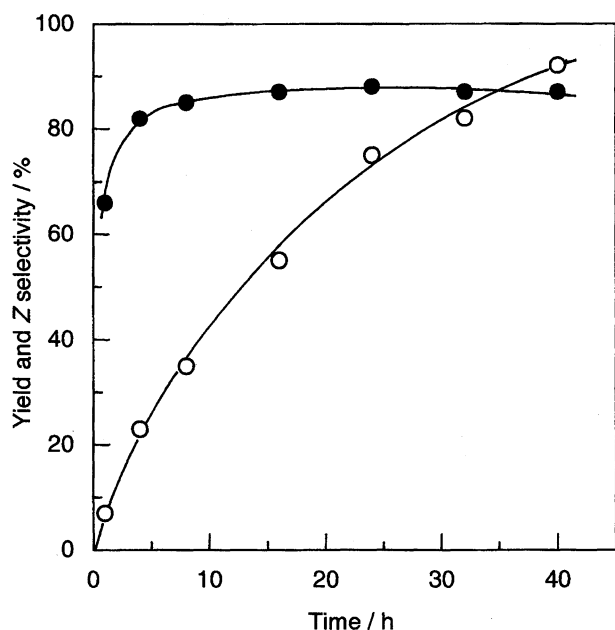


Fig. 1. Variation of yield and stereoselectivity with time in cyanation of (*Z*)-3-bromo-3-hexene. Reaction conditions: See Run 18. ○: Yield, ●: $Z \text{ Selectivity} = 100 \times [Z/(Z+E)]$.

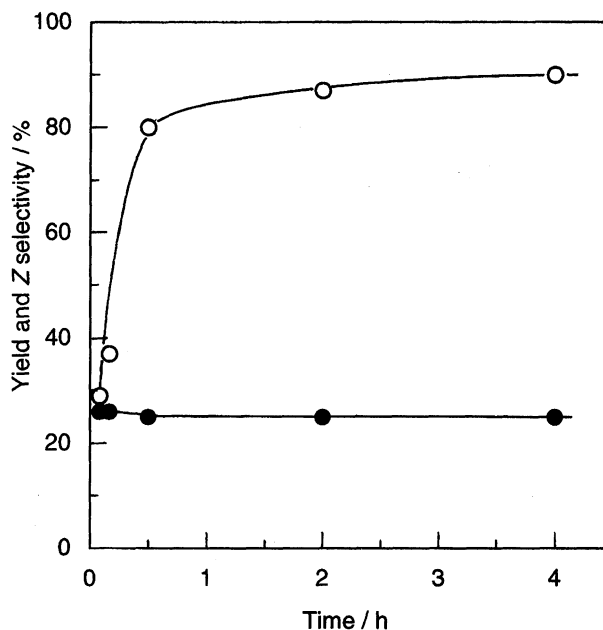


Fig. 2. Variation of yield and stereoselectivity with time in cyanation of (*Z*)-1-bromo-2-ethoxyethene. Reaction conditions: See Run 21. ○: Yield, ●: $Z \text{ Selectivity}$.

decreased to 8% at 75% conversion. Without the catalyst the yield did not exceed 2% under the same conditions, although vinyl halides bearing electron-withdrawing groups at the carbon in the β position are susceptible to nucleophilic attacks.³⁹⁾ The cyanation of ethyl α -bromoacrylate was examined by Procedures B' and C' using MCN–MeCN, MeCOMe, or THF because α -bromoacrylate and α -cyanoacrylate appeared to be extremely apt to polymerize in DMF and HMPA as a solvent. However, these attempts were unsuccessful due to polymerization of their acrylates, as exemplified by the KCN–MeCN system⁴⁰⁾ (Run 24).

The present work was partially supported by a Grant-in-Aid for Scientific Research No. 354172 from the Ministry of Education, Science and Culture.

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- 35) When a mixture of equal amounts (each 15 mmol) of (*E*)- β -bromostyrene and bromobenzene was allowed to react under the conditions similar to those of Run 8 in Table 1, the yield of cinnamonnitriles at 4 h was 93% in constant to 1% for benzonitrile, suggesting a strong coordination ability of (*E*)- β -bromostyrene compared with bromobenzene.
- 36) It is suggested that oxidative addition of vinyl halides proceeds by an initial π -coordination to metal: a) J. P. Collman and L. S. Hegedus, "Principles and Applications of Organotransition Metal Chemistry," University Science Books, Mill Valley, California (1980), p. 203; b) J. Rajaram, R. G. Pearson, and J. A. Ibers, *J. Am. Chem. Soc.*, **96**, 2103 (1974).
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- 38) A mixture of equal amounts (each 15 mmol) of (*E*)- and (*Z*)- β -bromostyrenes was allowed to react under the conditions similar to those of Run 17 in Table 1. Consequently, the initial relative rate, $E/Z=2.5$, observed suggests that the (*E*)-bromide undergoes the coordination-oxidative addition more rapidly than the *Z*-isomer.
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