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# Structural Determination, DFT Calculation, and Formation Mechanism of Ethyl 2-cyano-3-alkoxy-pent-2-enoates Synthesized via Ru-mediated Coupling Reaction between $\alpha,\beta$ -unsaturated Acetals and Cyanoacetate

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Mitsunobu Sato received his doctor's degree in engineering from the University of Tokyo in 1985. After he joined the National Science Museum as a researcher in Chemistry, he moved to Kogakuin University as a Lecturer in 1991. He became a full Professor in 2002. His current research interest is fabrication and characterization of functional thin films for lithium ion battery, photocatalyst *etc.*, utilizing coordination compounds and coating technology.

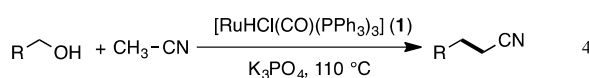
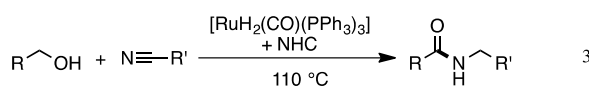
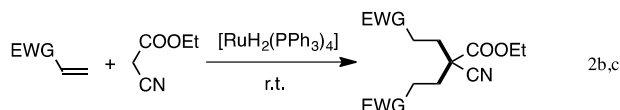
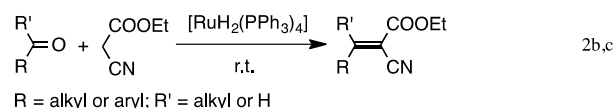
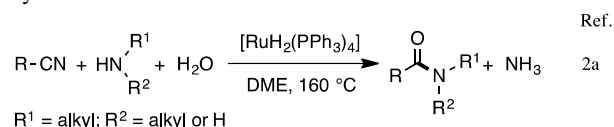
## Abstract

Ethyl 2-cyano-3-alkoxy-pent-2-enoates were synthesized in moderate yields via the coupling reaction between  $\alpha,\beta$ -unsaturated acetals and cyanoacetate, catalyzed by  $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$ . The *E*- and *Z*-isomers were separated and determined by X-ray crystallography for the first time. Structural distortion associated with steric hindrance around the tetrasubstituted alkene moiety was revealed: *e.g.*, the C(carbonyl)–C( $\alpha$ )–C( $\beta$ ) angle expands to about 125°. Density functional theory calculation was performed, and the restricted B3LYP hybrid functional with the 6-31G(*d,p*) basis set was found to successfully elucidate the solid-state structure and conformation, as well as spectroscopic properties. A plausible formation mechanism was proposed, in which the Ru complex catalyzed the C=C bond migration of the  $\alpha,\beta$ -unsaturated acetal to give the corresponding ketene acetal and assisted the subsequent condensation reaction with cyanoacetate to some extent.

## Introduction

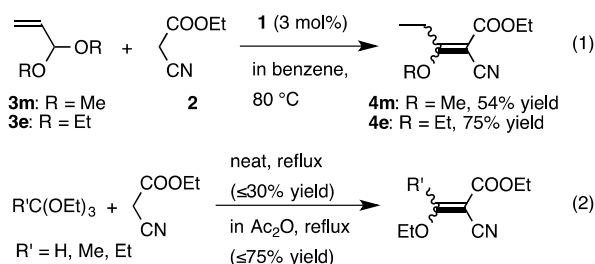
Ruthenium-mediated coupling reactions are becoming increasingly important in the synthesis of organic fine chemicals.<sup>1</sup> Low-valent ruthenium hydride complexes are often used for bond formations via the activation of nitriles, which usually involve a nucleophilic attack to the cyano group or cleavage of  $\alpha$ -C–H bonds (Figure 1). Early works in this field have been extensively conducted by Murahashi and co-workers, who demonstrated that various coupling reactions of nitriles via both types of pathways are conveniently catalyzed by  $[\text{RuH}_2(\text{PPh}_3)_4]$  under mild and non-acidic or non-basic conditions.<sup>2</sup> Recently, Hong's group performed the atom-economic synthesis of amide via a coupling reaction between alcohol and nitrile by combining  $[\text{RuH}_2(\text{L})(\text{PPh}_3)_3]$  ( $\text{L} = \text{PPh}_3, \text{CO}$ ) with an *N*-heterocyclic carbene (NHC) ligand as catalyst

precursors.<sup>3</sup> In contrast, Ryu's group reported the  $\alpha$ -alkylation of acetonitrile utilizing primary alcohols, catalyzed by  $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$  (**1**) in the presence of a base.<sup>4</sup> Previous studies have shown that **1** is also effective in activating the cyano moiety and induces the coupling of nitrile molecules in the coordination sphere to form certain metallacyclic structures in non-catalytic manners.<sup>5</sup> In addition, **1** has been widely investigated for its reactivity toward alkenes, and a large number of insertion products at the Ru–H bond have been reported.<sup>6</sup> Transformations of alkenes catalyzed by **1** include *E/Z* isomerization,<sup>6c</sup> double bond migration,<sup>6f,h,7,8</sup> addition of organic moieties,<sup>7d,9</sup> and silyl group transfer from vinyl- and allylsilanes.<sup>10</sup>



**Figure 1.** Coupling reactions of nitriles, catalyzed by low-valent ruthenium hydrides.

In our research on the reactivity of **1** with nitriles and alkenes, we found that **1** catalyzes the coupling reaction of ethyl cyanoacetate (**2**) with acrolein acetals (**3**) to give  $\beta$ -alkoxy- $\alpha$ -cyano- $\alpha,\beta$ -unsaturated esters **4** (Eq. 1). The same type of products have been previously obtained, for example, from the condensation of cyanoacetates with orthoesters (Eq. 2)<sup>11</sup> and utilized as precursors of various heterocyclic compounds with intriguing biological activities.<sup>11b,c,e,f,12</sup> In comparison to traditional methods, the ruthenium-catalyzed formation of **4** proceeded under mild reaction conditions. Although the concurrent formation of separable *E*- and *Z*-isomers during the syntheses of **4** has long been known, the stereochemistry assignment has only been discussed based on nuclear magnetic resonance (NMR) measurements.<sup>13</sup> In this paper, we report the first X-ray crystallographic analysis of both isomers that enables an unequivocal determination of the *E/Z* configurations, and an accompanying theoretical study to elucidate their structural and spectroscopic properties in both solid and solution states.



## Results and Discussion

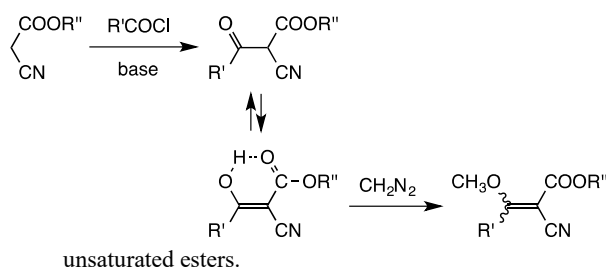
### 1. Coupling Reaction of Ethyl Cyanoacetate with Acrolein Acetals in the Presence of [RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>].

When a benzene solution containing **2** and 1.1 equiv. of **3** (R = Me, Et) was stirred at 80 °C in the presence of **1** (3 mol%),  $\beta$ -alkoxy- $\alpha$ -cyano- $\alpha,\beta$ -unsaturated esters **4** were formed in moderate yields (Eq. 1). No reaction took place without the addition of **1**, indicating that the ruthenium species derived from **1** plays a key catalytic role. The <sup>1</sup>H NMR spectra of the crude reaction mixtures showed sets of signals corresponding to the *E*- and *Z*-forms of **4**, and the ratios of the two isomers were estimated to be 87:13 for both the  $\beta$ -MeO and  $\beta$ -EtO derivatives. These stereoisomers, as well as unreacted **2**, were successfully separated using silica gel chromatography, and the two isomers of **4** were isolated in their pure forms. NMR measurements of these pure samples showed no indication of dynamic *cis-trans* isomerization at room temperature. However, they slowly isomerized at 80 °C in a benzene solution; a pure sample of the major isomer underwent 3–4% conversion to the minor isomer after 1 day, and the isomeric ratio gradually shifted closer to 87:13 over 3 weeks. The addition of 3 mol% of **1** accelerated the isomerization process, resulting in mixtures of isomers (87:13) after 1 day at 80 °C. These final isomeric ratios are probably values at thermodynamic equilibrium, and it has been concluded that neither the  $\beta$ -MeO nor  $\beta$ -EtO group exerts any significant difference on the isomeric ratio.

The formation of **4** from **2** and **3** is regarded as a condensation reaction, accompanied by the elimination of ROH and migration of the C=C bond. In a preceding study,  $\alpha$ -cyano- $\beta$ -alkoxy- $\alpha,\beta$ -unsaturated esters have been synthesized from the condensation reaction between **2** and trialkyl orthoesters, which is associated with the elimination of two alcohol molecules (Eq. 2).<sup>11</sup> These transition metal-free reactions require a higher temperature compared to our method, and the modified procedures that use excess acetic anhydride only just provide the yields observed in our process. Although the crude products obtained from these metal-free procedures would also be *E/Z*

isomeric mixtures, these are not analyzed in detail but are directly subjected to an isolation process to separate the major isomer. Another synthetic route known for a long time is particularly effective for the preparation of  $\beta$ -methoxy derivatives, in which  $\alpha$ -cyano- $\beta$ -hydroxy- $\alpha,\beta$ -unsaturated esters (the tautomeric form of  $\alpha$ -acyl- $\alpha$ -cyanoacetates) are prepared via the  $\alpha$ -acylation of **2** and subsequently converted into methyl ethers by treatment with diazomethane (Scheme 1).<sup>11d,13–15</sup> This method, performed at low temperature (*i.e.*, room temperature or below), produces increased amount of the less thermodynamically stable isomers, and their isolation has been reported in the literature.<sup>13,14</sup> In spite of these preceding studies, the determination of the *E/Z* configuration remains unsolved for both isomers except for the assumption made based on NMR chemical shifts.<sup>13</sup>

### Scheme 1. Synthetic route via $\alpha$ -cyano- $\beta$ -hydroxy- $\alpha,\beta$ -

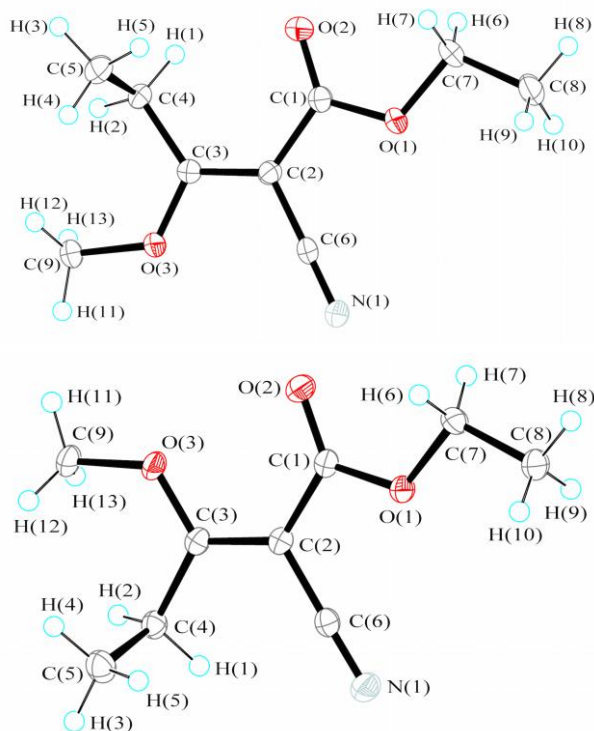


### 2. Crystal Structures of *E*- and *Z*-Forms of Ethyl 3-Alkoxy-2-cyanopent-2-enoate.

Using the pure samples, we successfully prepared single crystals of two **4m** stereoisomers (R = Me) and determined their structures via X-ray diffraction study. A crystallographic analysis of the major **4e** isomer (R = Et) was also carried out, and the result was essentially analogous to the corresponding **4m** isomer. Figure 2 clearly demonstrates that the configurations of the major and minor isomers are *E* and *Z*, respectively. Both isomers adopt planar conformations, in which non-hydrogen atoms almost lie on one common plane except for the  $\delta$ -carbon (C(5)), which is vertically oriented from the plane (torsion angles, C(2)–C(3)–C(4)–C(5): 90.12(14)° for *E*-**4m** and 92.28(10)° for *Z*-**4m**). The conjugated C=C and C=O double bonds take an *s-cis* conformation in each isomer. The carbon atom of the methoxy group in *E*-**4m** or *Z*-**4m** is directed toward the opposite of the neighboring cyano or the carbonyl group, respectively, probably due to steric congestion.

Important bonding parameters for the crystal structures of *E*-**4m** and *Z*-**4m** are summarized in Table 1. The bond lengths in both molecules agree well with standard values, and no essential difference can be observed between the respective bonds of the *E*- and *Z*-isomers. The slightly elongated C(2)–C(3) bond and the shortened C(3)–O(3) bond are attributed to a conjugated system involving these bonds (Scheme 2). An sp<sup>2</sup>-character is suggested for the O(3) atom based on its large bond angle (~120°). It is recognized that the bond angles around the quadruply substituted alkene moiety are remarkably distorted. For each isomer, the  $\alpha$ -carbon atom (C(2)) shows good planarity, with the sum of the three bond angles at almost 360°, while the C(1)–C(2)–C(3) angle is considerably wider (124.42(9)° and 125.49(8)° for *E*- and *Z*-**4m**, respectively) than the ideal value of 120° for sp<sup>2</sup>-hybridization. This deviation presumably arises from the steric repulsion between the  $\alpha$ -carbonyl group and the  $\beta$ -substituent located at *cis* positions each other, as commonly observed for other related  $\beta$ -disubstituted  $\alpha$ -cyanoacrylates.<sup>16,17</sup> With respect to the  $\beta$ -carbon, it is evident that the C(2)–C(3)–C(4) angle in *E*-**4m** increased to 125.41(9)° owing to spatial congestion that results from the adjacent  $\alpha$ -carbonyl. The

enlargements of these angles in **E-4m** are rather conspicuous in comparison to another closely related molecule (*E,E*-*p*-Me<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>COCH=C(COOEt)C(OEt)=C(CN)COOR (R = Me, Et).<sup>18</sup> The closest intramolecular contact between the  $\alpha$ -carbonyl and the  $\beta$ -ethyl groups of **E-4m** is the O(2)⋯H(1) distance at 2.30(1) Å, which is less than the sum of van der Waals radii (2.7 Å).<sup>19</sup> At the opposite side of the C=C bond, the  $\alpha$ -cyano and the  $\beta$ -methoxy groups are separated only by 2.600(2) Å between the C(6) and the O(3) atoms. In contrast, the  $\beta$ -carbon atom in **Z-4m** is free from severe angular distortions and has close to an ideal sp<sup>2</sup>-geometry. The shortest interatomic distances between the  $\alpha$ - and  $\beta$ -substituents at mutually *cis* locations are 2.759(2) Å for O(2)⋯O(3) and 2.44(1) Å for C(6)⋯H(1), indicating less steric crowding compared to **E-4m**.



**Figure 2.** Crystal structures of **E-4m** (top) and **Z-4m** (bottom), showing thermal ellipsoids at 50% probability level.

In order to study the contributing factors responsible for the conformations and angular strains of the aforementioned crystal structures, optimizations of molecular geometries were performed at the B3LYP levels using the 6-31G(*d,p*) basis set. By examining diverse conformations of **E-4m**, the lowest conformational energy structure was revealed to be fundamentally identical to the crystal structure, *i.e.* all non-hydrogen atoms lie on an identical plane except for the  $\delta$ -carbon, which is pointing away from the plane (Figure 3). The bonding parameters of the calculated structure are shown in Table 1 and agree well with those of the crystal structure. When geometry optimizations were performed with the out-of-plane methoxy group in the initial conformations, the group could always be found at the in-plane positions after convergence. In the resulting molecular orbitals, the delocalization of the  $\pi$ -system over the methoxy O atom is appreciable (Scheme 2). The order of natural population analysis (NPA) charges of O atoms is  $-0.636$  (O2) <  $-0.546$  (O1) <  $-0.496$  (O3), so that O2 and O3 have negative and positive charges relative to O1, respectively (see Figure S1, the atom numbering is identical to that shown in Figure 2). The values of NBO analysis show that the C1-C2, C2-C6, and C3-O3 bonds have a partial double bond character because the bond

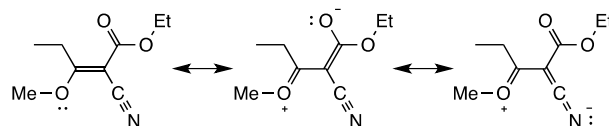
orders of C1-C2 (0.947), C2-C6 (1.014), and C3-O3 (0.906) are smaller than those of C1-O2 (1.273) and C2-C3 (1.200) but are larger than those of the normal single bonds C4-C5 (0.813) and C9-O3 (0.683) (see Figure S2). These results confirm the delocalization of the  $\pi$ -system. There is also a local minimum energy conformation, in which all non-hydrogen atoms are situated almost on a common plane. In this conformation, the methoxy carbon is directed toward the neighboring cyano group, and the methoxy O and  $\delta$ -C atoms are *syn*-periplanar with respect to the C( $\beta$ )-C( $\gamma$ ) bond, resulting in an increase of steric energy (+5.1 kJ/mol relative to the most stable conformation). It also appears that the *s-trans* conformations are energetically higher (by 13.3 kJ/mol) than the *s-cis* form. It is to be noted that the majority of related  $\alpha$ -cyano- $\alpha,\beta$ -unsaturated esters have been revealed to crystallize in the *s-cis* form.<sup>16-18,20</sup> The geometry optimization for **Z-4m** also revealed a structure that is consistent with that determined by the aforementioned X-ray crystallographic study.

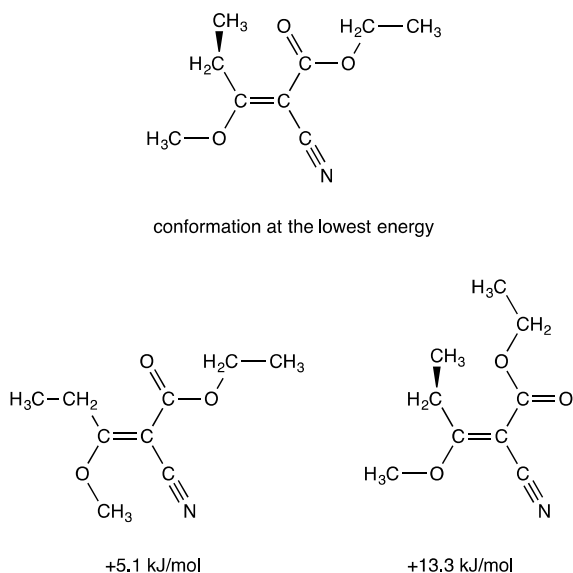
**Table 1.** Selected bond lengths (Å) and angles (deg) in **E-4m** and **Z-4m**

	<b>E-4m</b>		<b>Z-4m</b>	
	X-ray	DFT <sup>a)</sup>	X-ray	DFT <sup>a)</sup>
C1–O1	1.351(1)	1.347	1.350(1)	1.353
C1–O2	1.210(1)	1.222	1.206(1)	1.215
C1–C2	1.475(1)	1.480	1.486(1)	1.486
C2–C3	1.374(2)	1.379	1.373(2)	1.380
C2–C6	1.434(1)	1.429	1.431(1)	1.427
C3–O3	1.335(1)	1.340	1.331(1)	1.332
C3–C4	1.490(1)	1.503	1.505(2)	1.509
C4–C5	1.539(2)	1.544	1.536(1)	1.544
O3–C9	1.455(2)	1.435	1.455(1)	1.435
C6–N1	1.149(1)	1.164	1.151(1)	1.166
O1–C7	1.457(1)	1.449	1.456(1)	1.447
O1–C1–O2	123.10(10)	123.02	124.14(9)	123.39
O1–C1–C2	110.12(8)	110.75	109.24(7)	110.22
O2–C1–C2	126.78(11)	126.23	126.62(9)	126.39
C1–C2–C3	124.42(9)	123.45	125.49(8)	123.84
C1–C2–C6	117.61(10)	118.08	116.90(9)	117.85
C3–C2–C6	117.96(9)	118.47	117.60(9)	118.31
C2–C3–C4	125.41(9)	125.03	121.59(8)	121.90
C2–C3–O3	114.45(9)	114.85	117.93(9)	117.91
C4–C3–O3	120.05(10)	120.10	120.40(9)	120.14
C3–C4–C5	110.37(10)	112.24	111.17(8)	112.37
C3–O3–C9	120.88(8)	122.15	120.15(8)	121.82
C2–C6–N1	178.88(11)	179.63	177.83(9)	178.94
C1–O1–C7	115.38(7)	116.28	116.30(7)	115.98
C2–C3–C4–C5 <sup>b)</sup>	90.12(14)	90.03	92.28(10)	92.77

a) Optimized at the B3LYP level of theory with the 6-31G(*d,p*) basis set. b) Torsion angle (deg).

**Scheme 2.** Resonance structures of **E-4m**.





**Figure 3.** Conformational energies calculated for **E-4m**.

**3. NMR Spectra of the Four Products: E-4m, Z-4m, E-4e, and Z-4e.** The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra for the four unsaturated esters were unambiguously assigned via a combination of 1D and 2D (HMQC, HMBC) experiments. The  $\beta$ -carbon signals (185–189 ppm) appeared at a lower field relative to those of the carbonyl carbon (161–164 ppm) as a result of the accumulated effects of the  $\alpha$ - and  $\beta$ -substituents.<sup>21</sup> In contrast, the  $\alpha$ -carbon peaks shifted to the high field (85–86 ppm) mainly owing to the influences of the  $\alpha$ -cyano and  $\beta$ -alkoxy groups.

The experimental values of  $^1\text{H}$  NMR chemical shifts that correspond to the  $\gamma$ - and  $\delta$ -protons of the four products are summarized in Table 2. In comparison to the *Z*-isomers, the  $\gamma$ -proton signals of the *E*-isomers exhibit a low-field shift of 0.29 ppm and their  $\delta$ -protons are slightly shifted to the opposite direction (−0.08 ppm). In order to elucidate these chemical shifts, theoretical calculations using the gauge-independent atomic orbital (GIAO) method were performed, and the NMR parameters calculated for the  $\gamma$ - and  $\delta$ -protons are also listed in Table 2. Although the calculations were performed only for the most stable conformations (*i.e.*, optimized using the density functional theory (DFT) method (*vide supra*)), the simulated NMR chemical shifts appeared to account reasonably well for the observed data. Owing to the fixed conformation, two  $\gamma$ -protons are differentiated in each calculated model, giving two chemical shifts. In accordance with the dynamic site exchange of these protons (between two energetically equivalent conformations), the averaged value sufficiently reproduces the signal position that is measured in solution. Although there are numerous possible conformations in the solution phase, this observation suggests that the most stable conformer is a dominant contributor in these cases.

With respect to **E-4m** and **E-4e**, the two peak positions of the  $\gamma$ -protons (calculated for the fixed conformation) are appreciably separated from each other. The lower field signal at around 3.8 ppm is derived from the  $\gamma$ -proton that is located closer to the carbonyl group, which causes a deshielding effect ( $\text{H}\cdots\text{O}$  separation at 2.223 Å for **E-4m**). Meanwhile, one  $\gamma$ -proton approaches the adjacent cyano group in **Z-4m** and **Z-4e** ( $\text{H}\cdots\text{C}$  separation at 2.452 Å for **Z-4m**). Its NMR peak was computed at 2.8 ppm, which is 1 ppm upfield as compared to the aforementioned *E* isomers, indicating a smaller long-range effect imparted by the cyano group. The other  $\gamma$ -proton is directed toward the  $\beta$ -alkoxy group in both geometrical configurations,

and its chemical shift was calculated in the range of 2.2–2.5 ppm.

**Table 2.** Selected  $^1\text{H}$  NMR chemical shifts of the  $\gamma$ - and  $\delta$ -protons in **4**

	$\gamma$ -protons		$\delta$ -protons	
	Obsd <sup>a)</sup>	Calcd <sup>b)</sup>	Obsd <sup>a)</sup>	Calcd <sup>b)</sup>
<b>E-4m</b>	3.03	3.79, 2.26 av. 3.03	1.22	1.39, 1.27, 1.03 av. 1.23
<b>Z-4m</b>	2.74	2.80, 2.49 av. 2.65	1.30	1.21, 1.32, 1.34 av. 1.29
<b>E-4e</b>	3.01	3.78, 2.24 av. 3.01	1.21	1.02, 1.29, 1.25 av. 1.19
<b>Z-4e</b>	2.72	2.81, 2.47 av. 2.64	1.29	1.18, 1.33, 1.34 av. 1.28

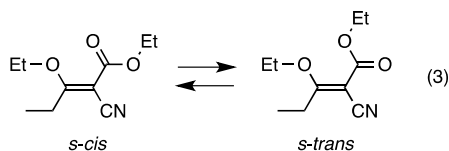
a) Measured in  $\text{CDCl}_3$  at 25 °C. b) Calculated for the fixed conformations at the lowest energy in  $\text{CHCl}_3$  using the GIAO method. Chemical shifts for individual hydrogen atoms and their averaged values (av.) are shown.

Regarding the discrimination of *cis* and *trans* isomers of analogous compounds, *i.e.*  $\alpha$ -cyano- $\beta$ -alkoxy- $\beta$ -alkylacrylic esters, Hayashi *et al.* have previously described the remarkable difference observed for the  $^1\text{H}$  NMR peak positions (0.29 ppm) between the  $\gamma$  protons of the isomers. However, the assignment of the configurations could not be clarified owing to the complicated effects of both the ester bond and the cyano group.<sup>13</sup> The configurations assumed by those authors based on NMR spectra have been confirmed correct by the present study.

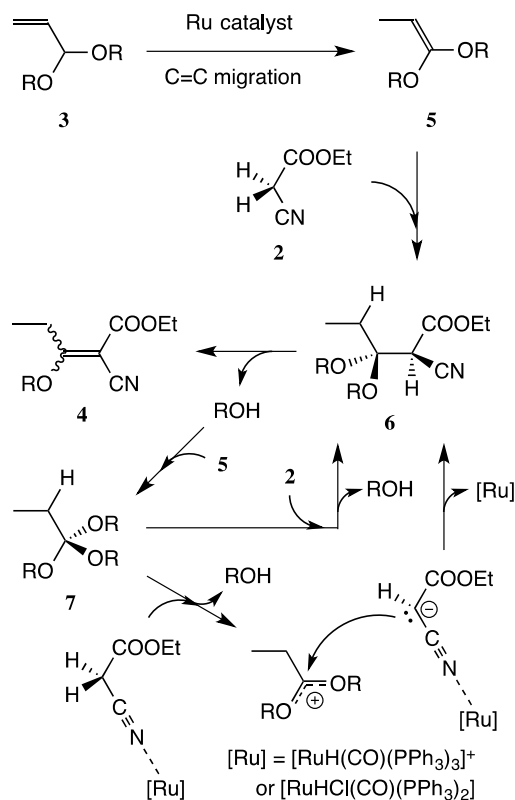
**4. IR Spectra of the Four Products: E-4m, Z-4m, E-4e, and Z-4e.** Infrared (IR) measurements of **E-4m**, **E-4e**, and **Z-4m** were performed via the KBr method using crystalline samples, while the spectrum of a neat sample was recorded for **Z-4e** (a liquid at room temperature). Each spectrum shows the absorption characteristic of cyano group, in the range of 2217–2220  $\text{cm}^{-1}$ . The frequencies of the C=C bond stretch depend on the *E/Z* geometries as those of the *E*-isomers (1562 and 1563  $\text{cm}^{-1}$  for **E-4m** and **E-4e**, respectively) are shifted to a region approximately 10  $\text{cm}^{-1}$  lower than those of the *Z*-isomers (1574 and 1571  $\text{cm}^{-1}$  for **Z-4m** and **Z-4e**, respectively).

The C=O stretching mode of **E-4m** appeared at 1714  $\text{cm}^{-1}$ , which is characteristic of  $\alpha,\beta$ -unsaturated carbonyl compounds. The corresponding absorption frequency of **E-4e** showed an almost identical value (1707  $\text{cm}^{-1}$ ), while that of **Z-4m** (1724  $\text{cm}^{-1}$ ) was observed at a higher frequency (by 10  $\text{cm}^{-1}$ ) relative to **E-4m**. In contrast, the absorption of **Z-4e** was split to 1696 and 1730  $\text{cm}^{-1}$ . This presumably indicates the presence of rotational isomers in the liquid state of **Z-4e** as shown in Eq. 3, whereas the conformations of the other three compounds are fixed in the crystal form, *i.e.* the C=C and C=O bonds are oriented in an *s-cis* configuration. The conformational equilibrium between the *s-cis* and *s-trans* forms of the  $\alpha,\beta$ -unsaturated carbonyl compounds is known,<sup>22</sup> and the distinct conformations of certain derivatives have been distinguished based on their IR spectra.<sup>23</sup> To test the hypothesis that **Z-4e** exists as *s-cis* and *s-trans* conformers, DFT vibrational analyses were performed to compare the C=O stretching frequencies. The theoretical values at the B3LYP/6-31G(*d,p*) level are 1723 and 1694  $\text{cm}^{-1}$  for the *s-cis* and *s-trans* forms, respectively; and these values agree well with the observed peaks. The calculation for **Z-4e** also suggests that the *s-cis* form is more stable than the *s-trans* form, whereas the small difference in the theoretical energies ( $\Delta G = 7.4$  kJ/mol at 25 °C) is consistent with the existence of both rotational isomers. Owing to a small energy difference as well as a low rotational barrier, the exchange between the two rotational isomers occurs much faster than the

NMR time scale. As such, all derivatives of **4** are observed as a single species from solution NMR spectra.



**5. Plausible Reaction Mechanisms.** The plausible mechanisms for the formation of **4** are shown in Scheme 3. Krompiec *et al.* have previously demonstrated that some Ru complexes (including **1**) catalyze the C=C bond migration of various  $\alpha,\beta$ -unsaturated acetals to give the corresponding ketene acetals.<sup>24</sup> It has been confirmed by NMR measurements that treating **3e** with 3 mol% of **1** in benzene at 80 °C led to the complete consumption of **3e** within 1 h, along with the formation of ketene diethyl acetal **5e** (R = Et). Under the same conditions, **3e** remained unchanged in the absence of **1**, regardless of whether **2** was present or not. The C=C bond of **5** is susceptible to an electrophilic addition of the active C–H bond of **2** that results into addition product **6**, which is further converted to **4** by the elimination of one alcohol molecule. An NMR study monitoring the reaction of **5e** with **2** in the absence of **1** confirmed that these steps proceeded even without the aid of a catalyst. After heating at 80 °C for 1 h, 28% yield of **4e** (*E/Z* = 75/25) and 63% of unreacted **2** were observed when the reaction was conducted without **1**. Conversion was improved only slightly in the control experiment using 3 mol% of **1** (36% of **4e** (*E/Z* = 87/13) and 56% of **2**), indicating a little accelerating effect of the catalyst. Lewis acidic Ru complexes have been shown to enhance the acidity of the  $\alpha$ -H in nitriles,<sup>2c,25</sup> and this may assist the electrophilic addition and alcohol elimination steps.



**Scheme 3.** Plausible mechanisms for the formation of **4**.

In the above (short-duration) reactions performed in the absence or presence of **1**, triethyl orthopropionate **7e** (R = Et) was also formed in 40% or 35% yields, respectively, by the

reaction of **5e** with ethanol, which is produced together with **4e**. These observations indicate that **5** reacts faster with alcohol than with **2**, thus making the condensation of **7** with **2** the predominant pathway to produce **4** in the later stage. The reaction of **7e** with **2** occurred even in the absence of catalysts, albeit more slowly than that of **5e** with **2**. Heating a benzene solution of **7e** and an equimolar amount of **2** at 80 °C produced **4e** in 36% crude NMR yield after 24 h, while the addition of 3 mol% **1** increased the yield to 55%. Despite the promotion of reaction by **1** likely by the activation of **2**, the yield of **4e** was lower in the reaction using **7e** than when the reaction was carried out using **3e** (75% isolated yield). The *E/Z* ratios of crude **4e** after 24 h at 80 °C were found to be identical (87/13) independent of the starting compounds, suggesting that it is determined by thermodynamic factors. The DFT calculations indicate that *E*-**4e** is more stable than *Z*-**4e** by 6.6 kJ/mol at 80 °C, leading to an estimated *E/Z* ratio of 90/10 at equilibrium. The calculated energy difference between *E*- and *Z*-**4m** is 8.9 kJ/mol at 80 °C, and the estimated *E/Z* ratio is 95/5.

### Conclusion

Herein, we have demonstrated a synthetic method to access ethyl 2-cyano-3-alkoxy-2-enoates via a coupling reaction between  $\alpha,\beta$ -unsaturated acetals and cyanoacetate, catalyzed by a Ru complex under relatively mild conditions. The reaction is believed to proceed via a C=C bond migration of the  $\alpha,\beta$ -unsaturated acetal to give the ketene acetal, followed by a condensation reaction with cyanoacetate. The Ru catalyst was shown to be indispensable in the former step. The *E*- and *Z*-isomers were concurrently produced in these reactions, and they were unambiguously determined via X-ray crystallography for the first time. The crystallographic study also revealed structural distortion due to steric hindrance around the tetrasubstituted alkene moiety. DFT calculation performed using the restricted B3LYP hybrid functional with the 6-31G(*d,p*) basis set agreed with the solid-state structure and conformation. It was confirmed that the theoretical values of <sup>1</sup>H chemical shifts and IR vibrational frequencies, estimated via the DFT study, are consistent with the experimental values.

### Experimental

**General Procedure.** Organic chemicals were obtained from commercial sources and used as received. [RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>] (**1**) was prepared according to a literature method.<sup>26</sup> NMR spectra were recorded on a JEOL ECX-400 spectrometer at 25 °C (<sup>1</sup>H at 400 MHz and <sup>13</sup>C at 100 MHz), and chemical shifts are reported in ppm downfield from SiMe<sub>4</sub>. IR spectra were measured on a JASCO FT/IR-600 spectrophotometer. Elemental analyses were performed using a Perkin-Elmer 2400 series II CHN analyzer.

#### Synthesis of Ethyl 2-Cyano-3-methoxypent-2-enoate.

A 20-mL Schlenk flask charged with [RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>] (**1**: 30 mg, 0.031 mmol) and a magnetic stirring bar was evacuated, and backfilled with nitrogen. Ethyl cyanoacetate (**2**: 115 mg, 1.00 mmol), acrolein dimethyl acetal (**3m**: 116 mg, 1.10 mmol), and benzene (0.25 mL) were added using a syringe, and the flask was then fitted to a reflux condenser, topped with a nitrogen bubbler. The reaction mixture was heated with stirring at 80 °C for 24 h under a slow stream of nitrogen, during which the color of the mixture turned from yellow to orange. After evaporating volatile materials from the crude mixture, the residue was subjected to column chromatography on silica gel and eluted with hexane/diethyl ether (1:1), which fractionated **2**, *E*-**4m**, and *Z*-**4m** in the listed order. The major product *E*-**4m** was isolated as a yellow solid (88 mg, 48% yield) and recrystallized from ethyl acetate/hexane to afford single crystals that are suitable for

X-ray analysis. The minor isomer **Z-4m** was purified further through recrystallization from ethyl acetate/hexane at 3 °C to give colorless crystals (12 mg, 6% yield).

**Data for E-4m:** <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.24 (q, 2H, *J* = 7.1 Hz, CO<sub>2</sub>CH<sub>2</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 3.03 (q, 2H, *J* = 7.6 Hz, CH<sub>3</sub>CH<sub>2</sub>C), 1.33 (t, 3H, *J* = 7.1 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.22 (t, 3H, *J* = 7.6 Hz, CH<sub>3</sub>CH<sub>2</sub>C). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ 188.7 (C=C–O), 163.4 (C=O), 115.2 (CN), 85.3 (CCN), 61.1 (CO<sub>2</sub>CH<sub>2</sub>), 56.5 (OCH<sub>3</sub>), 21.7 (CH<sub>3</sub>CH<sub>2</sub>C), 14.2 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 11.5 (CH<sub>3</sub>CH<sub>2</sub>C). IR (KBr): 2219 (s, C≡N), 1714 (s, C=O), 1562 (s, C=C) cm<sup>-1</sup>. Anal. calcd for C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>: C, 59.00; H, 7.15; N, 7.65%. Found: C, 59.20; H, 7.27; N, 7.66%.

**Data for Z-4m:** <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.20 (q, 2H, *J* = 7.0 Hz, CO<sub>2</sub>CH<sub>2</sub>), 4.05 (s, 3H, OCH<sub>3</sub>), 2.74 (q, 2H, *J* = 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>C), 1.300 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>C), 1.298 (t, 3H, *J* = 7.0 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ 186.1 (C=C–O), 161.5 (C=O), 117.1 (CN), 85.8 (CCN), 61.0 (CO<sub>2</sub>CH<sub>2</sub>), 57.8 (OCH<sub>3</sub>), 24.8 (CH<sub>3</sub>CH<sub>2</sub>C), 14.1 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 11.7 (CH<sub>3</sub>CH<sub>2</sub>C). IR (KBr): 2217 (s, C≡N), 1724 (s, C=O), 1574 (s, C=C) cm<sup>-1</sup>. Anal. calcd for C<sub>9</sub>H<sub>13</sub>NO<sub>3</sub>: C, 59.00; H, 7.15; N, 7.65%. Found: C, 58.96; H, 7.34; N, 7.48%.

**Synthesis of Ethyl 2-Cyano-3-ethoxypent-2-enoate.** A 20-mL Schlenk flask charged with [RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>] (**1**: 30 mg, 0.031 mmol) and a magnetic stirring bar was evacuated, and backfilled with nitrogen. Ethyl cyanoacetate (**2**: 115 mg, 0.994 mmol), acrolein diethyl acetal (**3e**: 152 mg, 1.11 mmol), and benzene (0.25 mL) were added using a syringe, and the flask was then fitted to a reflux condenser, topped with a nitrogen bubbler. The reaction mixture was heated with stirring at 80 °C for 24 h under a slow stream of nitrogen, during which the color of the mixture turned from yellow to reddish brown. After evaporating volatile materials from the crude mixture, the residue was subjected to column chromatography on silica gel and eluted with hexane/diethyl ether (2:1), which fractionated **2**, **E-4e**, and **Z-4e** in the listed order. The major product **E-4e** was isolated as a yellow solid (128 mg, 65% yield) and recrystallized from ethyl acetate/hexane to afford single crystals that are suitable for X-ray analysis. The minor isomer **Z-4e** was obtained in its pure form after repeated column chromatography as a yellow oil (20 mg, 10% yield).

**Data for E-4e:** <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.33 (q, 2H, *J* = 7.0 Hz, C=C–OCH<sub>2</sub>), 4.23 (q, 2H, *J* = 7.2 Hz, CO<sub>2</sub>CH<sub>2</sub>), 3.01 (q, 2H, *J* = 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>C), 1.44 (t, 3H, *J* = 7.0 Hz, C=C–OCH<sub>2</sub>CH<sub>3</sub>), 1.32 (t, 3H, *J* = 7.2 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.21 (t, 3H, *J* = 7.5 Hz, CH<sub>3</sub>CH<sub>2</sub>C). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ 188.5 (C=C–O), 163.6 (C=O), 115.3 (CN), 85.2 (CCN), 65.7 (C=C–OCH<sub>2</sub>), 61.1 (CO<sub>2</sub>CH<sub>2</sub>), 22.4 (CH<sub>3</sub>CH<sub>2</sub>C), 15.0 (C=C–OCH<sub>2</sub>CH<sub>3</sub>), 14.2 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 11.8 (CH<sub>3</sub>CH<sub>2</sub>C). IR (KBr): 2220 (s, C≡N), 1707 (s, C=O), 1563 (s, C=C) cm<sup>-1</sup>. Anal. calcd for C<sub>10</sub>H<sub>15</sub>NO<sub>3</sub>: C, 60.90; H, 7.67; N, 7.10%. Found: C, 60.88; H, 7.62; N, 7.25%.

**Data for Z-4e:** <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.29 (q, 2H, *J* = 7.0 Hz, C=C–OCH<sub>2</sub>), 4.21 (q, 2H, *J* = 7.0 Hz, CO<sub>2</sub>CH<sub>2</sub>), 2.72 (q, 2H, *J* = 7.6 Hz, CH<sub>3</sub>CH<sub>2</sub>C), 1.45 (t, 3H, *J* = 7.0 Hz, C=C–OCH<sub>2</sub>CH<sub>3</sub>), 1.30 (t, 3H, *J* = 7.0 Hz, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.29 (t, 3H, *J* = 7.6 Hz, CH<sub>3</sub>CH<sub>2</sub>C). <sup>13</sup>C{<sup>1</sup>H} NMR (CDCl<sub>3</sub>): δ 185.7 (C=C–O), 161.6 (C=O), 117.3 (CN), 85.7 (CCN), 67.0 (C=C–OCH<sub>2</sub>), 60.8 (CO<sub>2</sub>CH<sub>2</sub>), 25.4 (CH<sub>3</sub>CH<sub>2</sub>C), 15.0 (C=C–OCH<sub>2</sub>CH<sub>3</sub>), 14.1 (CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 11.9 (CH<sub>3</sub>CH<sub>2</sub>C). IR (neat): 2218 (s, C≡N), 1730, 1696 (s, C=O), 1571 (s, C=C) cm<sup>-1</sup>. Anal. calcd for C<sub>10</sub>H<sub>15</sub>NO<sub>3</sub>: C, 60.90; H, 7.67; N, 7.10%. Found: C, 60.77; H, 7.84; N, 6.96%.

**Reaction of 1,1-Diethoxypropene with Ethyl Cyanoacetate in the Absence of Ru Catalyst 1.** In a 20-mL Schlenk flask equipped with a magnetic stirring bar and a reflux condenser, a mixture of [RuHCl(CO)(PPh<sub>3</sub>)<sub>3</sub>] (**1**: 29 mg, 0.030 mmol), acrolein diethyl acetal (**3e**: 152 mg, 1.11 mmol), and

benzene-d<sub>6</sub> (0.50 mL) was heated with stirring at 80 °C for 1 h under a slow stream of nitrogen. Subsequently, the reflux condenser was removed, and the reaction vessel was connected with another 20-mL Schlenk flask equipped with a magnetic stirring bar through a glass U-shaped tube. Volatile materials were transferred to the latter flask by trap-to-trap distillation under vacuum at room temperature using a liquid nitrogen bath as a refrigerant. NMR analysis of the obtained colorless liquid showed the absence of **3e** and the presence of 1,1-diethoxypropene (**5e**) and triethyl orthopropionate (**7e**) in a 9:1 ratio. Ethyl cyanoacetate (**2**: 115 mg, 0.994 mmol) was added to this mixture using a syringe, and the flask was fitted to a reflux condenser and heated with stirring at 80 °C for 1 h under nitrogen. After cooling the resulting colorless liquid, naphthalene (30.1 mg, 0.235 mmol) was added as an internal standard, and the mixture was sampled for NMR measurements.

**NMR Data for 5e** (lit.<sup>27</sup>): <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>): δ 3.84 (q, 2H, *J* = 7.0 Hz, OCH<sub>2</sub>), 3.64 (q, 1H, *J* = 7.0 Hz, CH=C), 3.44 (q, 2H, *J* = 7.0 Hz, OCH<sub>2</sub>), 1.76 (d, 3H, *J* = 7.0 Hz, CH<sub>3</sub>CH=), 1.09, 1.01 (t, 3H each, *J* = 7.0 Hz, OCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C{<sup>1</sup>H} NMR (C<sub>6</sub>D<sub>6</sub>): δ 158.6 (C=C–O), 74.1 (CH=C), 63.6, 63.1 (OCH<sub>2</sub>), 15.1, 14.5 (OCH<sub>2</sub>CH<sub>3</sub>), 9.8 (CH<sub>3</sub>CH=).

**X-ray crystallography.** Single crystals were mounted on cryoloops with oil, and cooled to 113 K. All diffraction studies were performed on a Rigaku Mercury-CCD diffractometer, equipped with a graphite monochromatized Mo-Kα source (λ = 0.71070 Å). Data were processed using the CrystalClear program package<sup>28</sup> and corrected for absorption. Structure solution and refinements were performed using the CrystalStructure program package.<sup>29</sup> The positions of non-hydrogen atoms were determined via direct methods (SIR2008<sup>30</sup>), and refined with anisotropic thermal parameters using full-matrix least-squares techniques (SHELXL97<sup>31</sup>). All hydrogen atoms were found in Fourier maps and refined isotropically. Details of crystallographic studies are listed in Table 3. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Deposition numbers CCDC-1489271 for **E-4m**, 1489272 for **Z-4m**, and 1489273 for **E-4e**. Copies of the data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/conts/retrieving.html> (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; E-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

**Calculation.** All calculations were carried out using the Gaussian09 program package.<sup>32</sup> The restricted B3LYP hybrid functional was used with the 6-31G(*d,p*) basis set. Thermal energies were estimated from the values obtained via frequency analysis with the optimized structure in benzene. NMR spectrum was calculated using the GIAO method with the optimized structure in chloroform. The solvent effect of benzene or chloroform was modeled via the polarizable continuum model using the integral equation formalism variant (IEFPCM). It was confirmed that all optimized structures have no vibrational modes with imaginary frequencies. Theoretical infrared vibrational frequencies were compared with experimental values after scaling (factor = 0.9613).<sup>33</sup> Atomic charges and bond orders were calculated by natural population analysis (NPA) and natural bond orbital (NBO) bond order analysis, respectively.

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## Supporting information

NPA charges and NBO bond orders of **E-4m** (*s-cis*). Coordinates and energies of all conformers optimized by B3LYP/6-31G(*d,p*) in benzene. NMR spectra of **4m** and **4e**. This material is available electronically on J-STAGE.

**Table 3.** Crystallographic data of **E-4m**, **Z-4m**, and **E-4e**

	<b>E-4m</b>	<b>Z-4m</b>	<b>E-4e</b>
Formula	C <sub>9</sub> H <sub>13</sub> NO <sub>3</sub>	C <sub>9</sub> H <sub>13</sub> NO <sub>3</sub>	C <sub>10</sub> H <sub>15</sub> NO <sub>3</sub>
Formula weight	183.21	183.21	197.23
Space group	<i>P</i> -1	<i>P</i> -1	<i>P</i> 2 <sub>1</sub> / <i>n</i>
<i>a</i> /Å	6.369(1)	7.681(4)	12.308(5)
<i>b</i> /Å	7.734(1)	7.899(4)	7.671(3)
<i>c</i> /Å	10.640(2)	8.117(4)	12.406(4)
<i>a</i> /deg	100.390(3)	85.37(2)	90
<i>β</i> /deg	106.682(4)	83.05(2)	114.021(4)
<i>γ</i> /deg	101.530(3)	77.96(1)	90
<i>V</i> /Å <sup>3</sup>	475.9(2)	477.3(5)	1069.9(6)
<i>Z</i>	2	2	4
$\rho_{\text{calc}}$ /g cm <sup>-3</sup>	1.278	1.275	1.224
$\mu(\text{Mo } K\alpha)$ /mm <sup>-1</sup>	0.096	0.096	0.090
No. unique reflns	2167	2264	2531
<i>R</i> <sub>int</sub>	0.0215	0.0214	0.0185
Transmn factor	0.841–0.993	0.841–0.981	0.790–0.982
No. variables	170	170	187
<i>R</i> 1 <sup>a)</sup>	0.0357	0.0325	0.0330
<i>wR</i> 2 <sup>b)</sup>	0.0982	0.0962	0.0933
<i>gof</i> <sup>c)</sup>	1.074	1.091	1.067

<sup>a)</sup>  $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$  ( $F_o^2 > 2\sigma(F_o^2)$ ). <sup>b)</sup>  $wR2 = [\sum (w(F_o^2 - F_c^2)^2) / \sum w(F_o^2)^2]^{1/2}$  (all data);  $w = [(\sigma(F_o^2))^2 + (aP)^2 + bP]^{-1}$ ,  $P = (F_o^2 + 2F_c^2)/3$  <sup>c)</sup>  $gof = [\sum w(|F_o| - |F_c|)^2 / \{(\text{No. unique reflns}) - (\text{No. variables})\}]^{1/2}$ .

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## Graphical Abstract

Structural determination, DFT calculation, and formation mechanism of ethyl 2-cyano-3-alkoxybut-2-enoates synthesized via Ru-mediated coupling reaction between  $\alpha,\beta$ -unsaturated acetals and cyanoacetate

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The coupling reaction between  $\alpha,\beta$ -unsaturated acetals and ethyl cyanoacetate, catalyzed by  $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_3]$ , afforded ethyl 2-cyano-3-alkoxybut-2-enoates in moderate yields. The characterization of the *E*- and *Z*-isomers was performed using NMR and IR spectroscopies, as well as single crystal X-ray diffraction study. Excellent consistency between these characterization data and DFT calculations was confirmed.

