Acylcyanation of Terminal Acetylenes: Palladium-Catalyzed Addition of Aryloyl Cyanides to Arylacetylenes

Kyoko Nozaki, Naomasa Sato, and Hidemasa Takaya*

Division of Material Chemistry, Faculty of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-01, Japan

Summary: Two different electron-withdrawing carbon substituents (aryloyl group and nitrile group) were introduced into terminal arylacetylenes by a new method, palladium-catalyzed intermolecular acylcyanation of the acetylenic bonds.

Vicinal difunctionalization of terminal alkynes with carbon moieties is of much interest in organic synthesis as a simultaneous construction of two carbon–carbon bonds. Organopalladium chemistry has been widely used for this purpose,[1,2] but the functional groups so far employed are limited.[3] In this paper, we describe a new method to introduce two electron-withdrawing carbon substituents (aryloyl group and nitrile group) into terminal arylacetylenes via palladium-catalyzed intermolecular acylcyanation of the acetylenic bonds.[4]

First, an addition of acyl cyanides[5] on arylacetylenes has been investigated. When 4-toluoyl cyanide was allowed to react with phenylacetylene in the presence of Pd(OAc)$_2$, PPh$_3$ (1 equiv to Pd), and 1,4-bis(diphenylphosphino)-butane (dppb, 0.5 equiv to Pd) in 1,2-dichloroethane at 70 °C for 65 h,[6] acylcyanated β-cyano α,β-unsaturated ketone (Z)-**1a** was obtained in 74% yield accompanied by trace amounts of its regio isomer (E)-**2a** and acetylenic ketone **3a** (eq 1 and entry 1 of Table 1).[7,8] Reactions of other terminal arylacetylenes and aryloyl cyanides gave the
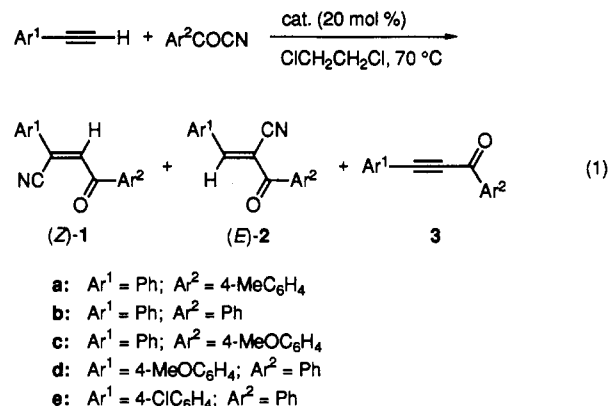
corresponding adducts (Z)-**1** in good yields (entries 2–5 in Table 1). When the reactions were stopped after 20 h, smaller amounts of (Z)-**1** were formed while **3** was formed in higher amounts (entries 1 and 6, 2 and 10, 3 and 11). The catalyst system Pd(OAc)$_2$–2PPh$_3$ was less effective than the mixed ligand system (entries 6 and 7), and the starting materials were recovered by the use of Pd(OAc)$_2$–dppb (entry 8) as catalyst. The yield of (Z)-**1a** by using Pd(OAc)$_2$–PPh$_3$–Ph$_2$PMe was comparable to that with Pd-(OAc)$_2$–PPh$_3$–0.5dppb (entries 6 and 9). The ligands and the ratio of phosphines to palladium complexes were essential to control the product ratios.[9] Remarkable solvent effect was also observed. The yield of the regio isomer (E)-**2a** increased in toluene (entry 12), and the selective synthesis of **3a** was accomplished in THF by use of catalyst system Pd(OAc)$_2$–2PPh$_3$ (entry 13). The use

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(1) Carbopalladation of alkynes with aryl- or alkenylpalladium species has mostly been used. For recent examples of palladium-catalyzed C–C bond-forming functionalization of alkynes, see: (a) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1985,** *41,* 5121. (b) Burns, B.; Grigg, R.; Sridharan, V.; Worakun, T. *Tetrahedron Lett.* **1988,** *29,* 4325. (c) Trost, B. M.; Lee, D. C. *J. Am. Chem. Soc.* **1988,** *110,* 7255. (d) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989,** *111,* 3454.

(2) Other carbometalation process of alkynes. (a) Review article: Normant, J. F.; Alexakis, A. *Synthesis* **1981,** 841. (b) Carbocupration: Jabri, N.; Alexakis, A.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1983,** 321, 332. (c) Carboalumination and carbozincation: Zweifel, G.; Miller, J. A. *Org. React.* **1984,** *32,* 375. Negishi, E.; Takahashi, T. *Aldrichim. Acta* **1985,** *18,* 31.

(3) (a) Vicinal dicarbomethoxylation of alkynes by use of palladium catalysts: Heck, R. F. *J. Am. Chem. Soc.* **1972,** *94,* 2712. (b) Alper, H.; Despeyroux, B.; Woell, J. B. *Tetrahedron Lett.* **1983,** *24,* 5691. (c) Hartstock, F. W.; McMahon, L. B.; Tell, I. P. *Tetrahedron Lett.* **1993,** *34,* 8067. (d) Negishi and his co-workers have recently found an intermolecular acylpalladation of internal alkynes and the following CO insertion to produce lactones. The 7th IUPAC Symposium on Organo-Metallic Chemistry directed toward Organic Synthesis (OMCOS) (Sept 19–23, 1993, Kobe, Japan). We thank Professor E. Negishi for private communications. (e) For rhodium-catalyzed three-component coupling reactions of an alkyne, an alkene, and carbon monoxide to produce lactones, see: Hong, P.; Mise, T.; Yamazaki, H. *Chem. Lett.* **1981,** 989. (f) For palladium-catalyzed lactone synthesis starting from 3-aryl-1-propynes, see: Huang, Y.; Alper, H. *J. Org. Chem.* **1991,** *56,* 4534.

(4) More works have been reported on palladium-catalyzed difunc-tionalization of alkenes; see, for example: Trost, B. M.; Verheven, T. R. In *Comprehensive Organometallic Chemistry;* Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, pp 799–938.

(5) A review article on acyl cyanides: Hünig, S.; Schaller, R. *Angew. Chem., Int. Ed. Engl.* **1982,** *21,* 36.

(6) (a) A similar catalyst system Pd(OAc)$_2$–PPh$_3$–dppb (1:4.3:2) was reported in the hydrocarboxylation of alkynes: Zargarian, D.; Alper, H. *Organometallics* **1993,** *12,* 712. (b) Mixed ligand systems with mono-phosphine–diphosphine were also used in Rh-catalyzed hydroformyla-tion: Hughes, O. R.; Unruh, J. D. *J. Mol. Catal.* **1981,** *12,* 71. Hughes, O. R.; Young, D. A. *J. Am. Chem. Soc.* **1981,** *103,* 6636.

(7) A typical procedure is as follows. A solution of phenylacetylene (0.10 g, 0.99 mmol) and 4-toluoyl cyanide (0.072 g, 0.50 mmol) in 1,2-dichloroethane (3.0 mL) was degassed by three freeze–thaw cycles. To the solution were added triphenylphosphine (0.026 g, 0.099 mmol) and 1,4-bis(diphenylphosphino)butane (0.021 g, 0.049 mmol), and the solution was again degassed by three freeze–thaw cycles. To the solution was added Pd(OAc)$_2$ (0.022 g, 0.099 mmol), and the resulting purple solution was stirred at 70 °C for 65 h. The crude product was purified by column chromatography on silica gel to give (Z)-3-cyano-1-(4-methylphenyl)-3-phenyl-2-propen-1-one ((Z)-**1a**) (0.091 g, 74% yield): mp 133.1–135.5 °C (benzene–hexane); R$_f$ = 0.41 (hexane:EtOAc = 3:1); ^{1}H NMR (CDCl$_3$) δ 2.45 (s, 3H), 7.33 (d, J = 8.25 Hz, 2H), 7.50–7.53 (m, 3H), 7.80–7.83 (m, 2H), 7.91 (s, 1H), 7.95 (d, J = 8.25 Hz, 2H); ^{13}C NMR (CDCl$_3$) δ 21.8, 116.1 (PhC*H*=C(CN)C(=O)R, $^3J_{CH}$ = 14.6 Hz), 124.5, 127.1, 128.8, 129.3, 129.7, 131.5, 132.6, 133.4, 134.2, 145.3, 186.5 (PhCH=C(CN)*C*(=O)R, $^3J_{CH}$ = 2.4 Hz); IR (Nujol) 2200, 1655, 1604 cm^{-1}; λ$_{max}$ = 315 nm (ε 17 000). Anal. Calcd for C$_{17}$H$_{13}$NO: C, 82.56; H, 5.31; N, 5.66. Found: C, 82.44; H, 5.49; N, 5.66.

(8) (a) The structures of the products (Z)-**1** and (E)-**1** were assigned by the comparison of their ^{13}C NMR spectra with those of authentic samples prepared by the reported procedure. Herzig, J.; Gottlieb, H. E.; Nudelman, A. *J. Chem. Res., Synop.* **1986,** 196. (b) The structures of the products (E)-**2** were assigned by the comparison of their ^{13}C NMR spectra with those of authentic samples prepared by the reported procedure. Marchalin, S.; Jehlicka, V.; Böhm, S.; Trska, P.; Kuthan, J. *Collect. Czech. Chem. Commun.* **1985,** *50,* 1935.

(9) The use of other palladium complexes such as Pd(OAc)$_2$–PPh$_3$ (1:4), Pd(PPh$_3$)$_4$, and PdCl$_2$(PPh$_3$)$_2$ resulted in no reaction under the same reaction conditions, while reactions with Pd(OAc)$_2$–P(cyclohexyl)$_3$ (1:2), Pd(OAc)$_2$–PPh$_3$ (1:1), Pd(OAc)$_2$–P(OPh)$_3$ (1:2), or Pd$_2$(dba)$_3$·CHCl$_3$ gave complex oligomers of acetylenes. Addition of Ag$_2$(CO)$_3$ (1 equiv to Pd) to the system Pd(OAc)$_2$–PPh$_3$–dppb (1:1:0.5) significantly retarded the reaction.

Table 1. Palladium-Catalyzed Acylcyanation of Arylacetylenes

run	Ar[1]	Ar[2]	catalyst	time (h)	yield[a] (%) (Z)-1	(E)-2	3
1	C_6H_5	4-MeC$_6$H$_4$	Pd(OAc)$_2$–PPh$_3$–0.5dppb	65	74	2[b]	1[b]
2	C_6H_5	C_6H_5	Pd(OAc)$_2$–PPh$_3$–0.5dppb	66	70	c	c
3	C_6H_5	4-MeOC$_6$H$_4$	Pd(OAc)$_2$–PPh$_3$–0.5dppb	66	70	c	8
4	4-MeO-C$_6$H$_4$	C_6H_5	Pd(OAc)$_2$–PPh$_3$–0.5dppb	65	72	c	c
5	4-Cl-C$_6$H$_4$	C_6H_5	Pd(OAc)$_2$–PPh$_3$–0.5dppb	65	60	c	c
6	C_6H_5	4-MeC$_6$H$_4$	Pd(OAc)$_2$–PPh$_3$–0.5dppb	20	55	2[b]	13[b]
7	C_6H_5	4-MeC$_6$H$_4$	Pd(OAc)$_2$–2PPh$_3$	20	34	1[b]	36[b]
8	C_6H_5	4-MeC$_6$H$_4$	Pd(O)Ac)$_2$–dppb	20	7	1[b]	8[b]
9	C_6H_5	4-MeC$_6$H$_4$	Pd(OAc)$_2$–PPh$_3$–MePPh$_2$	20	54	1[b]	29[b]
10	C_6H_5	C_6H_5	Pd(OAc)$_2$–PPh$_3$–0.5dppb	20	60	c	25
11	C_6H_5	4-MeOC$_6$H$_4$	Pd(OAc)$_2$–PPh$_3$–0.5dppb	20	33	4	62
12[d]	C_6H_5	4-MeC$_6$H$_4$	Pd(OAc)$_2$–PPh$_3$–0.5dppb	20	44	16	c
13[e]	C_6H_5	4-MeC$_6$H$_4$	Pd(OAc)$_2$–2PPh$_3$	20	c	c	93

[a] Isolation yield. [b] The yield was determined by GLC (10% SE 30 on Uniport HP packed in 5-mm × 2-m glass column, column temperature 230 °C, injection and detection temperature 250 °C, He 1.6 kg/cm^2) using tetracosane as an internal standard. [c] Not detected. [d] The reaction was carried out in toluene. [e] The reaction was carried out in THF.

Scheme 1
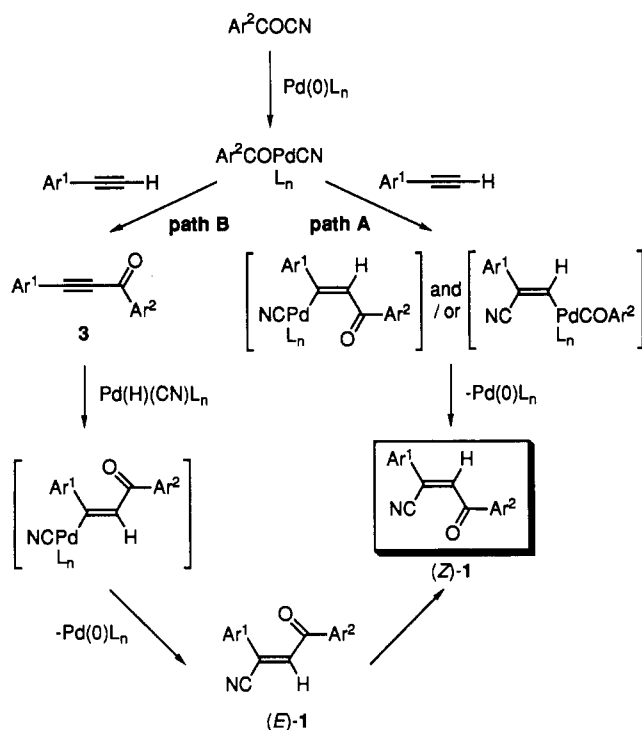
of 1-octyne in place of terminal arylacetylene or cyclohexanecarbonitrile for aryloyl cyanide resulted in no reaction. Internal acetylene such as diphenylacetylene was inert.

As illustrated in Scheme 1, *a priori* two possible mechanisms for the formation of β-cyano α,β-unsaturated ketones (Z)-1 could be considered. In both mechanisms, the first step involves the oxidative addition of acyl cyanide to Pd(0) to give acylpalladium cyanide.[10] The resulting intermediate can undergo an acetylenic insertion into the acylcarbon–palladium bond[3,11] or cyanocarbon–palladium

bond followed by a reductive elimination of (Z)-1 to reproduce Pd(0)[12] (see path A of Scheme 1). Alternatively, acylpalladium intermediate can lead to the formation of an acetylenic ketone 3,[13,14] which undergoes a hydrocyanation.[15] Isomerization of the (E)-1, formed by the *cis* addition of HCN, to (Z)-1 will produce the observed product (path B in Scheme 1).

In order to clarify the reaction pathway, the following reaction was carried out. 4-Anisoyl cyanide was allowed to react with phenylacetylene in the presence of acetylenic ketone 3a (phenylacetylene:4-MeOC$_6$H$_4$COCN:3a = 2:1:1). The β-cyano α,β-unsaturated ketone (Z)-1a was obtained in addition to the normal products (Z)-1c and 3c as shown in eq 2. The formation of (Z)-1a can be explained by the hydrocyanation of 3a. Thus, path B seems more plausible, though we can say nothing about whether or not path A is in effect at the same time. In addition, the increase of (Z)-1c and the disappearance of 3c after the longer reaction time (entries 3 and 11 in Table 1) is also clearly explained by path B, because the yield of (Z)-1c after 66 h (70%) was higher than the sum of (Z)-1c yield after 20 h (33%) and unreacted acyl cyanide (maximum 1%) at that moment.

Hydrocyanation of acetylenic ketones 3 required the presence of palladium catalyst. In the absence of palladium catalyst, acetylenic ketone 3a was recovered after treatment with KCN and acetic acid in a mixture of 1,2-dichloroethane and H$_2$O or ethanol and H$_2$O at 25 °C for 140 h and 70 °C for 48 h.[16] We consider that the hydrocyanation proceeded by the addition of Pd(H)(CN)-

(10) A mechanism involving the oxidative addition of aryloyl cyanides to Pd(0) has been proposed by Murahashi and his co-workers in their studies on Pd(0)-catalyzed decarbonylation of aryloyl cyanides at high temperature; see: Murahashi, S.; Naota, T.; Nakajima, N. *J. Org. Chem.* **1986**, *51*, 898.

(11) (a) Insertion of an acetylenic bond into the acylpalladium has been reported in a stoichiometric intramolecular reaction. Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505. (b) An intermolecular study was also reported using acylnickel in place of acylpalladium. Carmona, E.; Gutiérrez-Puebla, E.; Monge, A.; Marin, J. M.; Paneque, M.; Poveda, M. L. *Organometallics* **1989**, *8*, 967.

(12) Reductive elimination of alkenyl nitrile to reproduce Pd(0) was observed in the palladium-catalyzed transformation of alkenyl halides into alkenyl nitriles. (a) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3298. (b) Sekiya, A.; Ishikawa, N. *Chem. Lett.* **1975**, 277. (c) Dalton, J. R.; Regan, S. L. *J. Org. Chem.* **1979**, *44*, 4443. (d) Yamamoto, K.; Suzuki, S.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 1653.
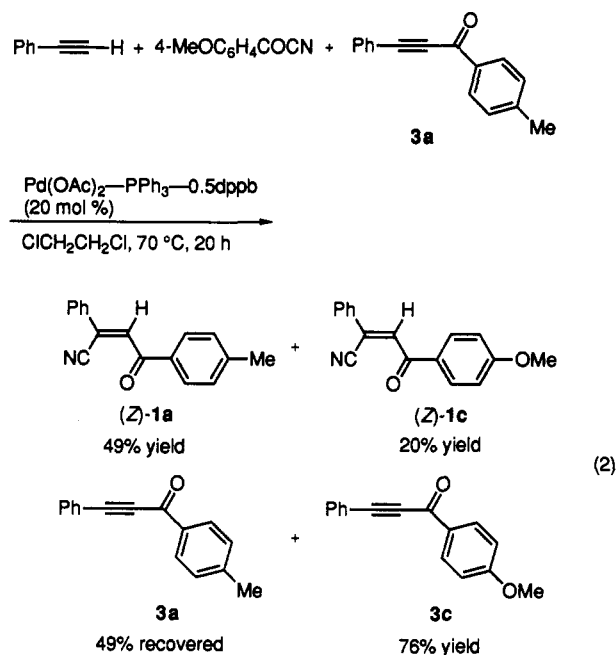
(13) Acetylenic ketones 3 were reported to be formed from acyl chlorides and terminal acetylenes in the presence of CuI, Pd(OAc)$_2$, and Et$_3$N. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777. Transmetalation of acylpalladium chlorides and copper acetylides was postulated in the catalytic cycle.

(14) Alper and his co-workers reported a similar intermediate, acetylenic ketone, in their synthesis of 3-arylidenebutenolide by the reaction of 3-arylpropyne with CO catalyzed by Pd complexes; see ref 3f.
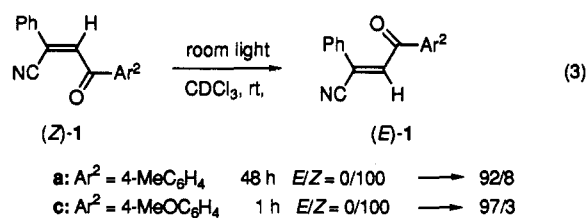
(15) In order to prepare an acetylenic ketone from an acyl halide and a terminal acetylene, CuI has been required in addition to Pd as reported in ref 13. In the present case, the mechanism for the formation of acetylenic ketone might be different. We assume the oxidative addition of the C–H bond of a terminal acetylene to an acylpalladium cyanide giving a Pd(IV) intermediate from which acetylenic ketone 3 eliminates reductively. The resulting H–Pd–CN might add to 3 to produce (E)-1a.

$$Ph\!-\!\!\equiv\!\!-H + 4\text{-MeOC}_6H_4COCN + Ph\!-\!\!\equiv\!\!-\overset{O}{C}\text{-}C_6H_4\text{-}Me$$

3a

Pd(OAc)$_2$—PPh$_3$—0.5dppb
(20 mol %)
———————————→
ClCH$_2$CH$_2$Cl, 70 °C, 20 h

(Z)-1a
49% yield

(Z)-1c
20% yield

3a
49% recovered

3c
76% yield

(2)

L$_n$ formed *in situ* to the acetylenic ketone **3** as described in Scheme 1. Transition metal catalyzed addition of HCN to an acetylenic bond usually proceeds in *cis* fashion.[17] In the present case, the products (Z)-1 seem to have arisen from initially formed (E)-1 by the isomerization during the reaction. To support this hypothesis, the addition of 4-MeOC$_6$H$_4$COCN to phenylacetylene was carried out in the presence of (E)-1a and Pd(OAc)$_2$–PPh$_3$–0.5dppb. The corresponding stereoisomer (Z)-1a was obtained as well as the normal product (Z)-1c, and no (E)-1a was recovered. On the other hand, no isomerization of (E)-1a into (Z)-1a was observed in the absence of palladium catalyst. Thus, we believe that palladium species Pd(H)(CN)L$_n$ acts as catalyst for (E)-1 → (Z)-1 isomerization.

room light
—————————→
CDCl$_3$, rt,

(Z)-1   (E)-1

(3)

a: Ar^2 = 4-MeC$_6$H$_4$ 48 h   *E/Z* = 0/100   ——→   92/8
c: Ar^2 = 4-MeOC$_6$H$_4$ 1 h   *E/Z* = 0/100   ——→   97/3

The acylcyanated products (Z)-1a and (Z)-1c are both yellow crystals and have UV absorptions at long wavelength

(λ_{max} = 315 nm, ϵ = 17 000 for (Z)-1a and λ_{max} = 324 nm, ϵ = 20 000 for (Z)-1c). These olefins (Z)-1a and (Z)-1c were observed to isomerize into their corresponding stereoisomers (E)-1a and (E)-1c (λ_{max} = 270 nm, ϵ = 12 000 for (E)-1a and λ_{max} = 297 nm, ϵ = 18 000 for (E)-1c) in CDCl$_3$ under room light when they were kept in pyrex NMR tubes.[18] No isomerization of the same compound was observed when the sample was kept under dark. Accordingly, the photoisomerization provides a useful method for the selective preparation of (E)-1.

The present acylcyanation method was extended to a four-component coupling reaction. The β-cyano α,β-unsaturated ketone (Z)-1a was formed in 29% yield by heating a mixture of 4-iodotoluene, phenylacetylene, and KCN in THF in the presence of Pd(OAc)$_2$–PPh$_3$–dppb (1:1:0.5, 20 mol %) as catalyst at 70 °C under carbon monoxide pressure (20 atm) for 94 h (eq 4).[19]

CO (20 atm), KCN
Pd(OAc)$_2$—PPh$_3$—0.5dppb
(20 mol %)
———————————→
THF, 70 °C, 94 h

(Z)-1a
29% yield

(4)
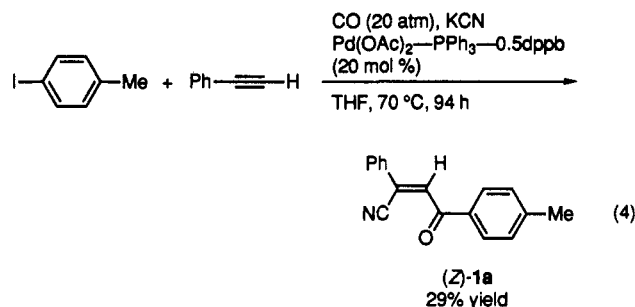
Thus, a new strategy, palladium-catalyzed acylcyanation of arylacetylenes, is established as a tool of difunctionalization of terminal acetylenes for the regio- and stereoselective synthesis of highly functionalized olefins. Further studies on the synthetic applications of β-cyano α,β-unsaturated ketones **1** are now on progress.

Supplementary Material Available: Experimental procedures and spectral data for all products (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) On the other hand, the addition of HCN to the corresponding enone 1-(4-methylphenyl)-3-phenyl-2-propen-1-one proceeded smoothly under the same conditions in 24 h. Ciller, J. A.; Seoane, C.; Soto, J. L. *Liebigs Ann. Chem.* **1985**, 51.

(17) For addition of HCN to acetylenic bonds catalyzed by Ni(0) complexes, see: Jackson, W. R.; Lovel, C. G. *Aust. J. Chem.* **1983**, *36*, 1975.

(18) A similar photoisomerization of α-cyanostyrene derivatives under UV irradiation was reported. Chatani, N.; Takeyasu, T.; Horiuchi, N.; Hanafusa, T. *J. Org. Chem.* **1988**, *53*, 3539.

(19) Aryloyl cyanides could be produced by the reaction of aryl iodide with carbon monoxide and KCN catalyzed by PhPdI(PPh$_3$)$_2$ in THF; see: Tanaka, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 637.