Example of Thermodynamic Control in Palladium-Catalyzed Allylic Alkylation. Evidence for Palladium-Assisted Allylic C–C Bond Cleavage

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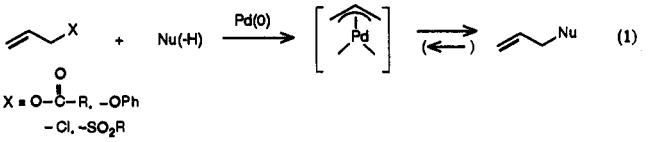
Abstract: Pd(0)-catalyzed reactions of a number of dienyl acetates with dialkyl malonates show that the regiochemistry of the reaction is very dependent on the reaction conditions. At low temperature and short reaction times the reaction is under kinetic control, but at elevated temperature and longer reaction times the reaction is under thermodynamic control. Under the latter conditions it was demonstrated that the kinetic allylic malonate rearranged to its thermodynamically more stable regioisomer in the presence of the Pd(0) catalyst. The results strongly support the cleavage of an allylic C–C bond by Pd(0), and thus the dialkyl malonate anion has acted as a leaving group.

Introduction

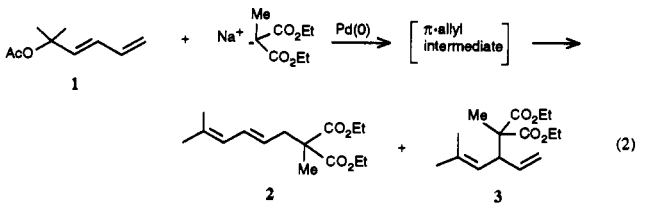
Palladium-catalyzed nucleophilic substitution of allylic substrates is a synthetically useful reaction for creation of new carbon–carbon or carbon–hetero atom bonds (eq 1).[1,2] The reaction



proceeds via a (π-allyl)palladium intermediate, and a large number of leaving groups and nucleophiles have been employed.[1-3] Some heteronucleophiles such as amines can also act as leaving groups in the product, which leads to a reversibility of the last step.[4] In such cases the regioselectivity of the reaction will be under thermodynamic control.

The corresponding reaction with stabilized carbon nucleophiles is usually considered to be irreversible and thus under kinetic control.[5] Only in special cases, such as in formation of a vinylcyclopropane via intramolecular attack by a stabilized carbon nucleophile, has reversibility been observed.[6,7]

In a recent synthesis toward marmelo oxides A and B, dienyl acetate **1** was used as substrate in a Pd(0)-catalyzed reaction with diethyl methylmalonate anion to give products **2** and **3** (eq 2).[8] It was observed that product **3** was converted to **2** on prolonged reaction time, indicating a reversibility between **3** and the π-allyl intermediate. We have now studied the regioselectivity of the reaction of eq 2 and analogous reactions, which lead to products where one of the isomers has the α-carbon of the malonate ester



in a bis-allylic position. We have also investigated the reactivity of the latter products such as **3** toward Pd(0) and found that stabilized carbon nucleophiles can act as leaving groups in such systems, leading to thermodynamic control in the allylic alkylation.

Results

A. Pd(0)-Catalyzed Allylic Alkylations under Thermodynamic and Kinetic Conditions. Six different substrates, **1**, **4-7**, and **9** (Table I), were used in the allylic alkylation studies. Two different phosphines, PPh_3 and PBu_3, were employed, and the reactions were run at different temperatures and reaction times.

1. Preparation of Starting Materials. Compound **1** was available according to ref 8. Dienyl acetate **4** was obtained from the reduction of butyl sorbate with $LiAlH_4$ followed by acetylation.[9] Bis-allylic acetates **5**,[10] **6**, and **7**[10] were prepared according to eq 3 by vinylmagnesium bromide reaction with the appropriate α,β-unsaturated aldehyde[11] and subsequent acetylation. Allylic sulfones **8**[12] and **9**[13] were prepared as shown in eq 4.

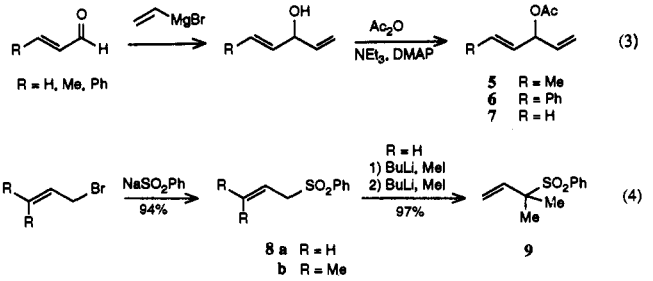


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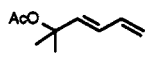
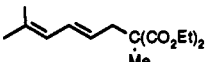
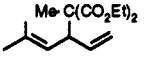
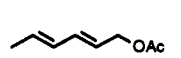
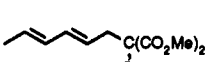
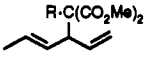
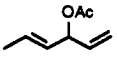
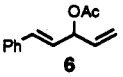
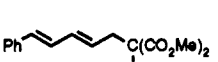
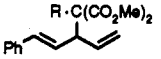
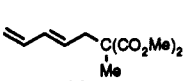
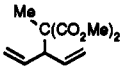
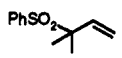
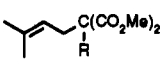
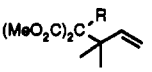
Table I. Pd(0)-Catalyzed Allylic Alkylations Under Thermodynamic and Kinetic Conditions[a]

Starting material	nucleophile	phosphine	time h	temp °C	conv. %	products[b]		
 1						 2		 3
	$^-C(Me)(CO_2Et)_2$	PPh_3	4	0	100	1[c]	:	1.3
		PPh_3	4	20	100	1.5[c]	:	1
		PBu_3	4	20	100	4[c]	:	1
		PBu_3	4	40	100	9[c]	:	1
 4						 10		 11
	$^-C(Me)(CO_2Me)_2$	PPh_3	24	0		2.3	:	1
		PBu_3	5.5	0	74	3.8	:	1
		PBu_3	4	40	100	4.9	:	1
	$^-CH(CO_2Me)_2$	PBu_3	4	20	64	3.8	:	1
		PBu_3	18	65	100	>98[d,e]	:	<2
 5	$^-C(Me)(CO_2Me)_2$	PBu_3	22	20	100	1.5	:	1
		PBu_3	4	65	90	2.0	:	1
		PBu_3	22	65	100	2.4	:	1
 6						 12		 13
	$^-C(Me)(CO_2Me)_2$	PBu_3	4	0	91	3	:	1
		PBu_3	4	65	100	>98[d]	:	< 2
	$^-CH(CO_2Me)_2$	PBu_3	4	0	100	4.5	:	1
		PBu_3	4	65	100	>98[d]	:	< 2
 7						 14		 15
	$^-C(Me)(CO_2Me)_2$	PPh_3	4	20	100	2.3	:	1
		PBu_3	4	20	90	5.6	:	1
 9						 16		 17
	$^-C(Me)(CO_2Me)_2$	PBu_3	4	0	65	2.8	:	1
		PBu_3	4	40	100	3.2	:	1
		PBu_3	4	60	100	3.3	:	1
	$^-CH(CO_2Me)_2$	PBu_3	24	20	84	1	:	2.2
		PBu_3	22	65	100	1	:	1.5

[a] To a 0.1 M solution of sodium dialkyl malonate in THF were added phosphine (20 mol %), $Pd(OAc)_2$ (5 mol %), and the allylic acetate or sulfone. Unless otherwise noted, 1.1 equiv of the nucleophile was used. [b] a: R = Me. b: R = H. The stereochemistry of the 2-alkenyl bond of the (2,4-dienyl)malonates was 70–90% E. [c] 1.5 equiv of the nucleophile was employed. [d] 2 equiv of the nucleophile was employed. [e] The product was contaminated with 11% of diallylated product.

2. Pd(0)-Catalyzed Substitution. Palladium-catalyzed substitution of allylic acetate **1** with $NaC(Me)(CO_2Et)_2$ in THF at 0 °C using triphenylphosphine as the ligand produced a 1:1.3 mixture between product **2** from terminal attack and product **3** from attack at the nonterminal position (Table I). The analogous reaction at 20 °C gave a 1.5:1 mixture between **2** and **3**. A change to tributylphosphine resulted in a further increase of the relative amount of terminal product, and at 40 °C the major product was **2** with the ratio of **2**:**3** being 9:1 (Table I).

A number of other substrates (**4**–**7**) which lead to a mixture of products where one of the regioisomers has the malonate in a bis-allylic position were investigated. Again the same trend was observed, i.e. the relative yield of terminal product increases with a change from PPh_3 to PBu_3 and/or with increased temperature. Thus, the palladium-catalyzed reaction of **4** with $NaC(Me)(CO_2Me)_2$ and PPh_3 at 0 °C gave **10** and **11** in a 2.3:1 ratio. A change to PBu_3 as ligand resulted in a 3.8:1 ratio at 0 °C and a 4.9:1 ratio at 40 °C between **10** and **11**. In analogy, the Pd(0)-catalyzed reaction of **6** and **7** with $NaC(Me)(CO_2Me)_2$ gave a similar variation with change of ligand or temperature.

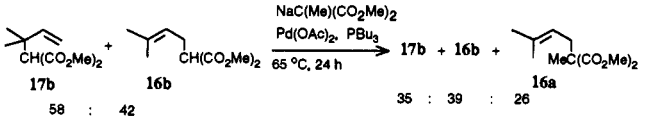
It is interesting to note that also the use of $NaCH(CO_2Me)_2$ as nucleophile showed the same trend. For example reaction of **4** with $NaCH(CO_2Me)_2$ at 20 °C for 4 h produced **10b** and **11b** in a ratio of 3.8:1. At 65 °C and 18 h of reaction the only regioisomer was **10b** (>98%).

To investigate reactions which lead to products with the α-carbon of malonate in a tertiary monoallylic position, substrate **9** was used. In the reaction of **9** with $NaC(Me)(CO_2Me)_2$ and $NaCH(CO_2Me)_2$, there was a difference between formation of terminal product as opposed to tertiary substituted product in the two cases. The use of $NaC(Me)(CO_2Me)_2$ afforded **16a** and **17a** in a ratio of 2.8–3.3:1 whereas $NaCH(CO_2Me)_2$ gave **16b**:**17b** in a ratio of 1:1.5–2.2. In both cases the relative amount of terminal product increased with temperature. Reaction of the regioisomeric allylic sulfone **8b** afforded essentially the same regioisomeric mixture.

The results in Table I suggest that the reactions are kinetically controlled at low temperature and short reaction times. Under these conditions there seems to be a significant difference between PBu_3 and PPh_3 as ligands, in that the former gives a higher relative yield of terminal product compared to the latter. This may be explained by a diminished carbonium character at the π-allyl carbons in the π-allyl intermediate by the electron-donating PBu_3, which would favor attack at the terminal carbon.[14,15] At higher temperature and longer reaction times there seems to be a thermodynamic control. To investigate this issue the stability of products under the reaction conditions was investigated. This is summarized in the next section.

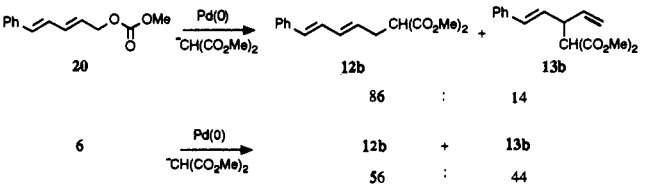
B. Pd(0)-Catalyzed Isomerization of Dialkyl Allylmalonates. Treatment of **19** with $NaC(Me)(CO_2Me)_2$ in the presence of the palladium catalyst for 4 h resulted in an isomerization to give the isomer **18** as the major product (**18**:**19** = 92:8).[16] On prolonged reaction time the ratio of **18**:**19** increased, and after 24 h there were no detectable amounts of **19** present. The corresponding isomerization of **11a** was slightly slower, and a 35:65 mixture of **10a** and **11a** needed 20 h at reflux to change into a >98:<2 mixture. Palladium(0)-catalyzed reaction of **11b** and **13b** for 24 h at elevated temperature led to complete isomerization in each case to give **10b** and **12b**, respectively. Unsubstituted, pentadienylacetate **15** also underwent isomerization. Thus, a 45:55 mixture of **14** and **15** isomerized to a >98:<2 mixture when treated with the palladium catalyst and $NaC(Me)(CO_2Me)_2$ for 20 h at reflux.

Control experiments showed that reaction of **11b** and $NaCH(CO_2Me)_2$ in the absence of a catalyst did not lead to any detectable isomerization.[17] This strongly indicates that the palladium(0) catalyst generated in situ is capable of cleaving the bis-allylic carbon–carbon bond to give a π-allyl complex, which results in a reversibility of the alkylation. Not only bis-allylic systems were found to undergo this Pd(0)-catalyzed C–C bond cleavage but also mono-allylic systems such as the tertiary malonate **17b**. In this case, however, the reaction is significantly slower. When a 58:42 mixture of **17b** and **16b** was treated with $NaC(Me)(CO_2Me)_2$ and the Pd(0) catalyst for 24 h at reflux, the mixture changed into a 35:39:26 mixture of **17b**, **16b**, and **16a**. The formation of the α-methylmalonate **16a** requires that dimethylmalonate has acted as a leaving group in **17b**.



Discussion

The present study shows that the regiochemical outcome of the Pd(0)-catalyzed allylic alkylation with dialkyl malonates may be under either kinetic or thermodynamic control. In many cases the nucleophilic attack may be reversible and the dialkyl malonate anion can be expelled as a leaving group. In particular this occurs easily if the α-carbon of the dialkyl malonate is situated in a bis-allylic position. In a recent study on the regiochemistry of metal-catalyzed allylic alkylations with dialkyl malonate, dienyl acetates or carbonates were utilized as substrates.[5,18] This leads to products where one of the isomers has the α-carbon of the malonate in a bis-allylic position. In a palladium-catalyzed reaction of **20** it was reported that **12b** was the major product, whereas the corresponding reaction of **6** afforded a 56:44 mixture of **12b**:**13b**. Different π-allyls together with a kinetically favored



attack at the terminal position was inferred as an explanation for these results. In view of the present results (Tables I and II), one has to be careful with the interpretation of the regiochemical outcome in these systems. The regiochemistry depends very much on the reaction conditions, and the reaction may become thermodynamically controlled.

Conclusion

The results presented in this paper strongly support the notion that dialkyl malonates can act as leaving groups under reaction conditions normally employed in palladium(0)-catalyzed allylic alkylation. In many cases a secondary allylic dimethyl malonate could be completely isomerized into a primary. These new findings are of importance in the interpretation of the mechanism of the palladium-catalyzed allylic alkylation with stabilized carbon nucleophiles, which previously has been considered to be an irreversible process.

Experimental Section

General Remarks. ^1H and ^{13}C NMR spectra were recorded at 400 and 100.6 MHz, respectively, from $CDCl_3$ solutions with tetramethylsilane (TMS) as the internal standard. Chemical shifts are reported in δ units, parts per million (ppm) upfield toward the standard. Infrared spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer from neat samples unless otherwise indicated. Mass spectrometry analyses were performed on a Finnigan Mat (INCOS 50) instrument. Gas chromatography was performed on a Varian 3400 capillary GC with a flame ionization detector. (All samples containing palladium were first eluted with methylene chloride through a short column of silica gel.) Merck silica gel 60 (230–400 mesh) was used for flash chromatography. THF and diethyl ether were distilled from deep blue potassium benzophenone ketyl solutions under N_2. Palladium acetate was purchased from Engelhard Industries. *n*-BuLi (1.6 M in hexane), vinylmagnesium bromide (1.0 M in THF), and PBu_3 were purchased from Aldrich. NaH (80% dispersion in mineral oil) and PPh_3 were purchased from Merck. Sodium benzenesulfonate (Aldrich, 99% grade) was used without further purification.

(*E*)-2-Methyl-3,5-hexadien-2-yl acetate (1) was prepared according to ref 8.

(*E,E*)-2,4-Hexadienyl acetate (4) was prepared from the commercially available alcohol using known procedures.[9] The crude acetate was purified by flash chromatography (pentane/ether, 70:30): ^1H NMR δ 6.25 (dd, J = 10.5, 15 Hz, 1H), 6.06 (ddd, J = 1.5, 10, 15 Hz, 1H), 5.76 (qd, J = 6.8, 15 Hz, 1H, CH_3CH), 5.63 (td, J = 6.5, 15 Hz, 1H, $CHCH_2$), 4.57 (d, J = 6.5 Hz, 2H, CH_2), 2.06 (s, 3H, CH_3), 1.76 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR δ 170.8, 134.9, 131.3, 130.3, 123.6, 64.9, 21.0, 18.1; IR (neat) 1739(s), 1362(m), 1236(s), 1024(s), 990(s), 957(m). (The spectral data of the alcohol was in complete accord with the literature.[11] IR (neat): 3346, 3019, 2855, 1662, 1627, 1438, 986, 925.)

(*E*)-1,4-Hexadien-3-yl Acetate (5).[10] To a stirred 1 M solution of vinylmagnesium bromide (71 mL, 71 mmol) in THF at 0 °C under an atmosphere of nitrogen was added crotonaldehyde (3.4 g, 48.5 mL) dropwise. The reaction mixture was stirred for 1 h at room temperature. Saturated aqueous ammonium chloride (25 mL) was added dropwise to the ice-cooled reaction mixture. After stirring for 1 h at 0 °C, a thick solid was formed and the organic layer was collected. The aqueous phase

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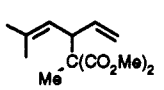
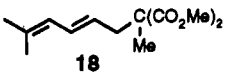
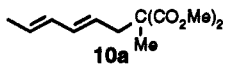
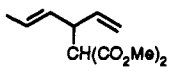
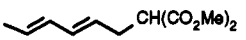
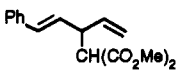
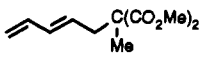
(15) At present we cannot exclude that the difference in relative yield of terminal product for PBu_3 and PPh_3 at low temperature is an effect of a thermodynamic control to a different degree, although a kinetic regioselectivity is consistent with the results of ref 14.

(16) This reaction can also be done in the absence of added $NaC(Me)(CO_2Me)_2$. In this case the reaction was much slower due to the very low concentration of free nucleophile ($-C(Me)(CO_2Me)_2$), and as a result the catalyst died before completion of the reaction.

(17) Two types of control experiments were performed. In one experiment both the $Pd(OAc)_2$ and PBu_3, which are the precursors for the active Pd(0)–phosphine complex, were omitted. In the other only $Pd(OAc)_2$ was omitted and the substrate was refluxed with PBu_3 and sodium dialkyl malonate. Neither of the experiments led to any detectable amounts of isomerization.

(18) Trost, B. M.; Urch, C. J.; Hung, M. H. *Tetrahedron Lett.* **1986**, *27*, 4949.

Table II. Pd(0)-Catalyzed Isomerizatioin of Allylic Malonates[a]

allylic malonate	added nucleophile	reaction temp (°C)	reaction time (h)	product
 **19**	$NaC(Me)(CO_2Me)_2$			 **18**
		40	4	**18:19** = 92:8
		40	24	>98% **18**
10a + **11a** 35 : 65	$NaC(Me)(CO_2Me)_2$			 **10a**
		20	4	**10a:11a** = 92:8
		65	20	>98% **10a**
 **11b**	$NaCH(CO_2Me)_2$	60	24	 **10b** (>98% **10b**)
 **13b**[b]	$NaCH(CO_2Me)_2$	65	24	 **12b** (>98% **12b**)
14 + **15** 45 : 55	$NaC(Me)(CO_2Me)_2$	65	20	 **14** (>98% **14**)

[a] To a 0.1 M solution of the sodium dialkyl malonate in THF were added PBu_3 (20 mol %), $Pd(OAc)_2$ (5 mol %), and the allylic malonate. [b] Contaminated with 11% of **12b**.

was extracted with ether (3 × 15 mL). The combined organic phases were concentrated under reduced pressure to give 4.74 g (99.6%) of the crude alcohol, which was sufficiently pure (according to NMR) to be used in the next step. The crude alcohol (17.57 g, 179 mmol), triethylamine (36.23 g, 358 mmol), acetic anhydride (36.55 g, 358 mmol), and 4-(dimethylamino)pyridine (2.19 g, 17.9 mmol) were mixed at 0 °C and stirred at room temperature for 0.5 h. Ether (70 mL) was added, followed by water (200 mL). After separation the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (30 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash chromatography (pentane/ether, 70:30) afforded 17.91 g (72%) of **5**: n^{24}_D 1.4380; ^{1}H NMR δ 5.84 (ddd, J = 6, 10.5, 17.3 Hz, 1H, CH_2=C*H*), 5.78 (dqd, J = 1, 6.5, 15.2 Hz, 1H, CH_3C*H*), 5.66 (bt, J = 6.5 Hz, 1H, CHC*H*CH), 5.48 (qdd, J = 1.8, 7, 15.2 Hz, 1H, CH=C*H*CH), 5.26 (td, J = 1.2, 17.3 Hz, 1H, CH=CH*H* (trans)), 5.19 (td, J = 1.2, 10.5 Hz, 1H, CH=CH*H* (cis)), 2.07 (s, 3H, OCH_3), 1.72 (ddd, J = 0.9, 1.8, 6.5 Hz, 3H, CH_3); ^{13}C NMR δ 169.9, 135.7, 130.0, 128.0, 116.6, 75.0, 21.2, 17.7; IR (neat) 1741 (s), 1371 (m), 1236 (s), 1017 (m), 966 (m), 932 (m).

(*E*)-5-Phenyl-1,4-pentadien-3-yl Acetate (6).[5] Acetate **6** was obtained in 94% yield from cinnamaldehyde (two steps) following the procedure described for preparation of acetate **5**. The acetate was used without further purification: ^{1}H NMR δ 7.32 (m, 5H, Ph), 6.64 (bd, J = 16 Hz, 1H, PhCH=C*H*), 6.18 (dd, J = 6.8, 16 Hz, 1H, PhC*H*=CH), 5.93 (ddd, J = 6, 10.3, 17 Hz, 1H, C*H*=CH_2), 5.88 (m, 1H, CHC*H*CH), 5.35 (dm, J = 17 Hz, 1H, CH=C*H*H, (trans)), 5.26 (dm, J = 10.3 Hz, 1H, CH=CH*H*), 2.09 (s, 3H, OCH_3); ^{13}C NMR δ 169.9, 135.3, 133.1, 128.5, 128.0, 127.0, 126.6, 126.1, 117.4, 75.0, 21.3; IR (neat) 1736 (s), 1371 (m), 1232 (s), 1017 (m), 966 (m), 936 (m), 750 (m), 693 (m).

1,4-Pentadien-3-yl Acetate (7).[10] Following the procedure described for **5**, 1,4-pentadien-3-ol was prepared from ethyl formate and vinylmagnesium bromide and the alcohol obtained was acetylated. The acetate **7** was obtained in 80% yield from ethyl formate (two steps). The acetate was eluted with pentane through a short column of silica gel: ^{1}H NMR δ 5.84 (ddd, J = 6, 10.5, 17.3 Hz, 2H, 2 CH_2C*H*), 5.70 (qt, J = 1.2, 6 Hz, 1H, CHC*H*CH), 5.30 (td, J = 1.2, 17.3 Hz, 1H, CH=C*H*H (trans)), 5.23 (td, J = 1.2, 10.5 Hz, 1H, CH=CH*H* (cis)), 2.08 (s, 3H, CH_3); ^{13}C NMR δ 169.9, 135.0, 117.4, 75.0, 21.2; IR (neat) 1744 (s), 1371 (m), 1232 (s), 1019 (m), 989 (m), 933 (m).

1-(Phenylsulfonyl)-3-methyl-2-butene (8b).[12] According to ref 19, the allyl phenyl sulfone (**8b**) was prepared from 1-bromo-3-methyl-2-butene and sodium benzenesulfinate in 94% yield (white crystals), mp = 52–53 °C; ^{1}H NMR δ 7.87 (m, 2H, Ph), 7.64 (m, 1H, Ph), 7.54 (m, 2H, Ph), 5.19 (tm, J = 8 Hz, 1H, CH), 3.79 (td, J = 0.6, 8 Hz, 2H, CH_2), 1.71 (s, 3H, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR δ 142.9, 138.7, 133.5, 128.9, 128.4, 110.4, 56.2, 25.8, 17.7; IR (solution in $CDCl_3$) 1306 (m), 1151 (s), 909 (m), 742 (s).

2-(Phenylsulfonyl)-2-methyl-3-butene (9).[13] Allyl phenyl sulfone (**8a**) was prepared in 68% yield from allyl bromide (20 g, 165 mmol) by stirring it with 1.7 equiv of sodium benzenesulfinate in DMF (400 mL) at 0 °C for 40 h according to ref 19. Allyl phenyl sulfone (**8a**) (2.94 g, 16.1 mmol) was dissolved in THF (60 mL). The solution was cooled to −78 °C, and *n*-BuLi (10.5 mL, 16.9 mmol) was added slowly followed by dropwise addition of methyl iodide (1.06 mL, 16.9 mmol). The reaction mixture was stirred at 0 °C for 1 h and then cooled to −78 °C, and another portion of *n*-BuLi (10.5 mL, 16.9 mmol) and methyl iodide (1.06 mL, 16.9 mmol) was added slowly. Again the reaction mixture was stirred for 1 h at 0 °C. Water (60 mL) was added, and the organic layer was collected. The aqueous layer was extracted with ether (4 × 20 mL). The combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure. The sulfone was purified by flash chromatography (pentane/ether, 50:50) to give 3.3 g (97%) of **9**: ^{1}H NMR δ 7.82 (m, 2H, Ph), 7.62 (m, 1H, Ph), 7.51 (m, 2H, Ph), 6.03 (dd, J = 10.5, 17.5 Hz, 1H, C*H*=CH_2), 5.27 (dd, J = 0.7, 10.5 Hz, 1H, CH=CH*H* (cis)), 5.08 (dd, J = 0.7, 17.5 Hz, 1H, CH=C*H*H (trans)), 1.44 (s, 6H, 2 CH_3); ^{13}C NMR (300 MHz) δ 136.6, 135.1, 133.5, 130.6, 128.3, 118.9, 64.7, 20.6; IR (solution in $CDCl_3$) 1296 (s), 1127 (m), 908 (s), 744 (m), 724 (m).

General Procedure for Pd(0)-Catalyzed Allylic Substitution with Sodium Dialkyl Malonates as Nucleophiles. To the malonate (5.23 mmol) in THF (50 mL) was added NaH (5.23 mmol), and the reaction mixture was flushed with N_2 several times until all the NaH had been consumed. The phosphine (1.14 mmol) was added followed by the $Pd(OAc)_2$ (0.29 mmol), and the reaction mixture was adjusted to the appropriate temperature. To the solution formed, the allylic substrate (4.76 mmol) was injected via syringe, and the reaction mixture was stirred for 4 h or

(19) (a) Sellén, M.; Bäckvall, J. E.; Helquist, P. *J. Org. Chem.* **1991**, *56*, 835. (b) Schank, v. K. *Justus Liebigs Ann. Chem.* **1967**, *702*, 75.
(20) Torii, S.; Uneyama, K.; Yamasaki, N. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 819.
(21) Cuvigny, T.; Julia, M.; Rolando, C. *J. Organomet. Chem.* **1985**, *285*, 395.

longer at constant temperature. Water (30 mL) was added, and the product was extracted with ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The analyses were carried out on the crude material or on the purified product mixture (flash chromatography, pentane/ether, 80:20).

General Procedure for Pd(0)-Catalyzed Isomerization of Bis-Allylic Dialkyl Malonates. To the malonate (1.83 mmol) in THF (20 mL) was added NaH (1.83 mmol). The reaction mixture was flushed with N_2 several times until all the NaH had been consumed. The tributylphosphine (0.40 mmol) was added followed by the $Pd(OAc)_2$ (0.10 mmol) and the bis-allylic dialkyl malonate (1.66 mmol). The reaction mixture was heated to reflux for 4–24 h. Water (15 mL) was added, and the product was extracted with ether (3 × 7 mL). The combined organic layers were washed with brine (7 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The product was purified by flash chromatography (pentane/ether, 80:20).

Allylic malonate 2:[8] ^{1}H NMR (300 MHz) δ 6.27 (dd, J = 10.8, 14.9, Hz, 1 H, C*H*=CHCH$_2$), 5.77 (d, J = 10.8, 1H, C*H*CH=CHCH$_2$), 5.40 (app dt, J = 7.5, 14.9 Hz, 1H, CH=C*H*CH$_2$), 4.18 (app tq, J = 1.6, 7.1 Hz, 4H, 2 × C*H*$_2$CH$_3$), 2.64 (d, J = 7.5 Hz, 2H, CH=CHC*H*$_2$), 1.74 (s, 3H, CH$_3$), 1.72 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_2$CC*H*$_3$), 1.24 (*t*, J = 7.1 Hz, 6H, 2 × CH$_2$C*H*$_3$); ^{13}C NMR (75.4 MHz) δ 172.0, 134.4, 130.9, 128.2, 124.5, 61.1, 53.8, 39.1, 25.9, 19.7, 18.2, 14.0; IR (CCl_4) 2982, 2937, 2911, 1733, 1240, 1106; MS m/z 268 (M$^+$, 13), 194 (47), 121 (43), 95 (100), 29 (57).

Allylic malonate 10a: ^{1}H NMR δ 6.02 (m, 2H, CH$_3$-CH=C*H*C*H*=CH), 5.62 (m, 1 H, CH$_3$C*H*, 5.39 (m, 1H, CH=C*H*CH$_2$), 3.73 (s, 6H), 2.61 (d, J = 7.5 Hz, 2H, CH$_2$), 1.73 (dd, J = 7 Hz, 3H, C*H*$_3$CH), 1.38 (s, 3H); ^{13}C NMR δ 172.3, 134.6, 131.1, 128.7, 124.5, 53.9, 52.4, 39.0, 19.9, 18.0; IR (neat) 2954 (m), 1736 (s), 1455 (m), 1251 (s), 1115 (s), 991 (m), 734 (m); MS m/z 226 (M$^+$, 15.8), 195 (2.1), 166 (49), 107 (100), 81 (76). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.46; H, 7.97.

Allylic malonate 10b: ^{1}H NMR (300 MHz) δ 6.04 (m, 2H, CH$_3$-CH=C*H*C*H*=CH), 5.60 (m, 1H, CH$_3$C*H*), 5.45 (m, 1H, CH=C*H*CH$_2$), 3.73 (s, 6H), 3.43 (t, J = 7.6 Hz, 1H, CH=CHCH$_2$C*H*), 2.65 (t, J = 7.5 Hz, 2H, C*H*$_2$), 1.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz) δ 169.2, 133.3, 130.9, 128.8, 125.8, 52.4, 51.7, 31.8, 17.9; IR (neat) 2954 (m), 1736 (s), 1438 (s), 1226 (s), 1157 (m); MS m/z 212 (M$^+$, 24.5), 181 (2.5), 152 (35), 93 (100), 81 (43). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.03; H, 7.62.

Allylic malonate 11a in a mixture (2.3:1) with the *E*,*Z*-isomer of **10a**: ^{1}H NMR δ 5.87 (m, 1H, C*H*=CH$_2$), 5.50 (m, 2H, CH$_3$C*H*=C*H*), 5.0 (m, 2H, CH=C*H*$_2$), 3.70 (s, 6H), 3.41 (bt, J = 8 Hz, 1H, CH$_2$=CHC*H*), 1.67 (td, J = 1, 5.5 Hz, 3H, C*H*$_3$=CH), 1.38 (s, 3H); ^{13}C NMR δ 171.5, 136.6, 128.8, 128.1, 117.1, 52.2, 52.1, 33.6, 18.1, 17.7; MS m/z 226 (M$^+$, <0.5), 195 (0.7), 167 (33), 107 (14), 81 (100), 41 (17). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.75; H, 8.01.

Allylic malonate 11b: ^{1}H NMR δ 5.78 (m, 1H, CH$_2$=C*H*), 5.57 (dqd, J = 1, 6.3, 15 Hz, 1H, CH$_3$C*H*), 5.39 (m, 1H, CH$_3$CH=C*H*), 5.10 (dd, J = 1, 17.5 Hz, 1 H, CH=CH*H* (trans)), 5.06 (dd, J = 1, 10 Hz, 1H, CH=CH*H* (cis)), 3.71 (s, 6H), 3.45 (m, 2H, C*H*CH(CO$_2$Me)$_2$), 1.66 (d, J = 6.5 Hz, 3H, C*H*$_3$); ^{13}C NMR δ 168.2, 137.2, 128.9, 128.0, 116.3, 56.7, 52.3, 46.9, 17.9; IR (neat) 2954 (m), 1740 (s), 1436 (m), 1258 (m), 971 (m); MS m/z 212 (M$^+$, <2), 180 (8), 153 (98), 93 (66), 81 (100). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.03; H, 7.70.

Allylic malonate 12a in a mixture (2.2:1) with the *E*,*Z*-isomer: ^{1}H NMR δ 7.46–7.15 (m, 5H, Ph), 6.72 (ddd, J = 1, 10.5, 15.5 Hz, 1H, PhCH=C*H*), 6.47 (bd, J = 15.5 Hz, 1H, PhC*H*), 6.27 (m, 1H, PhCH=CHC*H*), 5.68 (btd, J = 7.5, 15 Hz, 1H, CH$_2$C*H*), 2.70 (dd, J = 1, 7.5 Hz, 1H, CH$_2$), 1.43 (s, 3H, CH$_3$); ^{13}C NMR δ 172.1, 137.1, 134.6, 131.5, 128.4, 128.1, 127.3, 126.3, 126.1, 53.8, 52.4, 39.2, 19.9; MS m/z 288 (M$^+$, 25.1), 228 (17), 169 (35), 143 (100), 128 (61), 115 (24), 91 (21). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.58; H, 7.07.

Allylic malonate 12b[5] in a mixture (9.1:1) with the *E*,*Z*-isomer: ^{1}H NMR δ 7.29 (m, 5H, Ph), 6.71 (ddd, J = 0.7, 10.5, 15.5 Hz, 1H, PhCH=C*H*), 6.47 (d, J = 15.5 Hz, 1H, PhC*H*), 6.28 (ddm, 10.5, 15 Hz, 1H, PhCH=CHC*H*), 5.73 (td, J = 7.5, 15 Hz, 1H, =C*H*CH$_2$), 3.70 (s, 6H, 2OCH$_3$), 3.48 (t, J = 7.5 Hz, 1H, CH$_2$C*H*), 2.74 (dt, J = 1.5, 7.5 Hz, 2H, CH$_2$); ^{13}C NMR δ 169.2, 137.2, 133.4, 131.6, 129.4, 128.5, 128.4, 127.4, 126.2, 52.5, 51.6, 32.1; MS m/z 274 (M$^+$, 13), 214 (24), 155 (33), 142 (28), 128 (55), 115 (34), 91 (24), 77 (19), 69 (36), 59 (100).

Allylic malonate 13a: ^{1}H NMR δ 7.38–7.17 (m, 5H, Ph), 6.45 (d, J = 16 Hz, 1H, PhC*H*), 6.25 (dd, J = 8, 16 Hz, 1H, PhCH=C*H*), 5.96 (ddd, J = 8, 9.5, 17.5 Hz, 1H, C*H*=CH$_2$), 5.16 (d, J = 11.6 Hz, 1H, CH=C*H*H (cis)), 5.15 (d, J = 15.7 Hz, 1H, CH=CH*H* (trans)), 3.70 (s, 6 H), 3.61 (bt, J = 8 Hz, 1H, C*H*CH=CH$_2$), 1.44 (s, 3H, CH$_3$); ^{13}C NMR δ 171.4, 137.1, 136.0, 132.9, 128.5, 127.4, 127.3, 126.3, 118.0, 57.9, 52.5, 52.4, 18.1; IR (neat) 2951 (m), 1732 (s), 1434 (m), 1248 (s), 1102 (m), 972 (m), 748 (m); MS m/z 288 (M$^+$, 2), 229 (23), 143 (100), 128 (54). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.90; H, 7.20.

Allylic malonate 13b:[5] ^{1}H NMR δ 7.37–7.17 (m, 5H, Ph), 6.48 (d, J = 16 Hz, 1H, PhC*H*), 6.15 (dd, J = 8, 16 Hz, 1H, PhCH=C*H*), 5.89 (ddd, J = 7.5, 10, 17 Hz, 1H, C*H*=CH$_2$), 5.19 (bd, J = 17 Hz, 1H, CH=CH*H* (trans)), 5.13 (bd, J = 10.5 Hz, 1H, CH=C*H*H (cis)), 3.70 (m, 7H), 3.58 (d, J = 9 Hz, 1H); ^{13}C NMR δ 168.0, 136.9, 136.6, 132.2, 128.5, 127.7, 127.5, 126.3, 117.1, 56.6, 52.4, 47.0; IR (neat) 2953 (m), 1738 (s), 1435 (m), 1257 (s), 1157 (s), 970 (m), 749 (m); MS m/z 274 (M$^+$, 4), 214 (25), 155 (51), 142 (74), 128 (64), 28 (100).

Allylic malonate 14 in a mixture (3:1) with the *E*,*Z*-isomer: ^{1}H NMR δ 6.28 (td, J = 10.5, 17 Hz, 1H, CH$_2$=C*H*), 6.10 (m, 1H, CH$_2$=CHC*H*), 5.56 (td, J = 7.5, 15 Hz, 1H, CH$_2$C*H*), 5.13 (bd, J = 17 Hz, 1H, CH=CH*H* (trans)), 5.02 (bd, J = 10 Hz, 1H, CH=C*H*H (cis)), 3.71 (s, 6 H), 2.65 (dd, J = 1, 7.5 Hz, 2H, CH$_2$), 1.39 (s, 3H, CH$_3$); ^{13}C NMR δ 172.2, 136.5, 135.1, 128.0, 116.4, 53.8, 52.4, 38.9, 19.9; MS m/z 212 (M$^+$, 24), 181 (2), 152 (50), 93 (100), 67 (52). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.21; H, 7.72.

Allylic malonate 15 (in a mixture with **14** and its *E*,*Z*-isomer): ^{1}H NMR δ 5.87 (ddd, J = 7.9, 10.5, 17.2 Hz, 2H, 2C*H*=CH$_2$), 5.12 (m, 2H, CH=C*H*$_2$), 3.71 (s, 6H, 2OCH$_3$), 3.47 (qt, J = 1, 7.9 Hz, 1H, CHC*H*CH), 1.42 (s, 3H, CH$_3$); ^{13}C NMR δ 171.3, 135.8, 117.9, 57.5, 52.3, 19.8, 17.7; MS m/z 212 (M$^+$, 1), 181 (2), 153 (29), 93 (21), 67 (100), 59 (53), 41 (48).

Allylic malonate 16a: ^{1}H NMR (300 MHz) δ 4.99 (tm, J = 7.5 Hz, 1H, C*H*CH$_2$), 3.71 (s, 6H), 2.58 (d, J = 7.5 Hz, 2H, CH$_2$), 1.70 (s, 3H, CH$_3$), 1.62 (s, 3H, CH$_3$), 1.38 (s, 3H, CH$_3$); ^{13}C NMR (75 MHz) δ 172.6, 135.8, 117.8, 53.8, 52.4, 34.1, 25.9, 19.6, 17.8; IR (neat) 2954 (m), 1744 (s), 1435 (s), 1248 (s), 1108 (s), 912 (s), 738 (s); MS m/z 214 (M$^+$, 8), 154 (21), 139 (51), 95 (52), 69 (75), 59 (54), 41 (100). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.54; H, 8.46.

Allylic malonate 16b[20] in a mixture (4.9:1) with **17b**: ^{1}H NMR δ 5.03 (m, 1H, =C*H*CH$_2$), 3.71 (s, 6H), 3.34 (t, J = 7.5 Hz, 1H, CH$_2$C*H*), 2.57 (bt, J = 7.5 Hz, 2H, CH$_2$), 1.66 (bs, 3H, CH$_3$), 1.64 (bs, 3H, CH$_3$); ^{13}C NMR δ 169.6, 135.1, 119.4, 52.4, 51.9, 27.6, 25.7, 17.7; IR (neat) 2954 (m), 1736 (s), 1437 (m), 1243 (m), 1151 (m), 734 (m); MS m/z 200 (M$^+$, 13), 140 (35), 125 (45), 100 (32), 81 (100), 69 (73), 41 (63).

Allylic malonate 17a: ^{1}H NMR (300 MHz) δ 6.17 (dd, J = 11, 17 Hz, 1H, CH$_2$=C*H*), 5.03 (d, J = 11 Hz, 1H, CH=C*H*H (cis)), 5.01 (d, J = 17 Hz, 1H, CH=CH*H* (trans)), 3.70 (s, 6H), 1.42 (s, 3H, CH$_3$), 1.22 (s, 6H, 2 CH$_3$); ^{13}C NMR (300 MHz) δ 171.9, 144.2, 112.7, 59.8, 51.9, 41.3, 23.5, 18.8; IR (neat) 2953 (m), 1734 (s), 1248 (m), 1108 (m), 914 (m), 733 (m); MS m/z 214 (M$^+$, <0.5), 155 (6), 146 (42), 113 (22), 95 (10), 69 (100), 59 (70), 41 (39). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.40; H, 8.37.

Allylic malonate 17b[21] in a mixture (2:1) with **16b**: ^{1}H NMR δ 6.02 (dd, J = 10.5, 17.5 Hz, 1H, CH$_2$=C*H*), 5.01 (m, 2H, C*H*$_2$=CH), 3.71 (s, 6H), 3.35 (s, 1H, C*H*(CO$_2$Me)$_2$), 1.21 (s, 6H, 2 CH$_3$); ^{13}C NMR δ 168.3, 144.6, 112.3, 60.6, 52.0, 38.9, 25.0; MS m/z 200 (M$^+$, 2), 169 (2), 141 (47), 132 (23), 125 (21), 100 (24), 69 (100), 41 (64).

Allylic malonate 18 in a mixture (17:1) with the *E*,*Z*-isomer: ^{1}H NMR δ 6.27 (tdd, J = 1, 11, 15 Hz, 1H, C*H*=CHCH$_2$), 5.77 (bd, J = 11 Hz, 1H, (CH$_3$)$_2$C=C*H*), 5.38 (td, J = 7.5, 15 Hz, 1H, CH=C*H*CH$_2$), 3.72 (s, 6H), 2.65 (d, J = 7.3 Hz, 2H, CH$_2$), 1.75 (d, J = 8.5 Hz, 6H, (C*H*$_3$)$_2$C=CH), 1.41 (s, 3H); ^{13}C NMR δ 172.4, 134.6, 131.0, 124.6, 124.3, 54.0, 52.4, 39.3, 25.9, 19.9, 18.2; IR (neat) 2952 (m), 1735 (s), 1434 (s), 1244 (s), 1107 (s), 987 (m); MS m/z 240 (M$^+$, 19.9), 180 (41), 121 (31), 95 (100). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.20; H, 8.40.

Allylic malonate 19: ^{1}H NMR δ 5.86 (m, 1H, C*H*=CH$_2$), 5.12 (td, J = 1.2, 10.1 Hz, 1H, C*H*CHCH=CH$_2$), 5.05 (dd, J = 11.1, 15.8 Hz, 2H, CH=C*H*$_2$), 3.69 (m, 7H, 2 × OCH$_3$ + C*H*CH=CH$_2$), 1.73 (s, 3H, C*H*$_3$C=CH), 1.65 (s, 3H, C*H*$_3$C=CH), 1.40 (s, 3H); ^{13}C NMR δ 171.7, 136.9, 135.4, 120.6, 116.3, 57.7, 52.2, 37.4, 26.1, 18.0, 17.8; IR (neat) 2952 (m), 1740 (s), 1455 (m), 1434 (m), 1252 (s), 1103 (s); MS m/z 240 (M$^+$, 1.6), 181 (12), 146 (10), 95 (100). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.84; H, 8.29.