Palladium Catalyzed Regioselective β-Acetonation−α-Allylation of Activated Olefins in One Shot

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The reaction of certain activated olefins **4** with allyl acetoacetate **5** in the presence of catalytic amounts of $Pd(PPh_3)_4$ (5 mol %) in THF at room temperature gave the corresponding β-acetonated α-allylated double addition products **6** regioselectively in good to excellent yields. The nature of the electron-withdrawing group in activated olefins affected significantly the reactivity of substrates; at least one of two electron-withdrawing groups of **4** should be a CN group. A proposed mechanism for this unprecedented three-component coupling reaction involves oxa-π-allyl-π-allylpalladium intermediate **3a** (or its synthetic equivalents **3b**−**d**). The in situ generation of activated olefins **4**, from the aldehyde **11** and malononitrile **12**, followed by the palladium-catalyzed reaction with allyl acetoacetate **5** also worked well, producing the corresponding three-component coupling products in good yields. Furthermore, allyltributylstannane **13** and α-chloro acetone **14** could be used as the α-allylation and β-acetonation components, respectively, instead of allyl acetoacetate **5**. The scope and limitations of palladium-catalyzed regioselective β-acetonation−α-allylation reaction of activated olefins are described.

Introduction

The carbon−carbon bond-forming reaction is one of the most powerful tools for making new compounds and for developing creative synthetic methodologies. Such a reaction is in general most useful and efficient when performed catalytically. The use of organometallic compounds for catalytic carbon−carbon bond-forming reactions is quite attractive because the metal may activate the ligated organic moiety intrinsically and facilitate the desired reaction.[1] Among the complexes of a variety of transition metals for carbon−carbon bond formation employed previously, palladium complexes have been most often used because they display wide reactivity and higher selectivity than other transition-metal complexes.[2,3] Particularly, reactive π-allylpalladium complexes **1** are useful reaction intermediates for the above-mentioned purposes. In general, π-allylpalladium complexes **1** are electrophilic and react with various nucleophiles such as malonates,[4] β-keto esters,[5] and amines[6] to form carbon−carbon or carbon−heteroatom bonds under neutral or basic conditions. In addition, the carbon nucleophiles of organometallic compounds such as Zn,[7] B,[8] Al,[9] Sn,[10] and Si[11] can react with π-allylpalladium complexes **1** via transmetalation.

Meanwhile, we recently reported the catalytic double allylation of activated olefins via an amphiphilic bis-π-allylpalladium intermediate **2**.[12] In this instance, one of the two allyl moieties acted as a nucleophile and the another as an electrophile toward certain Michael acceptors, giving the β- and α-double-allylated derivatives of the activated olefins (Scheme 1).

This result prompted us to search for oxa-π-allyl-π-allylpalladium intermediate **3a** (or its synthetic equivalents **3b**−**d**, vide post) as an unsymmetric and functionalized version of the amphiphilic bis-π-allylpalladium **2**.

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(9) Reference 7c,d.

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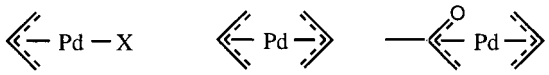
Scheme 1



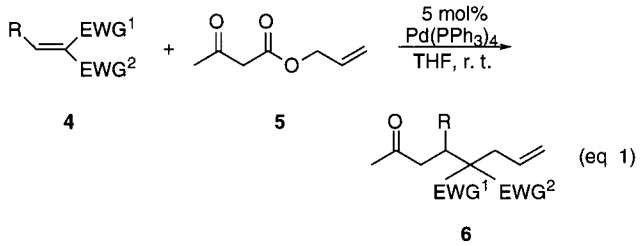
1 **2** **3a**

Table 1. Pd-Catalyzed β-Acetonation−α-Allylation of Benzylidenemalononitrile 4a with Allyl Acetoacetate 5[a]

entry	catalyst	solvent	yield of **6a**,[b] %
1	$Pd(PPh_3)_4$	THF	97 (89)[c]
2[d]	$Pd(PPh_3)_4$	THF	71
3[e]	$Pd(PPh_3)_4$	THF	94
4	$Pd(PPh_3)_4$	CH_3CN	74
5	$Pd(PPh_3)_4$	EtOH	54
6	$Pd(PPh_3)_4$	CH_2Cl_2	47
7	$Pd(PPh_3)_4$	toluene	<5
8	$Pd_2(dba)_3{\cdot}CHCl_3$	THF	no reaction
9	$Pd_2(dba)_3{\cdot}CHCl_3$−2DPPE	THF	54
10	$Pd_2(dba)_3{\cdot}CHCl_3$−2DPPB	THF	69

[a] All reactions were conducted at room temperature for 2 h in the presence of 5 mol % of catalyst, except where otherwise indicated. [b] ^1H NMR yield. *p*-Xylene was used as an internal standard. [c] Isolated yield, based on **4a**. [d] The reaction was carried out at 40 °C for 1 d. [e] The reaction was carried out at 70 °C for 2 h.

After a number of trials, we found that the reaction of certain activated olefins **4** with allyl acetoacetate **5** in the presence of $Pd(PPh_3)_4$ catalyst gave the β-acetonation−α-allylation products **6** in one shot in high chemical yields (eq 1).[13−15]



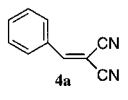
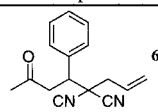
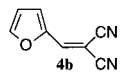
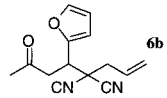
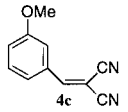
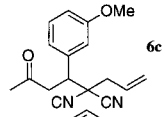
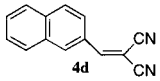
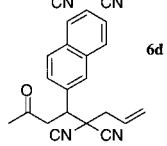
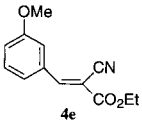
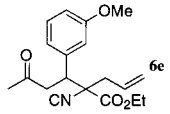
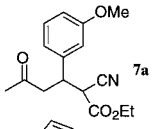
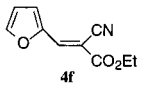
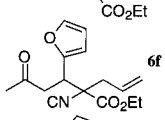
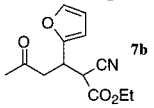
4 **5** (eq 1)

6

Results and Discussion

The reaction of benzylidenemalononitrile **4a** (0.5 mmol) with allyl acetoacetate **5** (1.2 equiv) in THF in the presence of $Pd(PPh_3)_4$ (5 mol %) at room temperature was monitored by analytical TLC, and the starting material **4a** was consumed completely after 2 h. GLPC analysis of the reaction mixture revealed that 5,5-dicyano-4-phenyl-7-octen-2-one **6a** was produced in essentially quantitative yield. Purification with silica gel column chromatography using *n*-hexane−ethyl acetate (10:1) as eluent gave **6a** in 89% isolated yield (Table 1, entry 1). The reaction at 70 °C for 2 h in THF in the presence of 5 mol % of $Pd(PPh_3)_4$ gave **6a** in 94% ^1H NMR yield, while the reaction at 40 °C for 1 day afforded **6a** in 71% ^1H NMR yield (entries 2 and 3). The use of CH_3CN, EtOH, and CH_2Cl_2 as a solvent gave **6a** in 47−74% ^1H NMR yields (entries 4−6), while the use of toluene afforded **6a** in less than 5% yield (entry 7). The reaction did not proceed in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ catalyst (entry 8). A palladium−bidentate phosphine ligand system, such as $Pd_2(dba)_3{\cdot}CHCl_3$−2DPPE or $Pd_2(dba)_3{\cdot}CHCl_3$−2DPPB, was also tested (entries 9−10), but the yields of **6a** were lower than those in the case of $Pd(PPh_3)_4$. Other transition metal catalysts, such as $Ni(PPh_3)_2(CO)_2$, $RuCl_2(PPh_3)_3$, and $RhCl(PPh_3)_3$, were totally ineffective. As a result of extensive examination of various reaction conditions, we found that the reaction of benzylidenemalononitrile **4a** with allyl acetoacetate **5** proceeded very smoothly at room temperature in the presence of $Pd(PPh_3)_4$ catalyst in THF to give the corresponding β-acetonated and α-allylated product **6a** in good yields.[16]

Table 2. Pd Catalyzed β-Acetonation-α-Allylation of 4 with 5[a]

entry	substrate	time	product	yield,[b] %
1	 **4a**	2 h	 **6a**	89
2	 **4b**	2 h	 **6b**	91
3	 **4c**	4.5 h	 **6c**	78
4	 **4d**	5 h	 **6d**	69
5	 **4e**	15 h	 **6e**	63 (58:42)[c]
			 **7a**	25 (58:42)[c]
6	 **4f**	1 d	 **6f**	53 (76:24)[c]
			 **7b**	19 (63:37)[c]

[a] Reactions were conducted in THF at room temperature. [b] Isolated yield, based on **4**. [c] Diastereomeric ratios were indicated in parentheses and the stereochemistries of those isomers were not determined since the selectivities were low.

The results for a variety of substrates are shown in Table 2. The activated olefins **4a−d** bearing two CN groups reacted effectively with allyl acetoacetate **5** to afford the desired products **6a−d** in good to excellent yields (entries 1−4). The application of this methodology

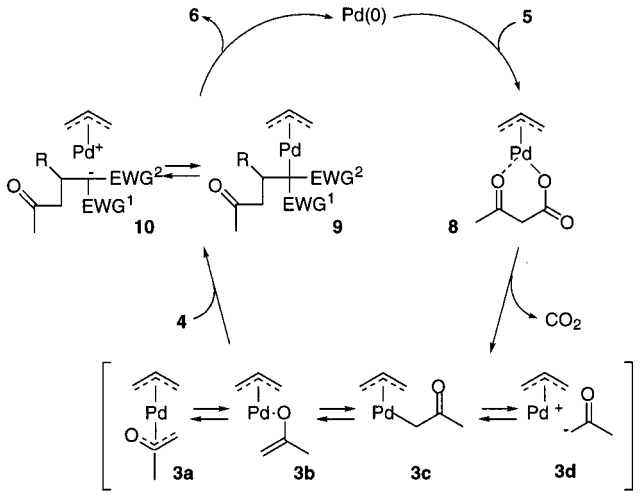
(13) The palladium(II) enolate complex may be formally expressed in three different structures: (1) palladiun(II) enolate, (2) oxa-π-allylpalladium(II), and (3) 2-oxoalkylpalladium(II) complex. See also: (a) Tsuda, T.; Chujo, Y.; Nishi, S.-I.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (b) Reference 10c.

(14) It was reported that palladium catalysts induced decarboxylation of allylic β-keto carboxylates to produce α-allylic ketones via a π-allylpalladium enolate; ref 13a.

(15) (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793.

(16) In the case of compound **4a**, the use of $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, and $PdCl_2(PhCN)_2$ did not induce the desired reaction.

Scheme 2



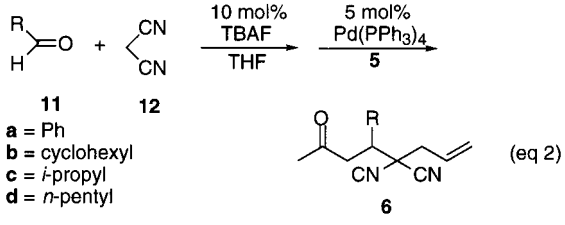
Phosphine omitted for clarity

to activated olefins **4e**,**f** having CN and CO_2Et as electron-withdrawing groups afforded the desired double-addition products **6e**−**f** as the major product along with minor amounts of the monoaddition products **7a**−**b** (entries 5−6). In the case of **4a**,**b**, even the use of 1 mol % of the catalyst was enough to complete the reaction; **6a** and **6b** were obtained in 81% and 81% yield, respectively.

When other activated olefins, such as $RCH{=}CHCO_2Et$ and $RCH{=}C(CO_2Et)_2$, or simple olefins were used, no double addition products were obtained, and the starting activated or nonactivated olefins were recovered. However, as shown above, the present double-addition reaction smoothly proceeded when we used cyano-substituted activated olefins, such as $RCH{=}C(CN)_2$ and $RCH{=}C(CN)(CO_2Et)$. This difference on the reactivity of activated olefins may be explained by the concept of steric inhibition of resonance proposed by Boeckman;[17] complete coplanarity of two esters is difficult due to the steric interaction, but the small cyano produces much less disruption than the ester overlap and the coplanarity can be maintained. Accordingly, the carbanion intermediate **10** (vide infra) is more stabilized in the case of the CN substituted olefins, promoting the double-addition reaction.

A mechanistic rationale for the present three-component coupling reaction is shown in Scheme 2. The oxidative addition of Pd(0) to allyl acetoacetate **5** would afford π-allylpalladium β-keto carboxylate **8**,[18] which would undergo decarboxylation to produce oxa-π-allyl-π-allylpalladium intermediate **3a** (or its synthetic equivalents **3b**−**d**). It is not possible at the present time to make clear which is the real intermediate. Activated olefins **4** would react with this intermediate to give the corresponding β-acetonated derivative **9** (or its zwitterionic complex **10**). The reductive elimination of Pd(0) would give the desired double-addition products **6**.[19]

In general, activated olefins **4** were synthesized from the reaction of aldehydes and acidic methylene compounds. The Michael acceptors containing active protons at the γ-position of activated olefins could not be prepared in allowable yields. Therefore, the substrates that have no γ-protons were utilized in Table 2. The reason for this instability of such substrates is not clear, but the presence of TBAF during the isolation step may cause the decomposition of the product. Accordingly, we attempted the in situ generation of the olefins followed by the palladium catalyzed double addition (all in one pot) (eq 2).



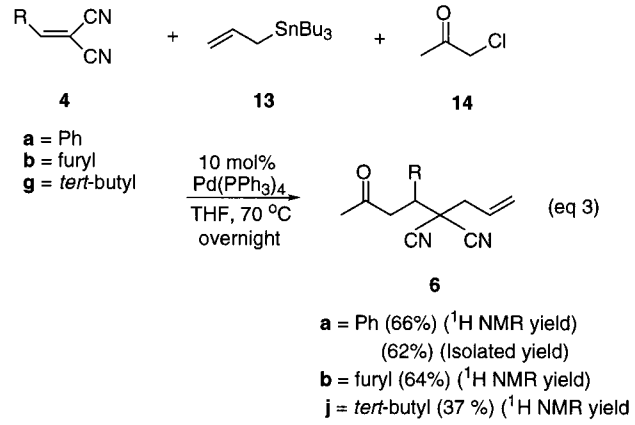
Cyclohexyl carboxaldehyde **11b** was treated with malononitrile **12** in THF in the presence of tetrabutylammonium fluoride (TBAF) (10 mol %) at room temperature for 1 h. The reaction progress was monitored by TLC. After the malononitrile **12** was consumed completely, 5 mol % of $Pd(PPh_3)_4$ and allyl acetoacetate **5** (1.2 equiv) were added successively. The resulting mixture was stirred at room temperature for an additional 1 h. The mixture was then extracted with Et_2O. The organic layer was dried over $MgSO_4$, concentrated in vacuo, and subjected to column chromatography on silical gel using *n*-hexane−ethyl acetate (10:1) as eluent. The desired compound **6g** was obtained as a light yellow oil (74%). Very similarly, isobutyraldehyde **11c** underwent the condensation and subsequent acetonation−allylation smoothly to give the desired product **6h** in 63% yield. By a similar procedure, benzaldehyde **11a** afforded **6a** in 66% yield. However, the reaction using *n*-hexanal **11d** afforded **6i** in 48% yield. It seems that *n*-pentylethylidenemalononitrile was decomposed slowly under the reaction conditions even prepared in situ from the *n*-hexanal **11d** and malononitrile **12**.

Furthermore, it occurred to us that the three-component coupling reaction may take place by using α-halo ketone and allyltributylstannane as an acetonate and an allyl source, respectively. After screening the various reaction conditions, we found that the reaction of activated olefins **4** (0.5 mmol), allyltributylstannane **13** (1.2 equiv), and α-chloro acetone **14** (1.2 equiv) took place in the presence of $Pd(PPh_3)_4$ (10 mol %) at 70 °C to give the corresponding regioselective β-acetonation−α-allylation products **6** in moderate to good yields (eq 3).

(17) Boeckman, R. K., Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033. See also: Shim, J.-G.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 3067.

(18) (a) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844. (b) Nokami, J.; Watanabe, H.; Mandai, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1989**, *30*, 4829.

(19) Reductive elimination of Pd(0) from π-allylpalladium complexes, in which a π-allyl group and a stabilized carbanion are coordinated to palladium, is known. (a) Takahashi, Y.; Sakai, S.; Ishii, Y. *Chem. Commun.* **1967**, 1092. (b) Hata, G.; Takahashi, K.; Miyake, A. *J. Org. Chem.* **1971**, *36*, 2116. (c) Jolly, P. W.; Mynott, R.; Raspel, B.; Schick, K.-P. *Organometallics* **1986**, *5*, 473. (d) Reference 12.



Conclusions

The results presented here are intrinsically interesting and useful as a new carbon−carbon bond-forming method. The two organic components of the oxa-π-allyl-π-allylpalladium complex **3a** (or its synthetic equivalents **3b**−**d**) are completely utilized for the addition reaction, and thus, the present three-component coupling is an atom economic reaction. The ordinary Michael addition followed by alkylation inevitably needs displacement step at the alkylation stage, which leads to release of a leaving group.[20]

Experimental Section

General Information. All solvents were purified and dried before use according to standard procedures. Reactions were conducted under an argon atmosphere in oven-dried glassware. The starting activated olefins (**4**) were prepared by the Knoevenagel condensation of aldehydes with acidic methylenes. Allyl acetoacetate (**5**) was purchased from Merck Co. Allyltributylstannane (**13**) and α-chloro acetone (**14**) were purchased from Aldrich Chemical Co. $Pd(PPh_3)_4$ was prepared according to the method in the literature.[21]

General Procedure (5,5-Dicyano-4-phenyl-7-octen-2-one, 6a). To a solution of **4a** (0.077 g, 0.5 mmol) and $Pd(PPh_3)_4$ (0.289 g, 0.025 mmol) in THF (5 mL) was added **5** (0.082 mL, 0.6 mmol) at room temperature under argon atmosphere, and the mixture was stirred for 2 h. The reaction progress was monitored by TLC, and reaction mixture was quenched with water when the starting ethylidene malononitrile **4a** was consumed completely. The mixture was extracted with Et_2O and dried over $MgSO_4$. After the usual workup, the analytically pure product **6a** was isolated in high yield (0.112 g, 89%) by column chromatography on silica gel using *n*-hexane−ethyl acetate (10:1) as eluent.

One-Pot Reaction of Aldehyde 11, Malononitrile 12, and Allyl Acetoacetate 5 Catalyzed by Pd(0). The synthesis of **6a** from **11a** is representative. A mixture of **11a** (0.051 mL, 0.5 mmol), malononitrile **12** (0.033 g, 0.5 mmol), and tetrabutylammonium fluoride (TBAF) (0.050 mL, 0.05 mmol) in 1 M THF solution was dissolved in THF (5 mL) at room temperature under argon atmosphere. The reaction mixture was stirred for 2 h. The reaction progress was monitored by TLC. After malononitrile **12** was consumed completely, $Pd(PPh_3)_4$ (0.289 g, 0.025 mmol) and allyl acetoacetate **5** (0.082 mL, 0.6 mmol) were added successively. The resulting mixture was stirred at room temperature for additional 2 h. Then the mixture was extracted with Et_2O and dried over $MgSO_4$. After the usual workup, the product **6a** was isolated in 66% yield (0.084 g) by column chromatography on silica gel using *n*-hexane−ethyl acetate (10:1) as eluent.

Three-Component Reaction of Activated Olefins 4, Allyltributylstannane 13 and α-Chloro Acetone 14 Catalyzed by Pd(0). The synthesis of **6a** from **4a** is representative. To a solution of **4a** (0.077 g, 0.5 mmol), allyltributylstannane **13** (0.199 g, 0.6 mmol), and Pd $(PPh_3)_4$ (0.578 g, 10 mol %) in THF (5 mL) was added α-chloro acetone **14** (0.048 mL, 0.6 mmol) at room temperature under argon atmosphere. The reaction mixture was moved to a preheated (70 °C) oil bath and then stirred for 1 day at that temperature. The reaction mixture was quenched with water and then extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The resulting crude oil was treated with EtOAc and a saturated KF solution. The mixture was stirred for 5 h and then extracted with Et_2O. The organic layer was washed with a saturated NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. The product **6a** was isolated in 62% yield (0.079 g) by column chromatography on silica gel using *n*-hexane−ethyl acetate (10:1) as eluent.

5,5-Dicyano-4-phenyl-7-octen-2-one (6a): white solid; mp 64−65 °C; ^{1}H NMR ($CDCl_3$) δ 7.38 (s, 5H), 5.94−5.80 (m, 1H), 5.36 (m, 2H), 3.75 (dd, 1H, J = 3.6, 10.0 Hz), 3.39 (dd, 1H, J = 10.0, 17.4 Hz), 3.17 (dd, 1H, J = 3.6, 17.4 Hz), 2.47 (dd, 1H, J = 7.2, 13.9 Hz), 2.35 (dd, 1H, J = 7.2, 13.9 Hz), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.401, 135.316, 129.180, 129.098, 128.802, 128.530, 123.307, 115.091, 114.326, 45.961, 45.837, 42.868, 40.253, 30.597; HRMS calcd for $C_{16}H_{16}N_2O$ 252.1261, found 252.1260. Anal. Calcd: C, 76.165; H, 6.392; N, 11.103. Found: C, 76.439; H, 6.560; N, 11.128.

5,5-Dicyano-4-(2-furyl)-7-octen-2-one (6b): white solid; mp 50−51 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (m, 1H), 6.39 (m, 2H), 5.95−5.81 (m, 1H), 5.38 (m, 2H), 3.95 (dd, 1H, J = 3.3, 10.5 Hz), 3.38 (dd, 1H, J = 10.5, 17.5 Hz), 3.08 (dd, 1H, J = 3.3, 17.5 Hz), 2.57−2.42 (m, 2H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 202.956, 148.441, 143.177, 128.241, 123.355, 114.448, 113.765, 110.747, 109.974, 43.846, 41.987, 39.643, 30.151; IR (neat) 2971, 2248, 1720, 1419, 1168, 746 cm^{-1}; HRMS calcd for $C_{14}H_{14}N_2O_2$ 242.1054, found 242.1049. Anal. Calcd: C, 69.406; H, 5.824; N, 11.563. Found: C, 69.285; H, 6.113; N, 11.415.

5,5-Dicyano-4-(*m*-methoxyphenyl)-7-octen-2-one (6c): white solid; mp 96−97 °C; ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 2H), 6.90 (m, 2H), 5.94−5.80 (m, 1H), 5.35 (m, 2H), 3.80 (s, 3H), 3.70 (dd, 1H, J = 3.6, 10.2 Hz), 3.35 (dd, 1H, J = 10.2, 17.2 Hz), 3.14 (dd, 1H, J = 3.6, 17.2 Hz), 2.48 (dd, 1H, J = 7.0, 14.0 Hz), 2.34 (dd, 1H, J = 7.0, 14.0 Hz), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.531, 159.923, 129.845, 128.554, 126.974, 123.150, 115.114, 114.456, 114.366, 55.212, 45.926, 45.219, 42.974, 40.153, 30.587; IR (neat) 2966, 2243, 1716, 1515, 1258, 837 cm^{-1}; HRMS calcd for $C_{17}H_{18}N_2O$ 281.1368, found 242.1381.

5,5-Dicyano-4-(2-naphthyl)-7-octen-2-one (6d): colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 4H), 7.52 (m, 3H), 5.95−5.81 (m, 1H), 5.34 (m, 2H), 3.93 (dd, 1H, J = 3.3, 10.3 Hz), 3.52 (dd, 1H, J = 10.3, 17.4 Hz), 3.26 (dd, 1H, J = 3.3, 17.4 Hz), 2.50 (dd, 1H, J = 7.3, 14.0 Hz), 2.36 (dd, 1H, J = 7.3, 14.0 Hz), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 203.359, 133.299, 133.110, 132.649, 129.088, 128.471, 128.364, 128.109, 127.665, 126.851, 126.744, 125.848, 123.314, 115.122, 114.374, 46.107, 45.992, 42.842, 40.292, 30.571; IR (neat) 3059, 2928, 2247, 1722, 1364, 1167, 756 cm^{-1}; HRMS calcd for $C_{20}H_{18}N_2O$ 302.1418, found 302.1430.

Ethyl 2-cyano-2-allyl-3-(*m*-methoxyphenyl)-5-oxohexanoate (6e): yellowish green oil; ^{1}H NMR ($CDCl_3$) δ 7.26 (m, 1H, minor diastereomer), 7.20 (m, 1H, minor diastereomer), 6.95 (m, 3H, major diastereomer), 6.83 (m, 3H, monor diastereomer), 5.74 (m, 1H, minor diastereomer), 5.69 (m, 1H, major diastereomer), 5.25 (m, 2H, minor diastereomer), 5.12 (m, 2H, major diastereomer), 4.28 (q, 2H, major diastereomer, J = 7.1 Hz), 3.92 (q, 2H, minor diastereomer, J = 7.1 Hz), 3.81 (s, 3H, major diastereomer), 3.78 (s, 3H, minor diastereomer), 3.74 (m, 2H, major and 1H, minor diastereomer), 3.27 (m, 1H, minor diastereomer), 3.22 (m, 1H, minor diastereomer), 3.02 (dd, 1H, minor diastereomer J = 4.0, 7.4 Hz), 2.80 (m, 1H, minor diastereomer), 2.74 (m, 1H, major diastereomer), 2.58 (dd, 1H,

(20) The present reaction releases CO_2 from **5**, and instead, the two carbon atoms of the activated olefins are introduced into the position at which CO_2 occupied in **5**.

(21) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

minor diastereomer, J = 6.8, 13.6 Hz), 2.47 (dd, 1H, major diastereomer, J = 8.1, 13.8 Hz), 2.09 (s, 3H, minor diastereomer), 2.05 (s, 3H, major diastereomer), 1.33 (t, 3H, major diastereomer, J = 7.1 Hz), 0.98 (t, 3H, minor diastereomer, J = 7.1 Hz); IR (neat) 2984, 2243, 1740, 1722, 1222 cm^{-1}; HRMS calcd for $C_{19}H_{23}NO_4$ 329.1627, found 329.1642. Anal. Calcd: C, 69.281; H, 7.038; N, 4.252. Found: C, 69.210; H, 7.406; N, 4.230.

Ethyl 2-cyano-2-allyl-3-(2-furyl)-5-oxohexanoate (6f): yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 1H, major diastereomer), 7.34 (m, 1H, minor diastereomer), 6.33 (m, 2H, major diastereomer), 6.29 (m, 1H, minor diastereomer), 6.21 (m, 1H, minor diastereomer), 5.78 (m, 1H, minor diastereomer), 5.70 (m, 1H, major diastereomer), 5.26 (m, 2H, minor diastereomer), 5.15 (m, 2H, major diastereomer), 4.27 (qd, 2H, major diastereomer, J = 7.1, 1.5 Hz), 4.12 (q, 2H, minor diastereomer, J = 7.1 Hz), 3.96 (dd, 1H, major diastereomer and 1H, minor diastereomer, J = 3.6, 10.4 Hz), 3.26 (dd, 1H, major diastereomer, J = 10.4, 17.2 Hz), 3.24 (dd, 1H, minor diastereomer, J = 9.6, 17.5 Hz), 2.97 (dd, 1H, minor diastereomer, J = 4.0, 7.4 Hz), 2.69 (dd, 1H, major diastereomer and 1H, minor diastereomer, J = 3.6, 17.2 Hz), 2.56 (m, 1H, major diastereomer and 1H, minor diastereomer), 2.20 (dd, 1H, major diastereomer, J = 6.6, 12.7 Hz), 2.14 (s, 3H, minor diastereomer), 2.09 (s, 3H, major diastereomer), 1.32 (t, 3H, major diastereomer, J = 7.1 Hz), 1.19 (t, 3H, minor diastereomer, J = 7.1 Hz); IR (neat) 2986, 2245, 1740, 1723, 1225 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_4$ 289.1312, found 289.1329. Anal. Calcd: C, 66.421; H, 6.619; N, 4.841. Found: C, 66.594; H, 6.596; N, 5.331.

5,5-Dicyano-4-cyclohexyl-7-octen-2-one (6g): light yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.99−5.85 (m, 1H), 5.38 (m, 2H), 2.84 (dd, 1H, J = 5.5, 18.7 Hz), 2.70 (m, 1H), 2.56 (m, 3H), 2.26 (s, 3H), 1.96−1.67 (m, 5H), 1.54−0.88 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 204.586, 128.670, 123.332, 115.453, 114.737, 42.506, 41.585, 41.108, 41.050, 40.154, 31.888, 30.103, 27.126, 26.336, 25.933; IR (neat) 2930, 2856, 2245, 1722, 1364, 1165 cm^{-1}; HRMS calcd for $C_{16}H_{22}N_2O$ 258.1730, found 258.1728. Anal. Calcd: C, 74.382; H, 8.583; N, 10.843. Found: C, 74.094; H, 8.409; N, 11.053.

5,5-Dicyano-4-isopropyl-7-octen-2-one (6h): light yellow oil; ^{1}H NMR ($CDCl_3$) δ 5.99−5.85 (m, 1H), 5.41 (m, 2H), 2.75 (m, 2H), 2.65−2.50 (m, 3H), 2.32 (m, 1H), 2.26 (s, 3H), 1.05 (d, 3H, J = 6.8 Hz), 0.90 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 204.477, 128.537, 123.166, 115.213, 114.588, 42.291, 41.765, 40.934, 39.774, 29.929, 29.452, 21.605, 16.366; IR (neat) 2968, 2881, 2247, 1720, 1369, 1169 cm^{-1}; HRMS calcd for $C_{13}H_{18}N_2O$ 218.1418, found 218.1417. Anal. Calcd: C, 71.527; H, 8.311; N, 12.832. Found: C, 71.214; H, 8.383; N, 12.691.

5,5-Dicyano-4-*n*-pentyl-7-octen-2-one (6i): colorless oil; ^{1}H NMR ($CDCl_3$) δ 5.95−5.84 (m, 1H), 5.40 (m, 2H), 2.68 (m, 4H), 2.55 (dd, 1H, J = 7.3, 14.1 Hz), 2.25 (s, 3H), 1.55 (m, 2H), 1.29 (m, 6H), 0.89 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 204.312, 128.611, 123.010, 114.744, 114.596, 44.807, 42.990, 39.552, 38.326, 31.656, 31.467, 30.052, 26.400, 22.247, 13.800; IR (neat) 2934, 2862, 2247, 1722, 1364, 1167, 935 cm^{-1}; HRMS calcd for $C_{15}H_{22}N_2O$ 246.1732, found 258.1716. Anal. Calcd: C, 73.133; H, 9.002; N, 11.371. Found: C, 72.887; H, 9.030; N, 11.270.

Ethyl 2-cyano-3-(*m*-methoxyphenyl)-5-oxohexanoate (7a): light yellow oil; IR (neat) 2983, 2250, 1743, 1716, 1259 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_4$ 289.1312, found 289.1311. Anal. Calcd C, 66.421; H, 6.619; N, 4.841. Found: C, 66.146; H, 6.428; N, 4.946.

Ethyl 2-cyano-3-(2-furyl)-5-oxohexanoate (7b): orange oil; IR (neat) 2986, 2253, 1744, 1717, 1252 cm^{-1}; HRMS calcd for $C_{13}H_{15}NO_4$ 249.1001, found 249.1007.

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