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Novel Synthesis of Conjugated Dienes Attached to a Quaternary Carbon Center via Pd(0)-Catalyzed Deconjugative Allylation of Alkenylidenemalonates

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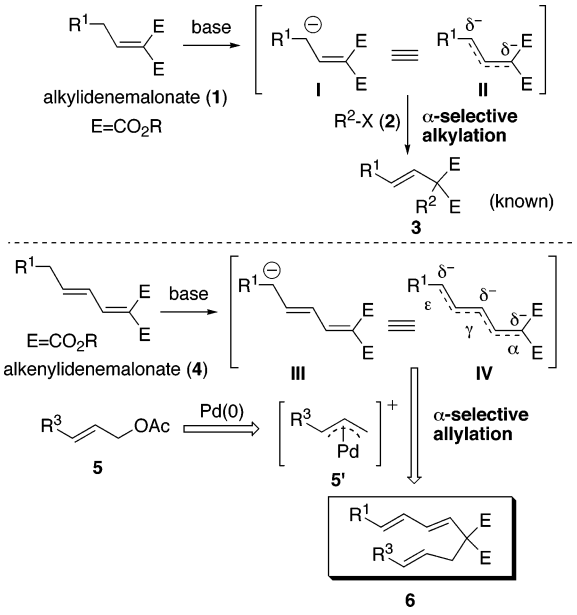
Abstract: Palladium(0)-catalyzed deconjugative allylation of alkenylidenemalonates and alkylidenemalonates was achieved for the first time. Reactions of dimethyl 2-((*E*)-but-2-enylidene)malonate with various allylic acetates using LHMDS as a base in DMF in the presence of Pd_2dba_3 (2.5 mol %) and PPh_3 (10 mol %) proceeded at room temperature to give the corresponding α-allylation products in good yields in a regio- and stereoselective manner. This reaction can also be used for allylation of dimethyl ethylidenemalonate or dimethyl 2-((*E*)-pent-2-enylidene)malonate and give the desired α-allylation products in good yields.

Deconjugative alkylation of alkylidenemalonate **1** is a useful method for the synthesis of a compound having an sp^2-carbon center that is attached to a quaternary carbon center.[1] During the course of our studies on transition-metal-catalyzed cycloadditions,[2] conjugated diene such as **6** was needed as a substrate that has a 1,3-diene unit next to a quaternary carbon center (Scheme 1). It was thought that α-selective deconjugative alkylation of alkenylidenemalonate **4** with an electrophile, R−X (**2**), in the presence of a strong base might be a straightforward method for synthesizing the desired diene. However, there is only one report on α-selective deconjugative alkylation of **4**,[3] although there are several examples of the similar reaction of alkylidenemalonate **1** in the literature.[1] For the α-selective deconjugative alkylation of **4**, Kasatkin et al. reported that alkylations of enolate, generated from diethyl 2-((*E*)-but-2-enylidene)-malonate **4a′** (R^1=H, E = CO_2Et) and dimethylsulfonium methylide ($Me_2S^+CH_2^-$), with methyl iodide, allyl bromide, propargyl bromide, and isopropyl 4-bromocrotonate (*E*-$BrCH_2CH{=}CHCO_2{}^i$Pr), gave the corresponding alkylated products in 50−65% yields.[3] We speculated that the negative charge of enolate **III** derived from **4** is highly delocalized through an α- to ϵ-carbon atom (i.e., **IV**) compared to the case of enolate **I** (i.e., **II**) derived from **1**, which results in low efficiency and limitation of α-selective deconjugative alkylation of **4**. Thus, a new strategy is needed to overcome this drawback.

SCHEME 1. Deconjugative Alkylation of Alkylidenemalonate



Palladium(0)-catalyzed allylation (Tsuji−Trost reaction) has been widely used in organic transformations and is known to be applicable to a variety of allylic compounds and nucleophiles.[4] We planned to synthesize a compound such as **6** having a 1,3-diene unit attached to a quaternary carbon center by using the Pd(0)-catalyzed allylation (Scheme 1). If the α-carbon of enolate **IV** can preferentially attack a π-allylpalladium intermediate **5′** derived from an allylic acetate **5**, α-allylation product **6** would be produced in a regio- and stereoselective manner. To date, there are no reports on Pd(0)-catalyzed deconjugative allylation of **1** or **4** in the literature.

At first, Pd(0)-catalyzed allylation of dimethyl 2-((*E*)-but-2-enylidene)malonate **4a** with allyl acetate **5a** was investigated, and the results are summarized in Table 1. When the reaction of **4a** with **5a** was carried out in the presence of Pd_2dba_3 (2.5 mol %) and PPh_3 (10 mol %) using dimethylsulfonium methylide ($Me_2S^+CH_2^-$), generated from trimethylsulfonium iodide [$(CH_3)_3SI$] and $CH_3S(O)CH_2Na$,[5] as a base, the desired product **6aa** was obtained in 41% yield (run 1). The use of $CH_3S(O)CH_2$-Na as a base under similar conditions produced **6aa** in 40% yield (run 2). The reaction of **4a** with **5a** in DMF using NaH as a base improved the yield of **6aa** to 63%

(1) (a) Cope, A. C.; Hancock, E. M. *J. Am. Chem. Soc.* **1938**, *60*, 2644. (b) Cope, A. C.; Hancock, E. M. *J. Am. Chem. Soc.* **1938**, *60*, 2901. (c) Cope, A. C.; Hartung, W. H.; Hancock, E. M.; Crossley, F. S. *J. Am. Chem. Soc.* **1940**, *62*, 314. (d) Cope, A. C.; Holmes, H. L.; House, H. O. *Org. React.* **1957**, *9*, 107. (e) Tsuboi, S.; Fujita, H.; Muranaka, K.; Seko, K.; Takeda, A. *Chem. Lett.* **1982**, 1909. (f) Tsuboi, S.; Muranaka, K.; Sakai, T.; Takeda, A. *J. Org. Chem.* **1986**, *51*, 4944.

(2) For examples, see: (a) Sato, Y.; Oonishi, Y.; Mori, M. *Organometallics* **2003**, *22*, 30. (b) Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1218. (c) Sato, Y.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 9310 and references cited therein.

(3) Kasatkin, A. N.; Biktimirov, R. Kh.; Tolstikov, G. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1989**, *12*, 2872.

(4) For reviews, see: (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Harrington, P. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science Ltd.: Oxford, UK, 1995; Vol. 12, p 797. (c) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; John Wiley & Sons Ltd.: Chichester, UK, 1995.

(5) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782. For preparation of the enolate from **4a** and $Me_2S^+CH_2^-$, see ref 3.

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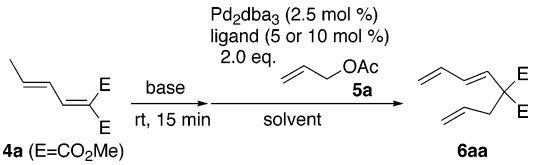
TABLE 1. Pd(0)-Catalyzed Deconjugative Allylation of 4a[a]



run	base	ligand	solvent	time (h)	yield (%)
1	$(CH_3)_2S^+-CH_2^-$	PPh_3	DMSO	15	41
2	$CH_3S(O)CH_2Na$	PPh_3	DMSO	0.5	40
3	NaH	PPh_3	DMF	1	63
4	NaH	PPh_3	THF	24	7
5	NaH	PMe_2Ph	DMF	1	41
6	NaH	P(*o*-tolyl)$_3$	DMF	5	29
7	NaH	P^{t}Bu$_3$[b]	DMF	12	23
8	NaH	dppe	DMF	1	46
9	NaH	dppb	DMF	1	54
10	NaH	DPEphos	DMF	5	63
11	NaH	dppf	DMF	5	59
12	NaH	BINAP	DMF	3	65

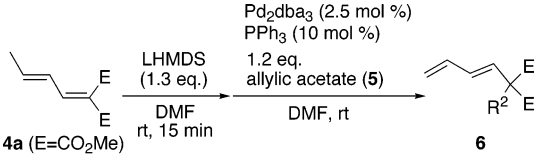
[a] All reactions were carried out using 1.3 equiv of a base at room temperature in the presence of 5 mol % (bidentate) or 10 mol % (monodentate) of ligand. [b] $[HP(^tBu)_3]BF_4$, which was purchased from Strem Chemicals, Inc., was used as precusor of P^{t}Bu$_3$ (cf. ref 6).

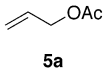
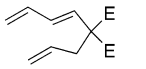
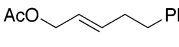
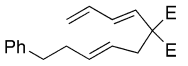
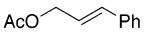
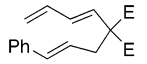
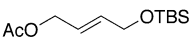
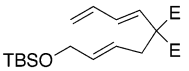
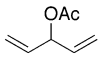
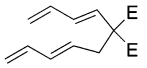
(run 3). On the other hand, the use of THF as a solvent under similar conditions slowed the reaction rate and decreased the yield of **6aa** (run 4), indicating that a polar solvent such as DMF or DMSO is suitable for this reaction. Accordingly, ligand effects in the reaction of **4a** with **5a** in DMF using NaH as a base were investigated. The use of an electron-rich phosphine (run 5) or sterically bulky phosphines (runs 6 and 7) decreased the yield of **6aa** compared to that from the reaction using PPh_3 (run 3). Bidentate ligands (runs 8−12) are also applicable, and **6aa** was obtained in 63% and 65% yields in reactions using DPEphos (run 10) and BINAP (run 12), yields comparable to that in the reaction using PPh_3.

It was found that the use of LHMDS as a base greatly improved the yield of **6aa**. That is, the reaction of **4a** with **5a** (2.0 equiv) using LHMDS (1.3 equiv) in the presence of Pd_2dba_3 (2.5 mol %) and PPh_3 (10 mol %) in DMF at room temperature proceeded in a completely regio- and stereoselective manner, and **6aa** was obtained in 90% yield as a sole product. In addition, the quantity of **5a** was reduced to 1.2 equiv under these conditions and **6aa** was obtained in 82% yield (Table 2, run 1).

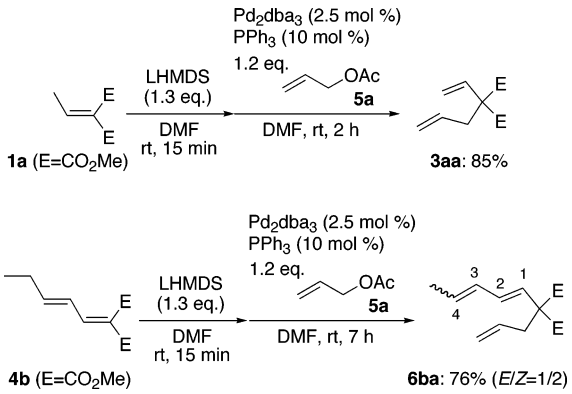
Subsequently, α-selective deconjugative allylation of **4a** with various allylic acetates was investigated (Table 2). The reaction of **4a** with an allylic acetate **5b** having an internal olefin under similar conditions gave the corresponding product **6ab** in 72% yield. Allylic acetates **5c** and **5d** having a conjugated olefin or a functional group containing an oxygen atom at allylic position were tolerated in this reaction, and the products **6ac** and **6ad** were produced in a regio- and stereoselectively manner in 82% and 88% yields, respectively. It is noteworthy that the reaction of **4a** with bis-allylic acetate **5e**[7] under

TABLE 2. Reactions of 4a with Various Allylic Acetates



allylic acetates (**5**)	time (h)	products (**6**)
 **5a**	5	 **6aa**: 82%
 **5b**	10	 **6ab**: 72%
 **5c**	8	 **6ac**: 82%
 **5d**	10	 **6ad**: 88%
 **5e**	10	 **6ae**: 77%

SCHEME 2



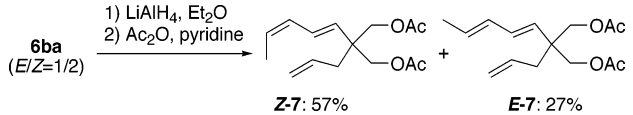
similar conditions also proceeded in a completely regio- and stereoselective manner, giving bis-diene **6ae** as a sole product in 77% yield.

As shown in Scheme 2, this reaction is also applicable to allylation of alkylidene malonate, and the reaction of diemethyl ethylidenemalonate **1a** with allyl acetate **5a** under similar conditions produced α-allylation product **3aa** as a sole product in 85% yield. In addition, the reaction of dimethyl 2-((*E*)-pent-2-enylidene)malonate **4b**

(6) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

(7) For Pd(0)-catalyzed substitution of bis-allylic acetates such as **5e** with malonates, see: Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1993**, *115*, 6609.

(8) The characterization and determination of the stereochemistry of **6ba** were achieved after conversion of **6ba** into the corresponding acetates **7** and its separation into ***Z*-7** and ***E*-7** (below; also see the Supporting Information).



with **5a** also proceeded regioselectively, giving α-allylation product **6ba** in 76% yield as an olefinic isomer with respect to the C3-position (3*E*/3*Z* = 1/2).[8]

In conclusion, we have succeeded in developing a Pd(0)-catalyzed deconjugative allylation of alkylidenemalonate **1** and alkenylidenemalonates **4** for the first time. Conjugated dienes are important reactive substances for various transformations in synthetic organic chemistry, including Diels−Alder reactions and transition metal-catalyzed cycloadditions. The present study has provided a useful method for the synthesis of a conjugated diene that has a 1,3-diene unit attached to a quaternary carbon center.

Experimental Section

Typical Procedure for Pd(0)-Catalyzed Allylation of 4a with Allyl Acetate 5a. A solution of $Pd_2dba_3{\cdot}CHCl_3$ (8.5 mg, 0.0083 mmol) and PPh_3 (8.7 mg, 0.033 mmol) in degassed DMF (0.5 mL) was stirred at room temperature for 15 min. To the mixture were added allyl acetate **5a** (43 μL, 0.40 mmol) and a DMF solution of lithium enolate, which was prepared from **4a** (60 mg, 0.33 mmol) and LHMDS (1.0 M in THF, 0.43 mL, 0.43 mmol) in DMF (2.8 mL), at 0 °C, and the mixture was stirred at room temperature for 5 h. Then saturated NH_4Cl aqueous solution at 0 °C was added, and the organic layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on silica gel (hexanes−Et_2O, 10/1) to afford **6aa** (61 mg, 82%) as a colorless oil.

Dimethyl 2-allyl-2-((*E*)-buta-1,3-dienyl)malonate (6aa): IR (neat) 1737, 1436, 1231 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 3.01 (dd, *J* = 7.4, 1.0 Hz, 2 H), 3.29 (s, 6 H), 4.89−5.03 (m, 4 H), 5.69−5.81 (m, 1 H), 6.18−6.33 (m, 2 H), 6.44 (d, *J* = 14.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.8, 52.6, 59.4, 118.2, 118.7, 129.2, 131.9, 132.4, 135.9, 169.8; LRMS (EI) *m*/*z* 224 (M^+), 192, 183, 165, 151, 133, 123, 105, 91, 79, 65; HRMS (EI) calcd for $C_{12}H_{16}O_4$ 224.1048, found 224.1049. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.14; H, 7.27.

Dimethyl 2-((*E*)-buta-1,3-dienyl)-2-((*E*)-5-phenylpent-2-enyl)malonate (6ab): IR (neat) 1736, 1435, 1228 cm^{-1}; ^1H NMR (400 MHz, acetonitrile-d_3) δ 2.25 (dt, *J* = 6.9, 6.9 Hz, 2 H), 2.60 (t, *J* = 6.9 Hz, 2 H), 2.68 (dd, *J* = 7.3, 1.2 Hz, 2 H), 3.66 (s, 6 H), 5.12−5.16 (m, 1 H), 5.23−5.33 (m, 2 H), 5.55 (dtt, *J* = 15.3, 6.9, 1.2 Hz, 1 H), 6.04 (d, *J* = 16.0 Hz, 1 H), 6.14 (dd, *J* = 16.0, 10.0 Hz, 1 H), 6.38 (ddd, *J* = 17.0, 10.0, 10.0 Hz, 1 H), 7.14−7.18 (m, 3 H), 7.24−7.28 (m, 2 H); ^{13}C NMR (100 MHz, acetonitrile-d_3) δ 34.9, 36.3, 39.2, 53.1, 60.5, 118.6, 124.6, 126.2, 128.8, 128.9, 130.6, 132.8, 135.0, 136.8, 142.4, 170.6; LRMS (EI) *m*/*z* 328 (M^+), 296, 268, 237, 209, 184, 152, 124, 91; HRMS (EI) calcd for $C_{20}H_{24}O_4$ 328.1674, found 328.1681. Anal. Calcd for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 73.25; H, 7.22.

Dimethyl 2-((*E*)-buta-1,3-dienyl)-2-cinnamylmalonate (6ac): IR (neat) 1735, 1435, 1227 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 2.94 (dd, *J* = 7.5, 1.3 Hz, 2 H), 3.71 (s, 6 H), 5.13 (dd, *J* = 10.0, 1.7 Hz, 1 H), 5.28 (dd, *J* = 10.0, 1.7 Hz, 1 H), 6.11 (dt, *J* = 15.5, 7.5 Hz, 1 H), 6.19 (d, *J* = 16.0 Hz, 1 H), 6.27 (dd, *J* = 16.0, 10.0 Hz, 1 H), 6.43 (ddd, *J* = 17.0, 10.0, 10.0 Hz, 1 H), 6.51 (dt, *J* = 15.5, 1.3 Hz, 1 H), 7.18−7.35 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 52.9, 60.0, 118.5, 123.6, 126.1, 127.2, 128.3, 129.5, 132.6, 133.8, 136.1, 136.8, 170.0; LRMS (EI) *m*/*z* 300 (M^+), 268, 240, 209, 181, 168, 152, 117, 91; HRMS (EI) calcd for $C_{18}H_{20}O_4$ 300.1362, found 300.1367. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.07; H, 6.87.

Dimethyl 2-((*E*)-buta-1,3-dienyl)-2-((*E*)-4-*tert*-butyldimethylsilyloxybut-2-enyl)malonate (6ad): IR (neat) 1738, 1436 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 0.02 (s, 6 H), 0.96 (s, 9 H), 3.05 (d, *J* = 7.4 Hz, 2 H), 3.32 (s, 6 H), 3.93 (d, *J* = 4.6 Hz, 2 H), 4.91 (dd, *J* = 9.1, 1.8 Hz, 1 H), 5.03 (dd, *J* = 15.5, 1.8 Hz, 1 H), 5.57 (dt, *J* = 15.3, 4.6 Hz, 1 H), 5.72 (dt, *J* = 15.3, 7.4 Hz, 1 H), 6.20−6.35 (m, 2 H), 6.46 (d, *J* = 15.2 Hz, 1 H); ^{13}C NMR (100 MHz, benzene-d_6) δ -4.6, 18.9, 26.5, 39.2, 52.5, 60.2, 63.6, 118.3, 124.1, 130.8, 132.9, 134.3, 136.7, 170.2; LRMS (EI) *m*/*z* 368 (M^+), 337, 321, 311, 279, 251, 219, 177, 159, 145, 117, 105; HRMS (EI) calcd for $C_{19}H_{32}O_5Si$ 368.2019, found 368.2035. Anal. Calcd for $C_{19}H_{32}O_5Si$: C, 61.92; H, 8.75. Found: C, 61.96; H, 8.67.

Dimethyl 2-((*E*)-buta-1,3-dienyl)-2-((*E*)-penta-2,4-dienyl)malonate (6ae): IR (neat) 1732, 1435 cm^{-1}; ^1H NMR (400 MHz, benzene-d_6) δ 3.05 (d, *J* = 7.5 Hz, 2 H), 3.29 (s, 6 H), 4.85−5.04 (m, 4 H), 5.66 (dt, *J* = 14.9, 7.5 Hz, 1 H), 6.01−6.34 (m, 4 H), 6.44 (d, *J* = 15.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.9, 52.9, 59.8, 116.5, 118.4, 127.5, 129.4, 132.6, 134.8, 136.1, 136.4, 170.0; LRMS (EI) *m*/*z* 250 (M^+), 218, 158, 131, 118, 91, 79, 67; HRMS (EI) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1230. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.20; H, 7.28.

Dimethyl 2-allyl-2-vinylmalonate (3aa): IR (neat) 1738, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.81 (ddd, *J* = 7.2, 1.2 Hz, 2 H), 3.74 (s, 6 H), 5.06−5.13 (m, 2 H), 5.20 (d, *J* = 17.8 Hz, 1 H), 5.33 (d, *J* = 10.8 Hz, 1 H), 5.69 (ddd, *J* = 17.0, 10.2, 7.2 Hz, 1 H), 6.28 (dd, *J* = 17.8, 10.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.6, 52.8, 60.3, 117.0, 118.9, 132.1, 134.2, 170.0; LRMS (EI) *m*/*z* 197 (M^+ − H), 166, 157, 138, 126, 107, 98, 79; HRMS (EI) calcd for $C_{10}H_{13}O_4$ (M^+ − H) 197.0814, found 197.0825. Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.73; H, 7.28.

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Supporting Information Available: Procedural information and characterization data for all other substrates. This material is available free of charge via the Internet at http://pubs.acs.org.

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