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Novel Knöevenagel-type reaction via titanium enolate derived from Ti(O-*i*-Pr)$_4$ and diketene☆

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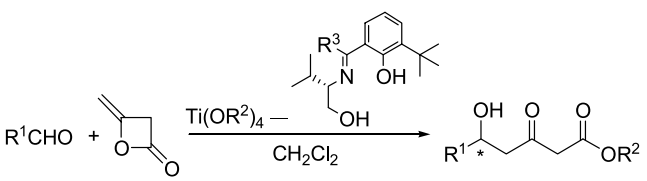
Abstract—Knöevenagel-type reaction between diketene and aldehydes proceeded in the presence of Ti(O-*i*-Pr)$_4$. This reaction proceeded via titanium enolate derived from Ti(O-*i*-Pr)$_4$ and diketene. As for the stereoselectivity of the products, *E*-isomers were produced predominantly in the case of aromatic aldehydes.

1. Introduction

The Knöevenagel reaction is a classical and well-known reaction as a condensation between carbonyl compounds and activated methylene compounds catalyzed by amines.[1] As activated methylene compounds, alkyl acetoacetates and dialkyl malonates have been often used.

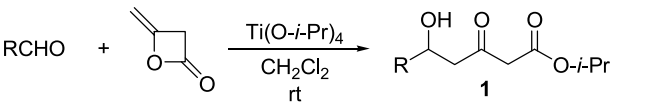
In 1994, we reported that the reaction of diketene with aldehydes was promoted by Ti(O-*i*-Pr)$_4$ and demonstrated the first example of an asymmetric version of this reaction. That is, chiral Schiff base-titanium alkoxide complexes promoted the enantioselective reaction of diketene to aldehydes which leads to the asymmetric synthesis of optically active 5-hydroxy-3-ketoesters (Eq. (1)).[2] This reaction was applied to asymmetric synthesis of potential inhibitors of HMG coenzyme reductase.[3]



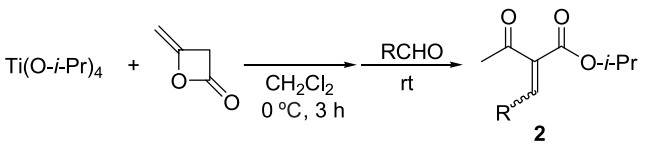
(1)

2. Results and discussion

During the course of our study of the reaction mechanism of Ti(O-*i*-Pr)$_4$-promoted reaction of diketene with aldehydes, we found that a change of the order of addition of the reagents afforded different products (Eqs. (2) and (3)). That is, 5-hydroxy-3-ketoesters **1** were obtained when diketene was added to the mixture of aldehydes and Ti(O-*i*-Pr)$_4$ in CH_2Cl_2. On the other hand, when diketene and Ti(O-*i*-Pr)$_4$ were mixed in advance and the mixture was stirred for 3 h, subsequent addition of aldehydes to the reaction mixture gave Knöevenagel reaction products **2**.



(2)



(3)

Since a mixture of **1** and **2** was obtained when aldehydes were added instantly after diketene and Ti(O-*i*-Pr)$_4$ were mixed, the stirring time of 3 h is important for the reaction of Eq. (3). The titanium enolate species were considered to be generated from Ti(O-*i*-Pr)$_4$ and diketene as intermediate. The reaction of titanium enolates prepared from titanium reagents/amine system with electrophiles such as alkyl halides and aldehydes has been well studied,[4] but to our knowledge, few examples of this type of Knöevenagel reaction using diketene were reported so far.[5,6] In this paper, we would like to report the details of a new type of Knöevenagel reaction via titanium enolate derived from Ti(O-*i*-Pr)$_4$ and diketene.

☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.06.018.

Keywords: Knöevenagel reaction; Titanium enolate; Diketene.
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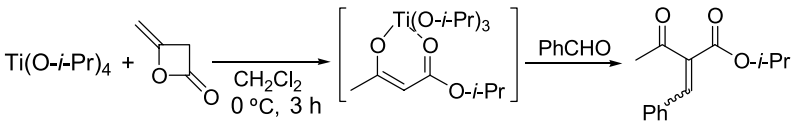
Table 1. Effect of the ratio of Ti(O-*i*-Pr)$_4$ and diketene on the chemical yield of the product[a]



Entry	Ti(O-*i*-Pr)$_4$/equiv	Diketene/equiv	Conditions		Product
			Temp/°C	Time/h	% Yield (*E*/*Z*)[b]
1	1	1	20	48	34 (88/12)
2	2	1	25	43	68 (89/11)
3	1	2	24	44	0 (–)

[a] 1.0 equiv. of PhCHO was used.
[b] *E*/*Z* ratio was determined by ^{1}H NMR analysis.

At first, we examined the effect of the ratio of Ti(O-*i*-Pr)$_4$ and diketene on the chemical yield of the product (Table 1). As shown in Table 1, the ratio of Ti(O-*i*-Pr)$_4$, diketene and benzaldehyde in 2:1:1 afforded the product in highest yield (68%). However, when 2.0 equiv of diketene was used, no product was obtained. To understand these results and to confirm the generation of titanium enolate, we measured the ^{1}H NMR spectra of mixtures of Ti(O-*i*-Pr)$_4$ and diketene in a variety of ratios (Figs. 1–3).

Figure 1 shows the ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in a ratio of 1:1 in $CDCl_3$ after 3.5 h. The generated species were assumed as titanium enolate **3b** with a double bond at the internal site of the isopropyl acetoacetate moiety. The peaks which appeared in 4.9 ppm of ^{1}H NMR and in 92 ppm of the ^{13}C NMR spectra should indicate the presence of double bond of internal titanium enolate. It should be noted that the peaks of Ti(O-*i*-Pr)$_4$ remained, although diketene disappeared completely in the reaction mixture. This result thus indicates that the diketene does not only react with Ti(O-*i*-Pr)$_4$ in a ratio of 1:1, but also reacts in the 1:2 ratio. We presumed that each peak of 1:1 and 1:2 enolates would be the same chemical shift value. When Ti(O-*i*-Pr)$_4$ was mixed with diketene in a ratio of 1:1, the product distribution was found to be 22% of 1:1 enolate, 31% of 1:2 enolate and 47% of Ti(O-*i*-Pr)$_4$. The ratio of 1:1 enolate, 1:2 enolate and Ti(O-*i*-Pr)$_4$ was calculated by integration of five methine proton peaks in isopropoxide moiety which appeared in the region of 4.9–4.5 ppm in Figure 1. The geometry of titanium enolate was determined by NOE experiment (see supplementary information).

Figure 2 shows the ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in a ratio of 1:2 in $CDCl_3$ after 6 h. The peaks of Ti(O-*i*-Pr)$_4$ were completely diminished. The product distribution was found to be 26% of 1:1 enolate, 74% of 1:2 enolate and 26% of diketene. Ti(O-*i*-Pr)$_4$ did not remain.

Furthermore, Figure 3 shows the ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in a ratio of 2:1 after 2.5 h which afforded the products in 5% of 1:1 enolate, 19% of 1:2 enolate and 76% of Ti(O-*i*-Pr)$_4$.

A possible mechanism of the Knöevenagel-type reaction via titanium enolate is illustrated in Scheme 1. The titanium enolate **3a** which has a double bond at the terminal site of the isopropyl acetoacetate moiety should be first generated from Ti(O-*i*-Pr)$_4$ and diketene. However, it will immediately isomerize to the internal titanium enolate **3b**. Therefore, the

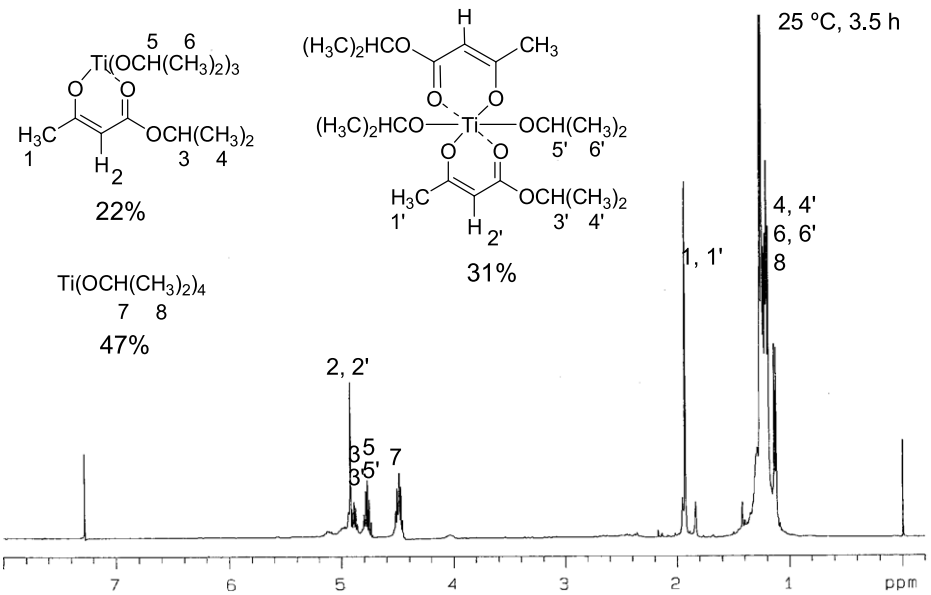


Figure 1. ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in the ratio of 1:1.

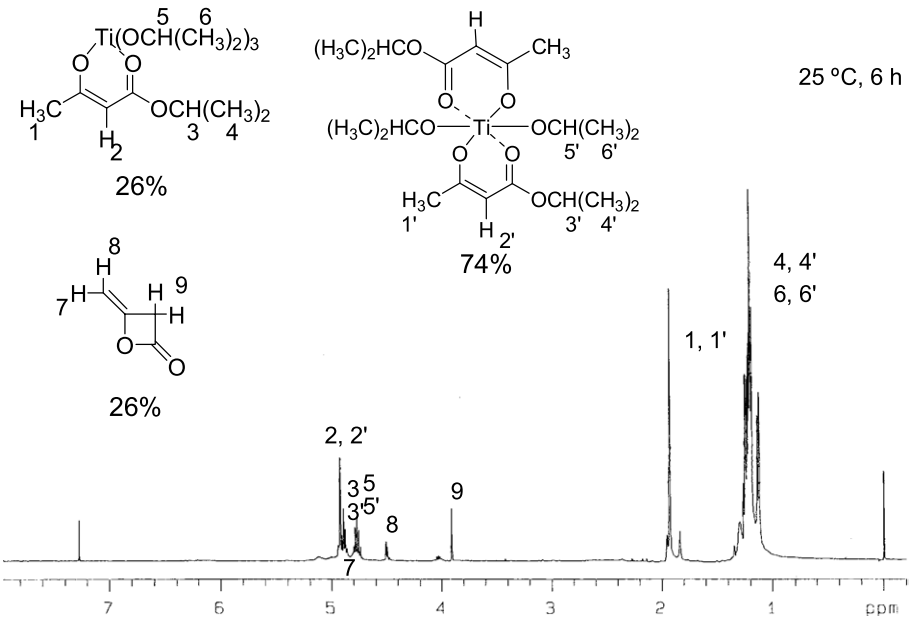


Figure 2. ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in the ratio of 1:2.

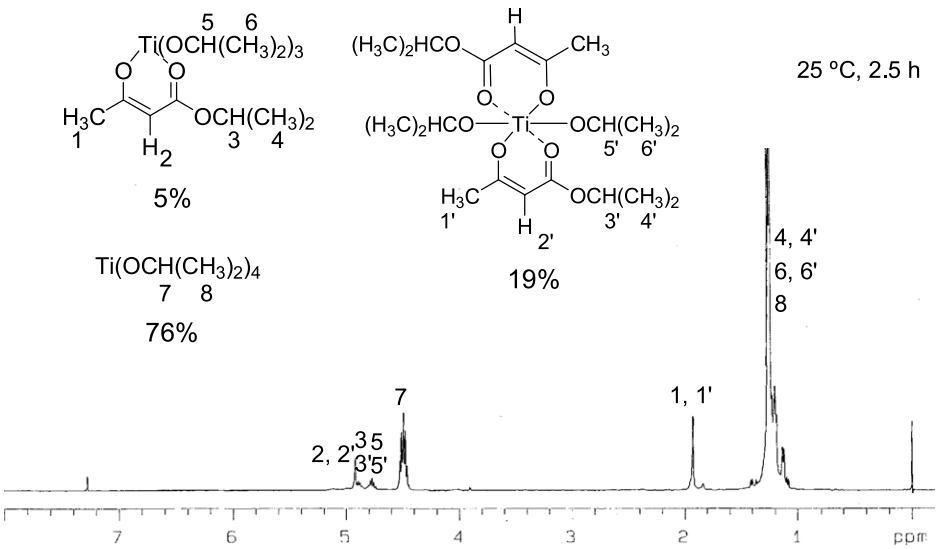
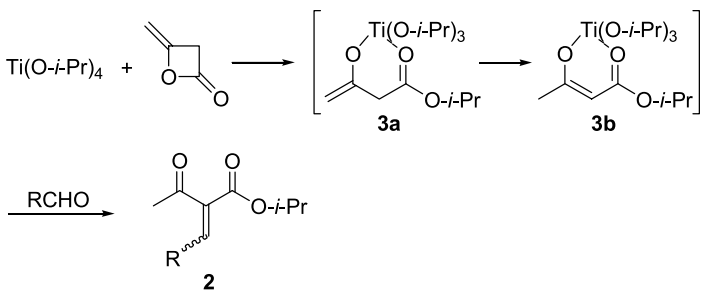


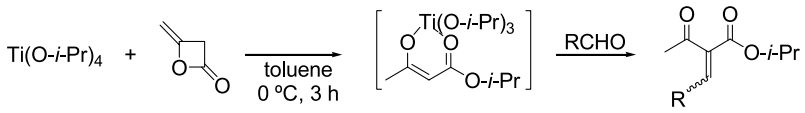
Figure 3. ^{1}H NMR spectrum of the mixture of Ti(O-*i*-Pr)$_4$ and diketene in the ratio of 2:1.

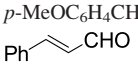
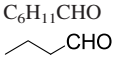
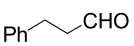


Scheme 1.

terminal titanium enolate **3a** was not observed by ^{1}H NMR. Subsequent reaction of internal titanium enolate **3b** with aldehydes produces Knöevenagel reaction products. When free Ti(O-*i*-Pr)$_4$ did not exist in the mixture (Fig. 2), the reaction did not proceed at all (entry 3 in Table 1). The fact that the presence of free Ti(O-*i*-Pr)$_4$ is necessary should indicate that titanium enolate **3b** itself has not enough reactivity to react with aldehydes. The activation of aldehyde by Ti(O-*i*-Pr)$_4$ will be required. We consider that the 1:1 enolate would be more reactive than 1:2 enolate.

Table 2. Reaction of titanium enolate with a variety of aldehydes[a]



Entry	Aldehyde	Conditions		Product	Conventional Knoevenagel condition[b]
		Temp/°C	Time/h	% Yield (*E*/*Z*)[c]	% Yield (*E*/*Z*)[c]
1	C_6H_5CHO	28	48	**2a** 79 (91/9)	48 (31/69)
2	*p*-ClC_6H_4CHO	21	46	**2b** 77 (96/4)	70 (40/60)
3	*p*-MeC_6H_4CHO	21	48	**2c** 70 (94/6)	62 (36/64)
4	*p*-$MeOC_6H_4CHO$	21	48	**2d** 62 (91/9)	54 (37/63)
5		21	6	**2e** 76 (60/40)	73 (35/65)
6	$C_6H_{11}CHO$	22	17	**2f** 80 (60/40)	80 (35/65)
7		21	5	**2g** 90 (31/69)	36 (35/65)
8		22	22	**2h** 70 (33/67)	46 (48/52)

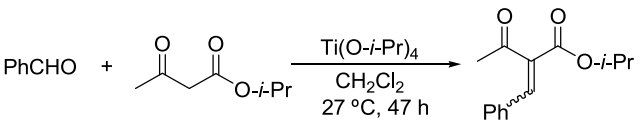
[a] The ratio of diketene: Ti(O-*i*-Pr)$_4$:aldehyde was 1:2:1.
[b] The ratio of isopropyl acetoacetate:aldehyde:piperidine was 1:1:0.1.
[c] *E*/*Z* ratio was determined by the integration of vinylic proton in the compounds **2a**–**2h** by ^{1}H NMR analysis.

Aiming at improvement of chemical yield and stereoselectivity, we examined solvents suitable for this reaction. As a result, it was found that toluene was a suitable solvent for this reaction.

A variety of aldehydes were employed in the reaction with titanium enolate (Table 2). Generally, aliphatic aldehydes exhibited higher reactivity than aromatic aldehydes. As for the geometry of the products, the reaction of aromatic aldehydes (entries 1–4) afforded *E*-geometrical isomers predominantly, which was in sharp contrast with the conventional Knöevenagel reaction.[7] The configurations of *E* and *Z* were identified by NOE experiment (see supplementary information). That is, when benzaldehyde was treated with isopropyl acetoacetate in the presence of piperidine, mixtures of *E*- and *Z*-isomers (31/69) were obtained.

On the other hand, in the cases of aliphatic aldehydes, the mixtures of *E*- and *Z*-isomers were obtained in different ratio in each aldehyde. The reaction of cinnamaldehyde and cyclohexanecarboxaldehyde furnished the *E*-isomer preferentially (60/40), but that of *n*-butanal and 3-phenyl propionaldehyde produced the *Z*-isomer preferentially (31/69 and 33/67, respectively). When we traced the reaction by ^{1}H NMR, the ratio of *E*/*Z* isomers was not changed during the reaction. Furthermore, we confirmed that it took 6–18 h to reach equilibrium (thermodynamic) ratio even at high temperature (90 °C) in the case of a cyclohexane derivative.[8] Although the detailed mechanism of this reaction including stereoselectivity is unclear, we consider that the reactivity of aldehydes affects the selectivity.

Finally, we found that when isopropyl acetoacetate was used as substrate instead of diketene, titanium enolate species were also generated from Ti(O-*i*-Pr)$_4$ and isopropyl acetoacetate. The reaction of isopropyl acetoacetate and benzaldehyde in the presence of Ti(O-*i*-Pr)$_4$ in the ratio of 1:1:2 gave Knöevenagel product **2** (59%) in the *E*/*Z* ratio of 97.3 (Eq. (4)).



59% (*E*/*Z* = 93:7) (4)

In conclusion, the present Knöevenagel reaction has the following characteristic features. (1) Alkyl acetoacetate is not used, but diketene was used as the C-4 unit source. (2) The reaction takes place not under basic conditions like the conventional Knöevenagel reaction, but proceeds under mild acidic conditions. (3) The stereoselectivity of the double bond of the products was in contrast to the conventional Knöevenagel reaction. Especially, in the case of aromatic aldehydes, *E*-isomers were produced exclusively.

3. Experimental

3.1. General methods

All melting points were measured on a Yanaco MP-500D and uncorrected. ^{1}H and ^{13}C NMR spectra (400 and 100.6 MHz, respectively) were recorded on a JEOL JNM-GX 400 by use of $CDCl_3$ containing TMS as the internal standard. IR spectra were measured on a HITACHI I-2000. Elemental analyses were performed on a Yanaco CHN Corder MT-5. Mass spectra were taken on a Shimadzu GCMS-QP 2000A. Thin-layer chromatography (TLC) was carried out on foil plates, Silica Gel 60 F254 (E. Merck; layer thickness 0.2 mm). Preparative column chromatography was carried out on Fuji Silysia BW-820MH.

3.2. Typical procedure for the Knöevenagel type reaction via titanium enolate

A mixture of Ti(O-*i*-Pr)$_4$ 2.95 mL (10 mmol) and toluene 5 mL was placed in a Shlenk tube under argon atmosphere. To this solution, diketene 0.39 mL (5 mmol) was added and stirred at 0 °C for 3 h. Then, benzaldehyde 0.51 mL (5 mmol) was added and the mixture was stirred at room temperature for 48 h. After the reaction mixture was poured into 1 N HCl and vigorously stirred at 0 °C for 1 h, it was extracted by ethyl acetate and the extract was washed with sodium bicarbonate and brine solution. The organic layer was dried with anhydrous sodium sulfate and evaporated. An aliquot for ^{1}H NMR measurement to determine the *E*/*Z* ratio was removed. After purification by silica-gel column chromatography (50:1 hexane–ethyl acetate), isopropyl 2-acetyl-3-phenyl-2-propenoate (**2**) 926.9 mg (79%) was obtained in the *E*/*Z* ratio of 91/9.

3.3. Typical procedure for the conventional Knöevenagel reaction catalyzed by piperidine

A mixture of isopropyl acetoacetate 0.77 mL (5 mmol), benzaldehyde 0.51 mL (5 mmol), and toluene 5 mL was placed in a Shlenk tube under argon atmosphere. To this solution, piperidine 0.05 mL (0.5 mmol) was added and stirred at room temperature for 48 h. After the reaction mixture was poured into 1 N HCl and vigorously stirred at 0 °C for 1 h, it was extracted by ethyl acetate and extract was washed with sodium bicarbonate and brine solution. Organic layer was dried with anhydrous sodium sulfate and evaporated. An aliquot for ^{1}H NMR measurement to determine the ratio of *E*- and *Z*-isomers was removed. After purification by silica-gel column chromatography (50:1 hexane–ethyl acetate), isopropyl 2-acetyl-3-phenyl-2-propenoate (**2**) 556.8 mg (48%) was obtained in the *E*/*Z* ratio of 35/65.

3.4. Reaction of benzaldehyde with isopropyl acetoacetate promoted by Ti(O-*i*-Pr)$_4$ (Eq. (4))

A mixture of isopropyl acetoacetate 0.77 mL (5 mmol), benzaldehyde 0.51 mL (5 mmol), and dichloromethane 5 mL was placed in a Shlenk tube under argon atmosphere. To this solution, Ti(O-*i*-Pr)$_4$ 2.95 mL (10 mmol) was added and stirred at room temperature for 47 h. After the reaction mixture was poured into 1 N HCl and vigorously stirred at 0 °C for 1 h, it was extracted by ethyl acetate and the extract was washed with sodium bicarbonate and brine solution. The organic layer was dried with anhydrous sodium sulfate and evaporated. An aliquot for ^{1}H NMR measurement to determine the *E*/*Z* ratio was removed. After purification by silica-gel column chromatography (50:1 hexane–ethyl acetate), isopropyl 2-acetyl-3-phenyl-2-propenoate (**2**) 685.2 mg (59%) was obtained in the *E*/*Z* ratio of 93/7.

3.4.1. (*E*)-Isopropyl 2-acetyl-3-phenyl-2-propenoate ((*E*)-2a). R_f=0.51 (5:1 hexane–ethyl acetate); mp 42.6–43.6 °C; IR (KBr, ν_{max} (cm^{-1})): 1704, 1620; ^{1}H NMR: δ 7.64 (s, 1H), 7.4–7.3 (m, 5H), 5.2–5.1 (m, 1H), 2.35 (s, 3H), 1.32 (d, *J*=6.0 Hz, 6H); ^{13}C NMR: δ 203.8, 163.9, 140.0, 134.2, 133.0, 130.4, 129.8, 128.9, 69.0, 31.6, 21.8; MS *m*/*z* (relative intensity): 232 (42%), 189 (62%), 173 (22%), 131 (47%), 103 (31%), 77 (22%), 43 (100%); Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.43; H, 7.06.

3.4.2. (*Z*)-Isopropyl 2-acetyl-3-phenyl-2-propenoate ((*Z*)-2a). R_f=0.32 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1666, 1620; ^{1}H NMR: δ 7.56 (s, 1H), 7.5–7.4 (m, 5H), 5.3–5.2 (m, 1H), 2.42 (s, 3H), 1.27 (d, *J*=6.0 Hz, 6H); ^{13}C NMR: δ 194.5, 167.3, 140.8, 135.0, 133.1, 130.6, 129.6, 128.7, 69.5, 26.6, 21.5; MS *m*/*z* (relative intensity): 232 (26%), 189 (36%), 173 (17%), 131 (28%), 103 (18%), 77 (12%), 43 (100%); Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.22; H, 7.02.

3.4.3. (*E*)-Isopropyl 2-acetyl-3-(*p*-chlorophenyl)-2-propenoate ((*E*)-2b). R_f=0.51 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1627, 1589; ^{1}H NMR: δ 7.57 (s, 1H), 7.34 (s, 4H), 5.2–5.1 (m, 1H), 2.35 (s, 3H), 1.31 (d, *J*=6 Hz, 6H); ^{13}C NMR: δ 202.9, 163.6, 138.6, 136.3, 135.0, 131.3, 130.8, 129.0, 69.3, 31.0, 21.6; MS *m*/*z* (relative intensity): 266 (10%), 231 (4%), 223 (6%), 209 (25%), 165 (18%), 43 (100%); Anal. Calcd for $C_{14}H_{15}O_3Cl$: C, 63.04; H, 5.67. Found: C, 63.07; H, 5.74.

3.4.4. (*Z*)-Isopropyl 2-acetyl-3-(*p*-chlorophenyl)-2-propenoate ((*Z*)-2b). R_f=0.32 (5:1 hexane–ethyl acetate); mp 49.0–51.0 °C; IR (KBr, ν_{max} (cm^{-1})): 1736, 1666, 1620, 1589, ^{1}H NMR: δ 7.49 (s, 1H), 7.41 (d, *J*=8.4 Hz, 2H), 7.36 (d, *J*=8.4 Hz, 2H), 5.3–5.2 (m, 1H), 2.41 (s, 3H), 1.28 (d, *J*=6.4 Hz, 6H), ^{13}C NMR: δ 194.0, 167.5, 139.0, 136.7, 135.3, 131.5, 130.8, 129.0, 69.9, 26.0, 21.4; MS *m*/*z* (relative intensity): 266 (5%), 231 (3%), 209 (13%), 189 (14%), 165 (12%), 43 (100%); Anal. Calcd for $C_{14}H_{15}O_3Cl$: C, 63.04; H, 5.67. Found: C, 63.04; H, 5.67.

3.4.5. (*E*)-Isopropyl 2-acetyl-3-(*p*-methylphenyl)-2-propenoate ((*E*)-2c). R_f=0.50 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1620, ^{1}H NMR: δ 7.61 (s, 1H), 7.29 (d, *J*=8.4 Hz, 2H), 7.17 (d, *J*=8.4 Hz, 2H), 5.2–5.1 (m, 1H), 2.36 (s, 6H), 1.31 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 203.7, 164.1, 140.9, 140.3, 133.5, 130.2, 129.8, 129.6, 69.1, 31.2, 21.8, 21.4; MS *m*/*z* (relative intensity): 246 (7%), 189 (47%), 145 (24%), 115 (25%), 43 (100%); Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.99; H, 7.51.

3.4.6. (*Z*)-Isopropyl 2-acetyl-3-(*p*-methylphenyl)-2-propenoate ((*Z*)-2c). R_f=0.34 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1666, 1604; ^{1}H NMR: δ 7.51 (s, 1H), 7.38 (d, *J*=8 Hz, 2H), 7.18 (d, *J*=8 Hz, 2H), 5.3–5.2 (m, 1H), 2.39 (s, 6H), 1.29 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 194.6, 167.6, 141.3, 140.8, 134.0, 130.1, 129.8, 129.5, 69.4, 26.5, 21.5; MS *m*/*z* (relative intensity): 189 (88%), 145 (37%), 115 (35%), 43 (100%); Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.43; H, 7.51.

3.4.7. (*E*)-Isopropyl 2-acetyl-3-(*p*-methoxylphenyl)-2-propenoate ((*E*)-2d). R_f=0.34 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1605; ^{1}H NMR: δ 7.58 (s, 1H), 7.36 (d, *J*=8.4 Hz, 2H), 6.88 (d, *J*=8.4 Hz, 2H), 5.3–5.2 (m, 1H), 3.83 (s, 3H), 2.37 (s, 3H), 1.31 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 203.9, 164.3, 161.4, 140.0, 131.8, 131.7, 125.6, 114.4, 69.0, 55.4, 31.2, 21.8; MS *m*/*z* (relative intensity): 262 (9%), 231 (15%), 189 (36%), 145 (12%), 43

(100%); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.52; H, 6.97.

3.4.8. (*Z*)-Isopropyl 2-acetyl-3-(*p*-methoxylphenyl)-2-propenoate ((*Z*)-2d). R_f=0.17 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1720, 1658, 1597; ^1H NMR: δ 7.49 (s, 1H), 7.45 (d, *J*=8.8 Hz, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 5.3–5.2 (m, 1H), 3.84 (s, 3H), 2.39 (s, 3H), 1.31 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 194.6, 167.9, 161.7, 140.7, 132.6, 131.8, 125.3, 114.3, 69.2, 55.4, 26.5, 21.6; MS *m/z* (relative intensity): 262 (5%), 231 (16%), 189 (37%), 145 (14%), 43 (100%); Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.48; H, 6.99.

3.4.9. (*E*,*E*)-Isopropyl 2-acetyl-5-phenyl-2, 4-pentadienoate ((*E*)-2e). R_f=0.53 (5:1 hexane–ethyl acetate); mp: 67.0–67.4 °C; IR (KBr, ν_{max} (cm^{-1})): 1689, 1604, 1574; ^1H NMR: δ 7.50 (d, *J*=7.6 Hz, 2H), 7.44 (d, *J*= 11.6 Hz, 1H), 7.4–7.3 (m, 3H), 7.30 (d, *J*=15.2 Hz, 1H), 7.06 (d, *J*=15.2 Hz, 1H), 5.2–5.1 (m, 1H), 2.45 (s, 3H), 1.33 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 200.5, 164.9, 145.4, 144.8, 135.7, 132.4, 129.8, 128.9, 127.8, 123.5, 68.8, 31.2, 21.8; MS *m/z* (relative intensity): 258 (8%), 215 (29%), 171 (22%), 128 (31%), 43 (100%); Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.31; H, 6.98.

3.4.10. (*Z*,*E*)-Isopropyl 2-acetyl-5-phenyl-2,4-pentadienoate ((*Z*)-2e). R_f=0.32 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1712, 1612, 1581; ^1H NMR: δ 7.49 (d, *J*=7.6 Hz, 2H), 7.42 (d, *J*=11.6 Hz, 1H), 7.4–7.3 (m, 3H), 7.30 (d, *J*=11.6 Hz, 1H), 7.09 (d, *J*=14.8 Hz, 1H), 5.3–5.2 (m, 1H), 2.40 (s, 3H), 1.39 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 195.5, 165.9, 145.5, 144.2, 135.7, 132.8, 129.9, 128.9, 127.7, 123.6, 69.0, 38.0, 21.9; MS *m/z* (relative intensity): 258 (6%), 215 (17%), 171 (15%), 128 (20%), 43 (100%); Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02. Found: C, 74.31; H, 6.98.

3.4.11. (*E*)-Isopropyl 2-acetyl-3-cyclohexyl-2-propenoate ((*E*)-2f). R_f=0.64 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1635; ^1H NMR: δ 6.69 (d, *J*=10.8 Hz, 1H), 5.2–5.1 (m, 1H), 2.36 (s, 3H), 2.4–2.3 (m, 1H), 1.7–1.6 (m, 4H), 1.28 (d, *J*=6.4 Hz, 6H), 1.3–1.2 (m, 6H); ^{13}C NMR: δ 201.4, 164.2, 152.5, 134.4, 68.7, 38.2, 31.9, 31.3, 25.6, 25.1, 21.7; MS *m/z* (relative intensity): 238 (3%), 195 (7%), 178 (26%), 135 (25%), 83 (12%), 43 (100%); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.49; H, 9.49.

3.4.12. (*Z*)-Isopropyl 2-acetyl-3-cyclohexyl-2-propenoate ((*Z*)-2f). R_f=0.50 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1674, 1628; ^1H NMR: δ 6.62 (d, *J*=10.0 Hz, 1H), 5.3–5.2 (m, 1H), 2.4–2.3 (m, 1H), 2.30 (s, 3H), 1.8–1.7 (m, 4H), 1.32 (d, *J*=6.4 Hz, 6H), 1.3–1.2 (m, 6H); ^{13}C NMR: δ 195.4, 166.3, 152.0, 135.6, 68.8, 39.2, 31.8, 26.9, 25.6, 25.2, 21.8; MS *m/z* (relative intensity): 238 (1%), 195 (3%), 178 (26%), 135 (22%), 83 (9%), 43 (100%); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.40; H, 9.39.

3.4.13. (*E*)-Isopropyl 2-acetyl-2-hexenoate ((*E*)-2g). R_f=0.61 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1705, 1635; ^1H NMR: δ 6.89 (t, *J*=7.6 Hz, 1H), 5.2–5.1 (m, 1H), 2.36 (s, 3H), 2.22 (q, *J*=7.6, 7.6 Hz, 2H), 1.6–1.5 (m, 2H), 1.29 (d, *J*=6.0 Hz, 6H), 0.90 (t, *J*=7.6 Hz, 3H); ^{13}C NMR: δ 201.2, 164.1, 148.4, 135.0, 68.8, 31.3, 31.1, 21.9, 21.8, 13.8; MS *m/z* (relative intensity): 198 (1%), 156 (13%), 137 (26%), 96 (44%), 43 (100%); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 65.26; H, 9.15.

3.4.14. (*Z*)-Isopropyl 2-acetyl-2-hexenoate ((*Z*)-2g). R_f=0.44 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1728, 1674, 1635; ^1H NMR: δ 6.83 (t, *J*=7.6 Hz, 1H), 5.3–5.2 (m, 1H), 2.31 (s, 3H), 2.29 (q, *J*=7.6, 7.6 Hz, 2H), 1.5–1.4 (m, 2H), 1.32 (d, *J*=6.0 Hz, 6H), 0.96 (t, *J*=7.6 Hz, 3H); ^{13}C NMR: δ 195.0, 166.1, 147.7, 137.5, 68.9, 31.7, 26.9, 21.7, 21.6, 13.8; MS *m/z* (relative intensity): 156 (4%), 137 (2%), 96 (11%), 43 (100%); Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 65.81; H, 9.21.

3.4.15. (*E*)-Isopropyl 2-acetyl-5-phenyl-2-pentenoate ((*E*)-2h). R_f=0.53 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1704, 1635, 1604; ^1H NMR: δ 7.3–7.2 (m, 5H), 6.92 (t, *J*=7.6 Hz, 1H), 5.2–5.1 (m, 1H), 2.78 (t, *J*=7.6 Hz, 2H), 2.58 (q, *J*=7.6, 7.6 Hz, 2H), 2.18 (s, 3H), 1.27 (d, *J*=6.0 Hz, 6H); ^{13}C NMR: δ 208.0, 163.9, 147.2, 140.5, 136.3, 128.6, 128.4, 126.3, 68.8, 34.7, 31.1, 30.8, 21.7; MS *m/z* (relative intensity): 218 (8%), 200 (19%), 104 (7%), 91 (100%); Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.59; H, 7.83.

3.4.16. (*Z*)-Isopropyl 2-acetyl-5-phenyl-2-pentenoate ((*Z*)-2h). R_f=0.38 (5:1 hexane–ethyl acetate); IR (KBr, ν_{max} (cm^{-1})): 1720, 1628; ^1H NMR: δ 7.3–7.2 (m, 5H), 6.83 (t, *J*=7.6 Hz, 1H), 5.2–5.1 (m, 1H), 2.81 (t, *J*=7.6 Hz, 2H), 2.65 (q, *J*=7.6, 7.6 Hz, 2H), 2.29 (s, 3H), 1.31 (d, *J*=6.4 Hz, 6H); ^{13}C NMR: δ 195.0, 165.8, 146.6, 140.3, 137.6, 128.5, 128.2, 126.3, 67.0, 34.4, 31.4, 27.0, 21.7; MS *m/z* (relative intensity): 260 (1%), 200 (15%), 104 (6%), 91 (81%), 43 (100%); Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.59; H, 7.83.

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5. Shibata and his co-workers reported the reaction of diketene with aldehydes promoted by bis(tributyltin) oxide ((n-$Bu_3Sn)_2O$) which afforded α,β-unsaturated methyl ketones accompanied by decarboxylation. We reinvestigated this reaction and found the product was not affected by the order of addition of the reagents. That is, in both cases when the diketene was added to the mixture of benzaldehyde and (n-$Bu_3Sn)_2O$, and when aldehyde was added to the mixture of diketene and (n-$Bu_3Sn)_2O$, the product was the same α,β-unsaturated methyl ketones. This was in contrast to the Ti(O-i-Pr)$_4$-promoted reaction, see: Shibata, I.; Nishio, M.; Baba, A.; Matsuda, H. *Chem. Lett.* **1993**, 1219–1222.
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