Palladium(II)-Catalyzed Acetalization of Allylic Acetates and Its Utilization for the Synthesis of 2-Cyanovinyl Ketones

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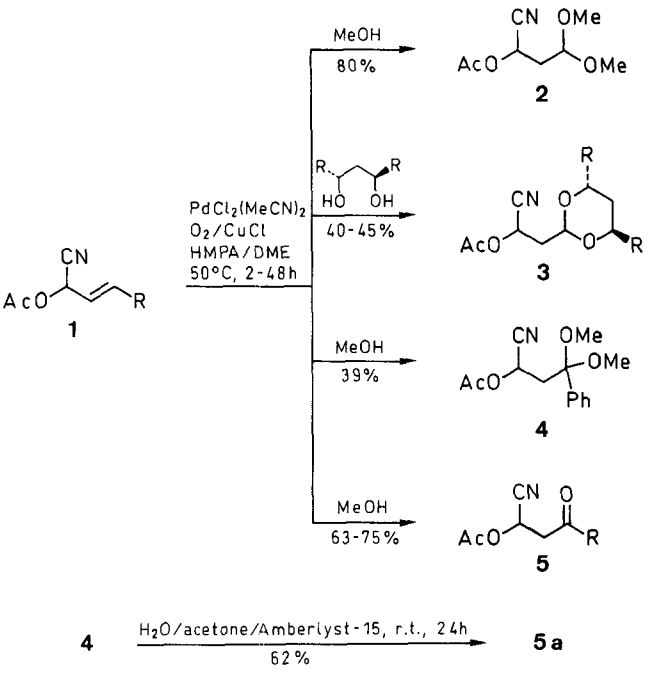
α-Cyanoallyl acetate (**1a**), when treated with methanol in the presence of bis(acetonitrile)dichloropalladium(II) catalyst, is acetalized at the terminal olefinic carbon to give 1-cyano-3,3-dimethoxypropyl acetate (**2**). γ-Substituted α-cyanoallyl acetates give 3-substituted 1-cyano-3-oxo-propyl acetates **5** from which 2-cyanovinyl ketones **11** are obtained in good yields.

Palladium(II)-catalyzed oxidative transformation of alkenes to various functional groups is one of the important synthetic processes,[1] among which a great deal of work has been done with oxygen nucleophiles.[2] Terminal alkenes bearing an alkyl group are known to be readily transformed into methyl ketones upon treatment with water[3] and alcohols.[4,5] With terminal alkenes bearing electron-withdrawing groups, a unique entry to terminal acetals is provided when diols or alcohols are utilized as nucleophiles.[6,7]

Allylic acetates are versatile synthetic precursors; however, little is known about their fundamental behavior towards Pd(II)-catalyzed oxidations with oxygen nucleophiles. In such a view, as well as to expand the scope of the oxypalladation of alkenes,[8] we have studied regioselective preparation of terminal acetals from allylic acetates. As the result, appendage of electron-withdrawing CN group at the allylic carbon led to the corresponding terminal acetals regioselectively. This paper describes the detail of the reaction and its utility for synthesizing 2-cyanovinyl ketones which were regarded as one of the useful activated olefins.

Allylic acetates undergo facile [1,3]-sigmatropic rearrangement of the OAc group under the influence of palladium(II) catalysts, e.g., bis(acetonitrile)dichloropalladium(II),[9] however, no such rearrangement occurred when α-cyanoallyl acetate (**1a**) (R=H) was reacted with methanol in the presence of bis(acetonitrile)dichloropalladium(II)/copper(I) chloride catalyst under oxygen atmosphere. Instead, acetal **2** was obtained as the sole product. Use of methanol as the solvent resulted in rather lower yield of **2** (64% in 2 hour); however, addition of hexamethylphosphoric triamide (HMPA)[10] (1 equiv per Pd) increased it up to 80%. When methanol was used as nuclophile in 1,2-dimethoxyethane (DME) solvent along with HMPA, the acetal **2** was also obtained in good yield (Table). Under these conditions, diols such as 1,3-propanediol also produce the corresponding acetals **3**. γ-Aryl substituted α-cyanoallyl acetate **1b** gives acetal **4**, while introduction of alkyl groups to the γ-position leads to the corresponding ketones **5**, regioselectively.

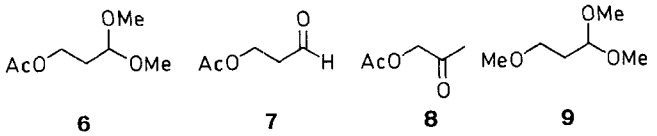
In general, alkyl substituted internal olefins appear to give the corresponding ketones in place of acetals.[4,7] Note that when bases such as disodium hydrogen phosphate were used as an additive, the acetalization was retarded (e.g., **2**; 35% in 2 hours).



1	R	3	R	5	R
a	H	a	H	a	Me
b	Ph	b	Me	b	Pr
c	Me			c	Ph
d	Pr				

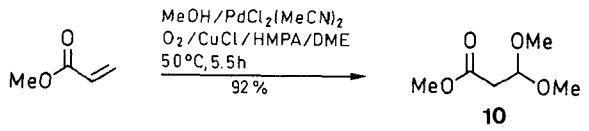
Scheme 1

Although the reaction of allyl acetate itself with methanol gave a complex mixture of products, its simplification was attained by the use of either HMPA or disodium hydrogen phosphate as an additive. However, the acetalization is nonselective and gives four products **6** (28%), **7** (3%), **8** (11%), and **9** (16%).[11] Thus, it is obvious that the appendage of electron-withdrawing CN group at the α-position of allylic acetates markedly controls the attacking direction of oxygen nucleophiles.



6 **7** **8** **9**

Compared to disodium hydrogen phosphate, the use of HMPA as the additive effectively promotes the oxidation. This effect must be general since the acetalization of methyl acrylate with methanol leading to **10** was accelerated nearly by a factor of 2, when HMPA (0.1 equiv) was present in the reaction.

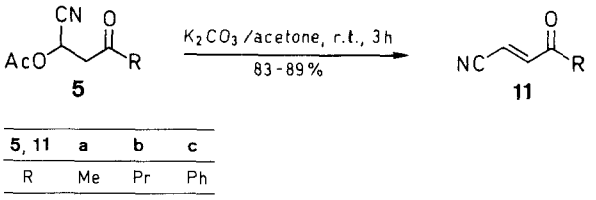


Scheme 2

In search for other promoters, HMPA was found to give the best result, and the effectiveness of others follows in the order of dimethylformamide > trimethyl phosphate > 1,1,3,3-tetramethylurea > dimethyl carbonate > none.

The formation of acetals is rationalized as reported previously.[5] Nucleophilic attack of methanol to the olefin coordinated palladium(II) chloride proceeds with loss of hydrogen chloride to give an oxypalladation adduct from which Pd—H elimination leads to a vinyl ether. Subsequent addition of another methanol to the vinyl ether affords acetals such as **2**. Considering the observed effect of disodium hydrogen phosphate, small amounts of hydrogen chloride formed in the stage of oxypalladation must affect the rate of oxidation. Coordination of HMPA to copper or palladium is thought to alter the reactivity of catalytic species, though the detail is not unambiguous.

The preparation of ketones **5a** and **5b** is readily performed on a gram scale. The corresponding ketone **5c** (R = Ph) is obtainable from acetal **4** upon hydrolysis. Treatment of these ketones **5a–c** with potassium carbonate affords high yields (83–89%) of 2-cyanovinyl ketones **11** which serve as good dienophiles because of their electron-deficient nature of the olefin (Scheme 4). The methyl ketone **11a** (R = Me) also becomes a precursor of siloxydiene **14**.



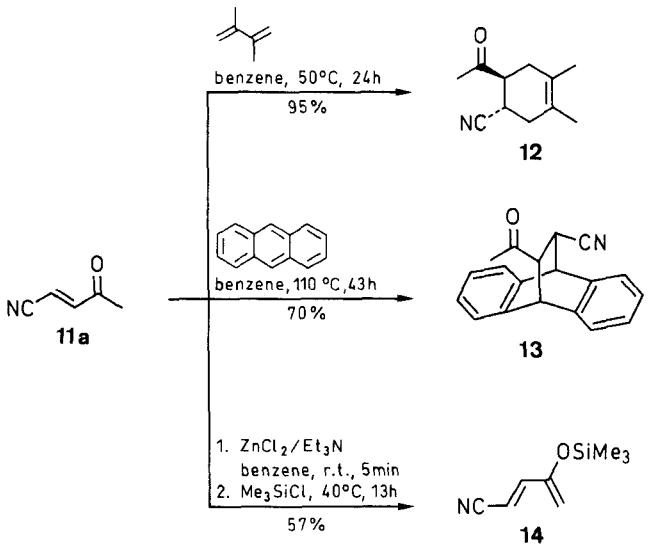
Scheme 3

2-Cyanovinyl ketones **11** have been reported to be prepared via a method involving an isomerization of 1-cyanoallyl acetates (e.g., **1c**) to γ-acetoxy-α,β-alkenylnitriles.[12] Since the isomerization is induced by palladium(0) catalysts,[13,14] the synthesis of cyanovinyl ketones is now available from **1b–d** by using either palladium(0) or palladium(II) catalyst.

Table. Acetals, Ketones **5**, and Cyanovinyl Ketones **11** Prepared

Product	Time (h)	Yield[a] (%)	mp (°C) or bp (°C)/Torr[b]	Molecular Formula[c] or Lit. Data	^{1}H NMR ($CDCl_3$/TMS) δ, J (Hz)
2	2	80	110–120/4	$C_8H_{13}NO_4$ (187.1)	2.13 (s, 3H), 2.20 (dd, 2H, J = 7.2, 5.6), 3.33 (s, 3H), 3.34 (s, 3H), 4.52 (t, 1H, J = 5.6), 5.36 (t, 1H, J = 7.2)
3a	4	45	112/2	$C_9H_{13}NO_4$ (199.2)	1.13–1.55 (m, 1H), 1.73–2.33 (m, 1H), 2.10 (s, 3H), 2.20 (dd, 2H, J = 7.2, 5.0), 3.37–4.35 (m, 4H), 4.70 (t, 1H, J = 5.0), 5.43 (t, 1H, J = 7.2)
3b	48	40	120/1.5	$C_{11}H_{17}NO_4$[d] (227.2)	1.10 and 1.20 (d, 3H, J = 6.1),[e] 1.21 (m, 1H), 1.83 (m, 1H), 2.14 (s, 3H), 2.17 (m, 2H), 3.96 (m, 1H), 4.27 (m, 1H), 5.02 and 5.04 (t, 1H, J = 5.3), 5.51 and 5.52 (t, 1H, J = 7.3)
4	24	39	–[f]	$C_{14}H_{17}NO_4$[d] (263.2)	1.74 (s, 3H), 2.48 (d, 1H, J = 7.4), 2.52 (d, 1H, J = 5.7), 3.08 (s, 3H), 3.19 (s, 3H), 5.00 (dd, 1H, J = 7.4, 5.7), 7.17–7.46 (m, 5H)
5a	7.5	75	94/7–9	$C_7H_9NO_3$ (155.1)	2.10 (s, 3H), 2.21 (s, 3H), 3.10 (d, 2H, J = 6.4), 5.63 (t, 1H, J = 6.4)
5b	48	63	143/4	$C_9H_{13}NO_3$ (183.2)	0.93 (t, 3H, J = 7.0), 1.63 (qt, 2H, J = 7.0, 7.2), 2.10 (s, 3H), 2.45 (t, 2H, J = 7.2), 3.04 (d, 2H, J = 6.6), 5.63 (t, 1H, J = 6.6)
5c	24	62[f]	–[g]	$C_{11}H_{11}NO_2$[d] (189.2)	2.03 (s, 3H), 3.50 (d, 1H, J = 6.1), 3.53 (d, 1H, J = 7.0), 5.73 (dd, 1H, J = 6.1, 7.0), 7.16–8.00 (m, 5H)
10	4	66	81/12	77/20[18]	2.63 (d, 2H, J = 6.0), 3.33 (s, 6H), 3.66 (s, 3H), 4.08 (t, 1H, J = 6.0)
11a	3	83	100/9	50–60/0.2[12]	2.35 (s, 3H), 6.23 (d, 1H, J = 16), 6.90 (d, 1H, J = 16)
11b	24	89	115–120/8	C_7H_9NO[d] (123.1)	0.96 (t, 3H, J = 6.6), 1.68 (qt, 2H, J = 6.6, 7.0), 2.60 (t, 2H, J = 7.0), 6.27 (d, 1H, J = 16), 6.93 (, J = 16, 1H)
11c	24	85	–[f]	80–82[12]	6.40 (d, 1H, J = 16), 7.73 (d, 1H, J = 16), 7.20–8.13 (m, 5H)

[a] Isolated yield based on starting material.
[b] Kugelrohr distillation.
[c] Satisfactory microanalyses obtained; C ±0.28, H ±0.22, N ±0.33; unless otherwise noted.
[d] No elemental analysis was done.
[e] A 1:1 mixture of two diastereomers.
[f] Purified by column chromatography.
[g] Yield from **4**.



Scheme 4

$PdCl_2(MeCN)_2$ was prepared from $PdCl_2$ and acetonitrile.[15] CuCl was purified according to the literature procedure.[16] 1-Cyanoallyl acetates were prepared by the literature procedure.[13,17] Allyl acetate, 1,3-propanediol, DME, and HMPA were all commercially available and distilled over CaH_2 prior to use. Na_2HPO_2 was purchased from Wako Pure Chemical Ind. Microanalyses were obtained using a Yanagimoto MT-3 CHN corder. IR spectra were obtained using a Hitachi 215 spectrophotometer or Shimadzu FT IR-400 spectrophotometer. ^1H NMR spectra were obtained using a JEOL JNM-PMX-60SI (60 Mz) or JEOL JMN-FX-100 (100 Mz) spectrometer. GLC for analyses were carried out on a JEOL Model JGC-20-KFP or a Shimadzu GC-8A flame ionization chromatography using a 1 m × 3 mm, 10% SE-30 on Uniport HP column with the conditions of injection temperature 200 °C and N_2 gas pressure 0.4 kg/cm^2.

1-Cyano-3,3-dimethoxypropyl Acetate (2); Typical Procedure:
Into a mixture of $PdCl_2(MeCN)_2$ (26 mg, 0.10 mmol), CuCl (10 mg, 0.10 mmol), and HMPA (18 mg, 0.10 mmol) was added a solution of α-cyanoallyl acetate (**1a**; 125 mg, 1.00 mmol) and dry MeOH (319 mg, 9.96 mmol) in DME (2 mL), and the resulting suspension was stirred at 50 °C for 2 h under O_2 (balloon). After cooling to r.t., the mixture was treated with Et_2O (20 mL), and the resulting insoluble materials were removed by filtration. After evaporation of the solvent, the residue was passed through Florisil (1.5 g, 13 × 12 mm, pentane/Et_2O, 9:1) to give **2**; yield: 149 mg (80%).

1-Cyano-3-oxobutyl Acetate (5a); Typical Procedure:
Into a mixture of $PdCl_2(MeCN)_2$ (649 mg, 2.50 mmol), CuCl (248 mg, 2.51 mol), and HMPA (450 mg, 2.51 mmol) in MeOH (10 mL, 248 mmol) and DME (45 mL) were added a solution of **1c** (6.96 g, 50.0 mmol) in DME (5 mL), and the mixture was rigorously stirred at 50 °C for 40 h under O_2 (balloon). After cooling, Et_2O (50 mL) was added, and the resulting insoluble material was removed by filtration. Removal of the solvent followed by Florisil column chromatography gave ketone **5a** as the sole product; yield: 5.59 g (72%).

Acetalization of Methyl Acrylate with Methanol in the Presence of Promoters:
Into a suspension of $PdCl_2(MeCN)_2$ (51.9 mg, 0.200 mmol), and CuCl (19.8 mg, 0.200 mmol), and CuCl (19.8 mg, 0.200 mmol) in DME (4 mL) was added successively dry MeOH (642 mg, 20.0 mmol), HMPA (35.8 mg, 0.20 mmol), methyl acrylate (174 mg, 2.02 mmol), and undecane (internal standard for GLC analysis) under O_2 (gas bullet). The mixture was stirred at 50 °C, and the progress of the reaction was monitored by O_2 uptake and GLC. The O_2 uptake correlates well with the amount of acetal **10** formed, and half a mol of O_2 is consumed for the production of 1 mol of acetal **10**. In the presence of HMPA, a 92% yield of acetal **10** was formed in 5.5 h, while in the absence of HMPA its yield was reduced to 46%. The results with other promoters are as follows; DMF (76%), trimethyl phosphate (72%), 1,1,3,3-tetramethylurea (67%), and dimethyl carbonate (64%).

Deacetalization of Acetal 4:
A mixture of acetal **4** (1.96 mmol), H_2O (150 mg), and Amberlyst-15 (150 mg) in acetone (5 mL) was stirred at r.t. for 24 h. Usual workup followed by silica gel column chromatography (eluent: hexane/EtOAc) gave ketone **5c** (Table); yield: 262 mg (62%).

2-Cyanovinyl Ketones 11; General Procedure:
A suspension fo ketones **5a–c** (11.8 mmol) and K_2CO_3 (82 mg, 0.59 mmol) in acetone (12 mL) was stirred at r.t. for 3 h. The mixture was extracted with Et_2O (4 × 20 mL) washed with H_2O and brine, and dried ($MgSO_4$). Removal of Et_2O gave 2-cyanovinyl ketones **11a–c** (Table).

5-Acetyl-4-cyano-1,2-dimethyl-1-cyclohexene (12).
A solution of **11a** (190 mg, 2.00 mmol) and 2,3-dimethyl-1,3-butadiene (0.34 mL, 3.0 mmol) in benzene (1 mL) was stirred at 50 °C for 24 h. Removal of the solvent gave adduct **12**; yield 337 mg (95%); mp 80.5–81.5 °C (Et_2O).

$C_{11}H_{15}NO$	calc.	C 74.54	H 8.53	N 7.90
(177.2)	found	74.40	8.51	7.88

IR (KBr): ν = 2240, 1710, 1120, 1060, 1010 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.63 (s, 3H), 1.65 (s, 3H), 2.04–2.09 (m, 1H), 2.25 (s, 3H), 2.30–2.41 (m, 3H), 2.89 (ddd, 1H, J = 5.5, 9.5, 9.5 Hz), 2.94 (ddd, 1H, J = 5.8, 9.5, 9.5 Hz).

11-Acetyl-12-cyano-9,10-dihydro-9,10-ethanoanthracene (13):
A mixture of olefin **11a** (97 mg, 1.02 mmol) and anthracene (182 mg, 1.02 mmol) in benzene (1 mL) was heated at 110 °C for 43 h in a sealed tube. Removal of the solvent gave adduct **13** (277 mg, 99%) which was recrystallized from EtOAc to give pure **13**; yield: 70%; mp 214–215 °C.

$C_{19}H_{15}NO$	calc.	C 83.49	H 5.53	N 5.12
(273.3)	found	83.20	5.78	4.99

IR (KBr): ν = 2240, 1711 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 2.31 (s, 3H), 3.13 (dd, 1H, J = 2.4, 4.8 Hz), 3.58 (dd, 1H, J = 2.4, 4.8 Hz), 4.52 (d, 1H, J = 2.4 Hz), 4.65 (d, 1H, J = 2.4 Hz), 7.03–7.57 (m, 8H).

4-Trimethylsiloxy-2,4-pentadienenitrile (14):
Into a mixture of $ZnCl_2$ (41 mg, 0.3 mmol) and Et_3N (3.2 mL, 23 mmol) was added a solution of **11a** (951 mg, 10.0 mmol) in benzene (30 mL) at r.t. After stirring for a few minutes, Me_3SiCl (2.5 mL, 20 mmol) was added, and the mixture was stirred at 40 °C for 13 h. Et_2O (25 mL) was added, and the resulting insoluble materials were removed by filtration through a pad of Celite. The filtrate was washed with sat. aq $NaHCO_3$ (3 × 50 ml) and dried ($MgSO_4$). Removal of the solvent followed by Kugelrohr distillation (54 °C/2 Torr) gave a mixture of **11a** and **14** (1102 mg) in a ratio of 21:79 (^1H NMR analysis); yield of **14**: 57%; ^1H NMR ($CDCl_3$/TMS as a mixture of **11a**): δ = 0.24 (s, 9H), 4.63 (s, 2H), 5.60 (d, 1H, J = 126 Hz), 6.80 (d, 1H, J = 16 Hz).

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(11) The ^{1}H NMR ($CDCl_3$/TMS) spectra of compounds **6, 7, 8** and **9** are as follows; **6**: δ = 1.93 (dt, 2H, J = 5.8, 6.6 Hz), 2.05 (s, 3H), 3.33 (s, 6H), 4.13 (t, 2H, J = 6.6 Hz), 4.50 (t, 1H, J = 5.8 Hz); **7**: δ = 2.04 (s, 3H), 2.75 (dt, 2H, J = 6.0, 1.6 Hz), 4.04 (t, 2H, J = 6.0 Hz), 9.72 (t, 1H, J = 1.6 Hz); **8**: δ 2.17 (s, 6H), 4.63 (s, 2H); **9**: δ 1.87 (dt, 2H, J = 5.8, 6.2 Hz), 3.33 (s, 9H), 3.44 (t, 2H, J = 6.2 Hz), 4.50 (t, 1H, J = 5.8 Hz).
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