Regioselective Cyclocarboxylation of Nonconjugated Dienes to Cyclic Keto Esters

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The carboxylation of 1,5-hexadiene in the presence of $(PPh_3)_2PdCl_2$ in 1-butanol at 100 °C gives butyl 2-(3-methyl-2-oxocyclopentyl)acetate (**1**) in good yield. Small amounts of linear diesters are also produced. A number of other olefins were also carboxylated to give mixtures of cyclic and linear products. Although carboxylation of monoolefins usually gives a mixture of regioisomers, cyclopentanone **1** is produced in >25:1 selectivity over the cyclohexanone regioisomer. Deuterium labeling and model studies were carried out in an attempt to explain the unusual regioselectivity observed. These studies suggest that although the reversible initial insertion of 1,5-hexadiene into Pd−H occurs with poor regioselectivity, the conversion of the regioisomer resulting from a 2,1-insertion to product is much faster than conversion of the other regioisomer to product.

Introduction

The carboxylation of alkenes catalyzed by group 10 metals has been studied extensively on two fronts: carboxylation of alkenes to esters and carboxylic acids[1] and preparation of olefin−CO copolymers.[2] Two mechanisms have been proposed for the carboxylation of olefins by Pd(II) catalysts. The first (Scheme 1, mechanism A) involves olefin insertion into Pd−H, followed by CO insertion into Pd−alkyl. Alcoholysis of Pd−acyl gives the ester product. In mechanism B (Scheme 1), nucleophilic attack by alcohol on Pd−CO gives the Pd−acyl complex, which inserts an olefin to give Pd−alkyl. Pd−alkyl is protonated to give the product. While mechanism A is invoked for most systems in the literature,[3] mechanism B has been suggested for systems involving strong acids or oxidants.[4,5]

Irrespective of the mechanism involved, the regioselectivity of the carboxylation of 1-alkenes is typically poor. This results from the poor regioselectivity of olefin insertion into the palladium complex (Scheme 2). In general, the insertion occurs with a moderate preference for 1,2-insertion. Systems which typically give linear esters as the major product are proposed to operate through mechanism A.[6] Conversely, mechanism B is often invoked for those systems which give branched products.

The cyclization of nonconjugated dienes and enynes by transition metal species is an important entry into carbocyclic organic systems.[7,8] Despite the high interest in olefin carboxylations, very little has been reported with regard to the behavior of these systems with nonconjugated dienes.[9,10] Brewis and Hughes[11] reported that the carboxylation of 1,5-hexadiene under harsh (1000 atm of CO, 150 °C) conditions in the presence of $(Bu_3P)_2PdI_2$ gave methyl 2-(3-methyl-2-oxocyclopentyl)acetate in 40% yield. Brewis and Hughes proposed the mechanism shown in Scheme 3. Because of the utility of γ-keto esters in the synthesis of such natural products as cedrene[12] and the Boschnia lactone family,[13,14] we were interested in improving the cyclocarboxylation of dienes as a method for preparing these compounds. We were also interested in gaining some mechanistic insight into the copolymerization of 1,5-hexadiene and CO that we recently reported.[15,16] In this paper, we describe the regioselective carboxylation of a series of nonconjugated dienes. Mechanistic studies are described that address the origin of the high regioselectivity observed.

Results

Carboxylation of 1,5-hexadiene in the presence of $(PPh_3)_2PdCl_2$ and 1-butanol[17] under greater than 1000 psig of CO pressure at 100 °C for 20 h resulted in the formation of cyclopentanone **1** in 70% yield, along with

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(2) Amevor, E.; Bronco, S.; Consiglio, G.; di Benedetto, S. *Macromol. Symp* **1995**, *89*, 443−54.
(3) Cavinato, G.; Toniolo, L. *J. Organomet. Chem.* **1990**, *398*, 187−195.
(4) Toda, S.; Miyamoto, M.; Kinoshita, H.; Inomata, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600−3606.
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(7) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 636−662.
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(10) Negishi, E.; Ma, S.; Amanfu, J.; Coperet, C.; Miller, M. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919−5931.
(11) Brewis, S.; Hughes, P. R. *J. Chem. Soc., Chem. Commun.* **1965**, 489−90.
(12) Irie, H.; Takeda, S.; Yamamura, A.; Mizuno, Y.; Tomimasu, H.; Ashizawa, K.; Taga, T. *Chem. Pharm. Bull* **1984**, *32*, 2886−2889.
(13) Sakan, T.; Murai, F.; Hayashi, Y.; Honda, Y.; Shono, T.; Nakajima, M.; Kato, M. *Tetrahedron* **1967**, *23*, 4635−52.
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(16) Borkowsky, S. L.; Waymouth, R. M. *Macromolecules* **1996**, *20*, 6377−6382.
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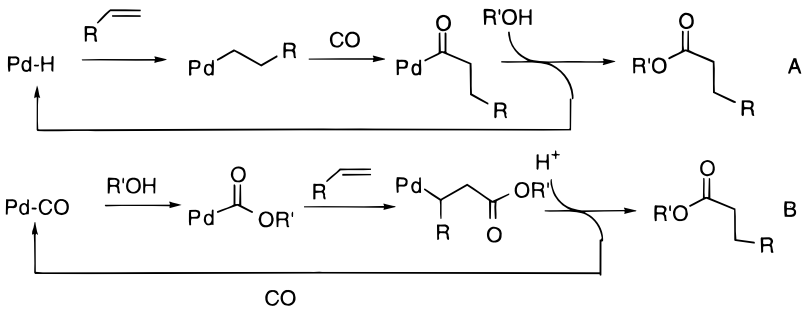
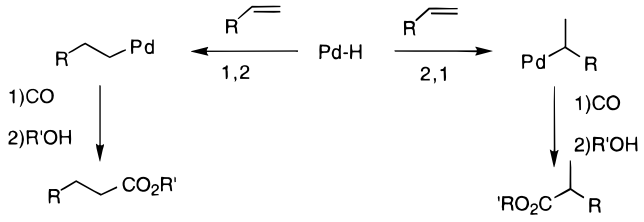
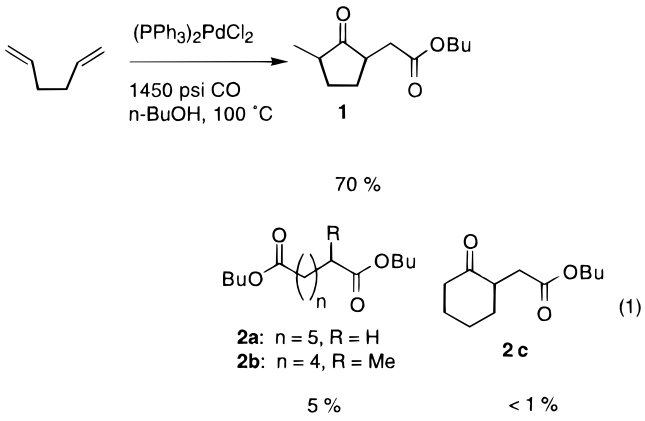
Scheme 1. Proposed Mechanisms of Metal-Catalyzed Olefin Carboxylation



Scheme 2. Regioselectivity of Olefin Insertion in Olefin Carboxylation



traces of linear diesters and the regioisomeric cyclohexanone product (eq 1). The cyclopentanone product was

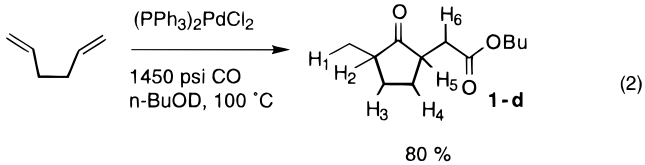


obtained as a 2.3:1 mixture of diastereomers. The reaction required initial CO pressures of at least 1000 psig, with higher pressures giving slightly higher yields. A reaction run under 500 psig of CO gave only a 14% yield of the cyclopentanone product. The reactions described here were run with CO pressures ranging from 1000 to 1500 psig. Carboxylations were typically run for >15 h, but for 1,5-hexadiene, reaction times as short as 2 h give comparable yields to reactions run for longer periods of time. The use of 1-butanol as the solvent gave the best results. Use of methanol as the solvent resulted in only a 45% conversion of 1,5-hexadiene and a 17% yield (by GC) of the methyl keto ester after 18 h. The reaction was also sensitive to the nature of the phosphine ligand used. Use of (dppp)-$PdCl_2$[18] in the reaction gave no conversion of 1,5-hexadiene. Use of $(Bu_3P)_2PdCl_2$, in analogy to Brewis and Hughes work,[11] also gave no conversion of 1,5-hexadiene after 24 h. The addition of phosphine lowered the yield of the reaction, although it improved the diastereocontrol of ring cyclization; the presence of one additional equivalent of PPh_3 lowered the yield of cyclopentanone to 33% (1,5-hexadiene conversion was 35%), but the product showed a 4:1 diastereomeric ratio.

The regioselectivity of 1,5-hexadiene carboxylation was very high for this system. In addition to cyclopentanone **1**, two regioisomeric diesters (dibutyl suberate and dibutyl 2-methylpimelate) were produced, as well as a trace amount of the cyclohexanone regioisomer **2c**. The ratio of products was insensitive to the 1,5-hexadiene concentration but did appear to be affected by CO pressure. The ratio of **1** to the minor products (**2a**, **2b**, and **2c**) increased when the pressure was increased from 500 to 1000 psig but did not change when the pressure was increased to 1500 psig (Table 1). The ratio of five- to six-membered ring regioisomers (**1** to **2c**) increased more significantly with increasing CO pressure.

Several nonconjugated dienes were carboxylated under the conditions described above. 2-Methyl-1,5-hexadiene reacted similarly to 1,5-hexadiene to give cyclopentanone **3** (Table 2, entry 2) in an 82% yield as a 1.5:1 mixture of two diastereomers, plus small amounts of linear mono- and diester products. Attempts to carboxylate homologous dienes were less successful. 1,4-Pentadiene gave only a 17% yield of cyclopentanone **4** (Table 2, entry 3) upon carboxylation. The major products in this case were unsaturated monoesters. Eighty-six percent of the monoesters contained an α-methyl branch, as determined by NMR. 1,6-Heptadiene also gave a low yield (30%) of cyclic product upon carboxylation. Cyclohexanone, **5**, was isolated as a 2:1 mixture of diastereomers (Table 2, entry 4). In this case, linear diesters were the major products obtained. Three isomeric linear diesters were produced in 45% overall yield. It was determined by ^1H NMR that 50% of all of the ester groups had α-methyl branches.

The carboxylation of 1,5-hexadiene under the standard conditions using 1-butan(ol-*d*) as the solvent (eq 2) yielded **1-*d*** with deuterium incorporation at H_1, H_2, and H_5. Deuterium incorporation was determined by



80 %

integration of the ^1H NMR spectrum. H_1 showed 26% incorporation or 0.79 D/Me groups. H_2 and H_5 overlap in the proton spectrum and showed a combined incorporation of approximately 67%. No deuterium incorporation at H_6 was observed (%D < 5%). Mass spectral analysis of the product showed a distribution of products containing from 0 to 4 deuterium atoms and an average deuterium incorporation of 2.15 D/molecule.

(18) dppp = 1,3-bis(diphenylphosphino)propane.

Scheme 3. Mechanism of 1,5-Hexadiene Carboxylation

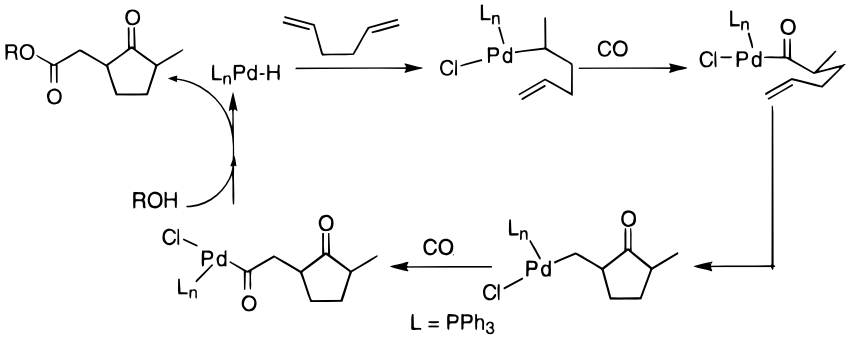
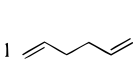
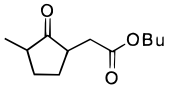
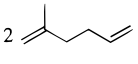
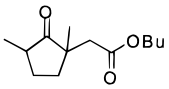
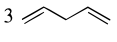
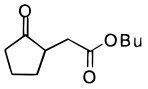
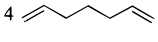
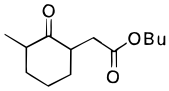
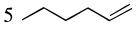
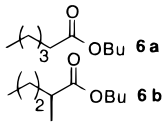


Table 1. Pressure Dependence on the Regioselectivity of 1,5-Hexadiene Carboxylation

reaction pressure[a]	ratio **1**:(**2a** + **2b** + **2c**)[b]	ratio **1**:**2c**[b]
500 psig	6.3	23.1
1000 psig	8.8	30.2
1500 psig	8.7	48.5

[a] Initial pressure. [b] Determined by GC.

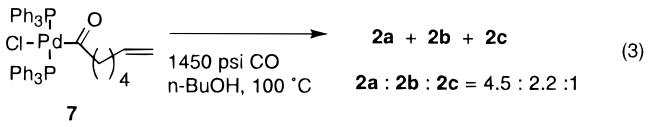
Table 2. Carboxylation of Nonconjugated Dienes to Cyclic Keto Esters and Linear Diesters

entry	diene	cyclic product[a]	monoester[a]	diester[a]
1		 **1** 70% 2.3 : 1 dr[b]	---.	5% 20% branched[c] 2 isomers 1.3 : 1[d]
2		 **3** 82% 1.5 : 1 dr[b]	(6%) % branched N.D. 3 isomers 2.1 : 1.1 : 1[d]	(8%) % branched N.D. 2 isomers 1.2 : 1[d]
3		 **4** 17%	23% 86% branched[c] 2 isomers 1.3 : 1[d]	8% 46% branched[c] 2 isomers 1.2 :1 [d]
4		 **5** 30% 2 : 1 dr[b]	(6%) % branched N.D. 2 isomers 1.8 : 1[d]	45% 50% branched[c] 3 isomers 3.4 : 2.8 : 1[d]
5		NA	 70% **6a : 6b** 2 : 1[d]	NA

[a] Reactions were carried out under 1000−1500 psig of CO at 100 °C for 15−24 h. Yields are isolated yields, except those in parentheses which were determined by GC. [b] Diastereomeric ratios (dr) determined by ^{1}H NMR. [c] Determined by ^{1}H NMR. [d] Ratio of isomers determined by GC. All isolated products gave satisfactory spectroscopic and combustion data.

A second carboxylation in 1-butan-*d*-ol was carried out to low conversion by stopping the reaction after 90 min. The conversion at this point was 62%, and **1-*d*** was isolated in 34% yield. The 1,5-hexadiene recovered from the reaction mixture contained a small (2.6%) incorporation of deuterium in the terminal vinylic protons. The level of incorporation is approximately 0.1 D/molecule of unreacted hexadiene. The cyclopentanone recovered from this experiment was deuterated in the same positions as that isolated from the full conversion experiment. The deuterium incorporation at positions H_2 and H_5 was approximately 60%, while the incorporation at H_1 was 33%, as determined by integration of the ^{1}H NMR spectrum. The total deuterium incorporation for the cyclopentanone product is 2.2 D/molecule, from integration of the ^{1}H NMR spectrum.

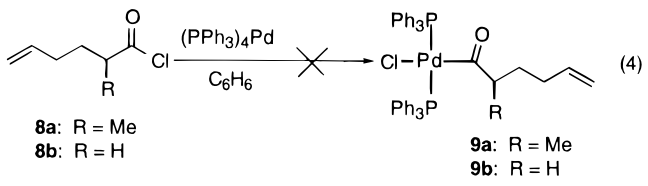
Palladium−acyl complex **7** was prepared by oxidative addition of 6-heptenoyl chloride to $(Ph_3P)_4Pd$.[19] A suspension of **7** was carboxylated at 1450 psig of CO at 100 °C for 24 h (eq 3). GC analysis of the reaction



7 (3)

mixture showed a 4.5:2.2:1 mixture of carboxylation products **2a**:**2b**:**2c**. Thus, the major products are linear diesters that result from simple alcoholysis of Pd−acyl, followed by carboxylation of the free olefin. The ratio of linear to branched products matches that observed for 1-hexene. Use of **7** to catalyze the carboxylation of 1,5-hexadiene gave a 73% yield of **1** (by GC). The amounts of **2a**, **2b**, and **2c** were slightly enhanced compared to the reactions catalyzed by $(PPh_3)_2PdCl_2$. This enhancement is in the range of that expected, due to products derived from **7**.

Attempts to prepare branched analogs of **7** were unsuccessful due to the instability of the palladium−acyl complexes. Oxidative addition of acid chloride **8a** to $(Ph_3P)_4Pd$ in benzene resulted in complete decomposition of the acid chloride to an uncharacterizable material over 3 h as observed by NMR (eq 4). Use of



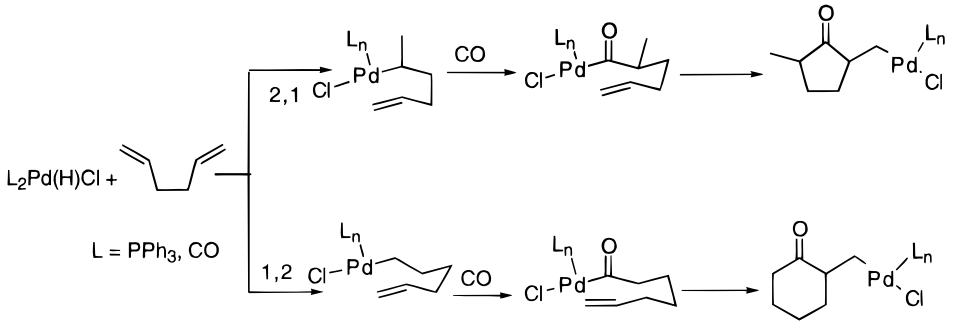
8a: R = Me
8b: R = H

9a: R = Me
9b: R = H (4)

acid chloride **8b**, resulted in formation of a complex analogous to **7** that was stable for a day in benzene, as observed by NMR. After 4 days, the complex had completely decomposed. Attempts to isolate **9b**, re-

(19) Fitton, P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 6−7.

Scheme 4. Formation of Regioisomers in the Carboxylation of 1,5-Hexadiene



sulted only in the recovery of uncharacterized Pd−phosphine complexes, which showed no alkyl resonances in the NMR.

Discussion

The carboxylation reaction described herein is an efficient method to prepare γ-keto esters from 1,5-hexadienes. Substitution at one olefinic position is tolerated, as shown by the high yield achieved in the carboxylation of 2-methyl-1,5-hexadiene (Table 2, entry 2). Only products resulting from initial insertion of the unsubstituted olefin were observed, showing the high degree of chemoselectivity possible in this reaction.

Homologous dienes gave poor cyclization selectivities. For 1,4-pentadiene, this was somewhat surprising. The $(PPh_3)_2PdCl_2$ carboxylation catalyst system favors an initial 1,2-insertion (*vide infra*) with simple 1-alkenes. An initial 1,2-insertion is required to form cyclopentanone **4**, but nevertheless acyclic, branched products resulting from 2,1-insertions were the major products. It is unclear as to why the selectivity is opposite to that expected. It is possible that a mechanism similar to that discussed for 1,5-hexadiene is responsible for an initial 2,1-insertion being favored. Cyclic products from 2,1-insertions are unlikely to form due to the strain involved in forming the cyclobutanone product.

Similarly, 1,6-heptadiene gave a poor cyclization selectivity. This is not unexpected as ring closure would be expected to be slower in this case due to the increased entropy of cyclization for the larger ring.[20] Presumably, the cyclization rate is slower than the rate of alcoholysis in our case, leading to a large proportion of linear products.

As mentioned in the introduction, there are two competing mechanisms proposed for the carboxylation of olefins (Scheme 1). On the basis of our deuterium labeling experiments, we can strongly implicate the Pd−H mechanism (mechanism A) under our conditions. The carboxylation of 1,5-hexadiene in 1-butan-*d*-ol produces cyclic products with multiple deuterium atoms in a variety of positions. Under mechanism B, deuterium is incorporated only in the protonation step. This should result in exclusive formation of monodeuteriated products. Under mechanism A, deuterium is incorporated upon olefin insertion into Pd−D. If β-hydride elimination occurs, then the olefin is left with an incorporated deuterium atom. Thus, reversible olefin insertion/β-hydride elimination before carboxylation can result in the incorporation of multiple deuterium atoms/molecule. Since the 1,5-hexadiene recovered from the reaction mixture shows very low levels of deuterium incorporation, deuteriation must occur without dissociation of the olefin from the metal center.

The regioselectivity for the formation of cyclopentanes **1** and **3** is exceptionally high considering the poor regioselectivity usually seen with these types of catalysts. Particularly interesting is the observation that **1** and **3** appear to result from a regioselective initial insertion of 1,5-hexadiene that occurs with an opposite regioselectivity to that observed with simple 1-alkenes. For example, the carboxylation of 1-hexene leads to a mixture of linear and branched esters, with the linear ester resulting from a 1,2-insertion being favored 2:1 over the branched isomer (Table 2, entry 5). It was initially expected that two regioisomeric products would be formed in this reaction (Scheme 4). Initial 1,2-insertion leads to cyclohexanone **G**, while initial 2,1-insertion would lead to **1**. In contrast to the selectivity seen with 1-hexene, the product selectivity for the carboxylation of 1,5-hexadiene is >25:1 in favor of the cyclopentanone, **1**, resulting from an initial 2,1-insertion of 1,5-hexadiene.

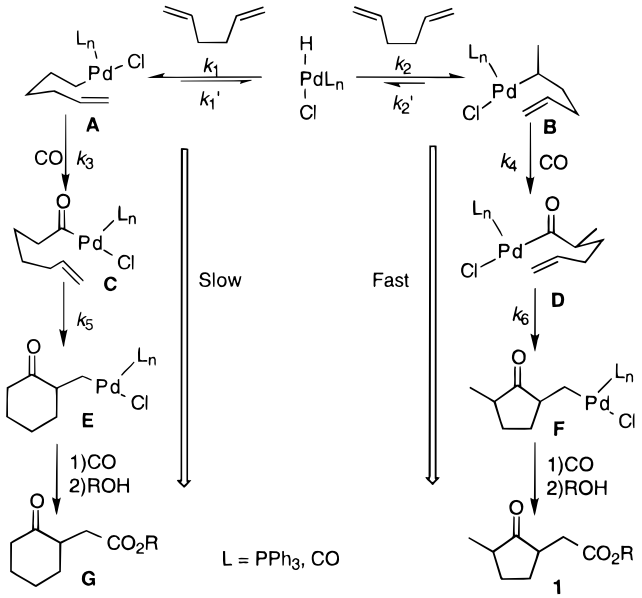
Two explanations for this reversal of regioselectivity can be proposed. One possibility is that coordination of 1,5-hexadiene to Pd−H occurs with some sort of chelation which favors 2,1-insertion. Alternatively, olefin insertion into Pd−H could be fast and reversible. In this case, the observed selectivity could be a function of the difference in the rate of conversion of the isomeric palladium−alkyls to carboxylated products.

The deuterium labeling studies suggest that olefin insertion is reversible, at least for primary olefin insertion, and that olefin insertion/β-hydride elimination occurs faster than conversion to products. The positions of deuterium incorporation are also illuminating. Incorporation of deuterium at H_2 and H_5 results from 1,2-insertions of 1,5-hexadiene into palladium−deuteride, while incorporation at H_1 and H_6 results from 2,1-insertions. Cyclopentanone **1-*d***, showed significant (67%) deuterium incorporation in positions H_2 and H_5. This suggests that a 1,2-insertion is highly reversible but that product formation from Pd−alkyl **A** is slow relative to β-hydride elimination. The **1-*d*** produced showed nearly 80% incorporation of one D at H_1 but no observable incorporation at H_6. This suggests that 2,1-insertion is followed by conversion to **1** at a rate significantly faster than β-hydride elimination (Scheme 5).

In light of the fast and reversible β-hydride elimination, there are two reasonable candidates for the product-determining step of the catalytic cycle: CO insertion or intramolecular olefin insertion. Cyclization to form the

(20) Samsel, E. G.; Norton, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 5505−5512.

Scheme 5. Proposed Mechanism of the Regioselectivity of 1,5-Hexadiene Carboxylation



five-membered ring would be expected to be significantly faster than cyclization to form the six-membered ring ($k_6 > k_5$) and appeared to us to be a logical product-determining step. For this explanation to be consistent with our results, CO insertion would have to be rapidly reversible. This is necessary because only traces of products derived from palladium−acyl **C** (acyclic diesters **2a** and **2b** and cyclohexanone **2c**) are observed in the product mixture, and we know that **A** is formed from the deuterium scrambling experiments. If CO insertion into **A** occurs at a rate comparable to insertion into **B**, then a significant amount of **C** would be formed.

Toniolo has provided evidence[21] that *trans*-acyl palladium chloride complexes are involved in catalytic carboxylation reactions similar to those described here. The *trans*-palladium−acyl **7** was prepared as a model complex for intermediate **C**. Pd−acyl **7** was carboxylated under the standard reaction conditions. If CO insertion were reversible from **7**, palladium−alkyl **A** would be formed. Our results show that **A** rapidly undergoes β-hydride elimination/reinsertion to give **B**, which will ultimately give **1**. However, we did not detect any cyclopentanone **1** from this experiment. This suggests that decarboxylation does not occur at a significant rate relative to 1-butanolysis or intramolecular olefin insertion of the *trans*-Pd−acyl. If, as this experiment suggests, CO expulsion does not occur under the reaction conditions, then the product selectivity is determined at or prior to the CO-insertion step of the mechanism. Attempts to prepare analogs of **D** were unsuccessful; thus, we were unable to show that **D** can be converted to **1** under the standard reaction conditions. As a result, it is not possible to rule out the possibility that **7** is not a good model for **C**, since it is possible that **C** is in fact the *cis* isomer. However, *in situ* IR studies[22] in a water/dioxane system have provided evidence for a Pd−acyl chloride complex, which had the same carbonyl stretching frequency as the *trans*-Pd−acyl complex isolated by Toniolo.[21]

The change in the regioselectivity of the reaction with increasing CO pressure led us to suspect CO insertion as the product-determining step. The ratio of cyclopentanone **1** to products arising from a 1,2-insertion (**2a**, **2b**, and **2c**) increases as the reaction pressure increases from 500 to 1000 psig. The problem with invoking carbonylation as the product-determining step is that this requires a significantly increased rate of CO insertion into a secondary Pd−alkyl **B** over a primary alkyl **A** (Scheme 5). It has been previously suggested that CO insertion into primary Pd−alkyl bonds should be faster than insertion into a secondary center.[23−25]

However, if we assume that the relative rate of formation of the acyls **D** vs **C** is responsible for the selectivity, then applying the steady-state assumption to intermediates **A** and **B** (Scheme 5) yields the following equations:

$$\frac{d[\mathbf{D}]}{dt} = [\mathrm{Pd{-}H}][\mathrm{CO}][\mathrm{C_6H_{10}}]\left(\frac{k_2k_4}{k_4[\mathrm{CO}] + k_2'}\right) \quad (5)$$

$$\frac{d[\mathbf{C}]}{dt} = [\mathrm{Pd-H}][\mathrm{CO}][\mathrm{C_6H_{10}}]\left(\frac{k_1k_3}{k_3[\mathrm{CO}] + k_1'}\right) \quad (6)$$

The relative rates are thus described by

$$\frac{d[\mathbf{D}]}{d[\mathbf{C}]} = \frac{\left(\frac{k_2k_4}{k_4[\mathrm{CO}] + k_2}\right)}{\left(\frac{k_1k_3}{k_3[\mathrm{CO}] + k_1}\right)} = \frac{k_2k_4(k_3[\mathrm{CO}] + k_1')}{k_1k_3(k_4[\mathrm{CO}] + k_2')} \quad (7)$$

Thus, if carbonylation is product determining, the selectivity does not depend only on the relative rate of carbonylation of **B** vs **A** (k_4[CO] vs k_3[CO]) but also on the relative rate of olefin insertion (k_2 and k_1) and β-hydride elimination (k_2' and k_1'). The fact that deuterium is readily incorporated into H_2 and H_5 indicates that k_1' is large relative to k_3[CO]. The fact that no deuterium is incorporated into H_6 indicates that k_2' is smaller than k_4[CO]. Assuming that k_3[CO] ≈ k_4[CO] (or k_3[CO] > k_4[CO]), these two results are consistent with the kinetic preference for **D** relative to **C**, as observed experimentally. Thus, the selectivity appears to depend not on the relative rate of carbonylation of **A** vs **B** but also on the relative rate of carbonylation vs β-hydride elimination for the isomeric alkyls **A** and **B**.

Literature precedent provides some support for a low rate of β-hydride elimination from **B**. For example, group 10 metallacycles are significantly more stable toward β-hydride elimination than their acyclic alkyl analogs.[26,27] Platinum metallacyclopentanes with α-methyl substituents (i.e., **10**) decomposed through β-hydride elimination at a rate 9100 times slower than the analogous dibutyl platinum compounds.[27]

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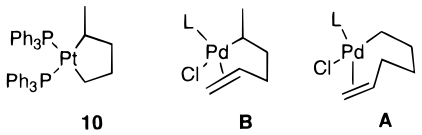

10 B A

Figure 1.

Comparison of Whitesides' platinum metallacycle **10**, Figure 1, with our proposed intermediate **B** shows it to be similar, if we invoke coordination of the olefin to the metal center. In the case of **A**, the intramolecular coordination of the olefin would be expected to be less stable due to the larger ring; the additional conformational flexibility would render this intermediate more susceptible to β-hydride elimination.

Conclusion

The carboxylation of 1,5-dienes can be achieved in high yield and with a high degree of regioselectivity. High yields are obtained only with 1,5-hexadienes, with modest diastereoselectivity. Mechanistically, this reaction presents an interesting example of high regioselectivity as the result of a kinetic selection of one of two regioisomeric palladium−alkyls to be carried on to product. The selectivity appears to be a result of the relative rate of carbonylation vs β-hydride elimination from the regioisomeric Pd−alkyls. This difference in the β-hydride elimination rates is likely a consequence of the formation of a stable, rigid chelate structure in the branched palladium−alkyl isomer, which leads to the observed product.

Experimental Section

General Considerations. All carboxylations were carried out in a stainless steel bomb stirred with a magnetic stirring bar. Heat was supplied by an external oil bath, and temperatures reported are for the oil bath. Carbon monoxide was C. P. grade and was supplied by Union Carbide. Dienes were supplied by Wiley and Aldrich and were dried over lithium aluminum hydride and vacuum transferred before use. 1-Butanol, 1-butan(ol-*d*) (98% d), triphenyl phosphine, 7-heptenoic acid, 5-hexen-2-one, and decane were purchased from Aldrich and were used as received. Palladium(II) chloride, tributyl phosphine, and dppp[18] were purchased from Strem and used as purchased. $(Ph_3P)_2PdCl_2$,[28] (dppp)$PdCl_2$,[29] and $(Bu_3P)_2PdCl_2$[29] were prepared according to literature procedures. GC data was obtained on a HP5980 GC using an SE-30 column (30 m × 0.32 mm i.d. × .25μ coating) with a fid detector. GC yields were determined by comparison of peak areas with an internal standard (decane), using response factors determined with authentic samples. Products were isolated by flash column chromatography using 200−400 mesh silica gel from Aldrich. ^{1}H, ^{2}H, ^{13}C, and ^{31}P NMR were performed on a Varian XL400 (^{1}H 400 MHz) spectrometer. Spectra were taken in $CDCl_3$, except for deuterium spectra. Peak shifts are reported in ppm downfield from TMS (0 ppm) for the H and C spectra. Spectra were referenced to internal TMS or to solvent peaks. ^{31}P NMR spectra were externally referenced to phosphoric acid (0 ppm). ^{2}H NMR spectra were obtained by observation of the deuterium lock signal of a preshimmed sample. Samples were dissolved in $CHCl_3$. Spectra were referenced to internal $CDCl_3$ (7.24 ppm) and are reported in ppm. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Mass spectral data were obtained at the University of California-Berkeley Mass Spectrometry center.

General Carboxylation Procedure: Preparation of Butyl 2-(3-Methyl-2-oxocyclopentyl)acetate (1). In a Schlenk tube under Ar were combined $(Ph_3P)_2PdCl_2$ (70 mg, 0.1 mmol), 1-butanol (10 mL), and decane (0.5 mL). This suspension was purged with Ar for 1 min. 1,5-Hexadiene (2.65 mL, 1.84 g, 22.5 mmol) was added to the catalyst suspension. The reaction mixture was then transferred via cannula to the reaction vessel which was under vacuum. After the reaction mixture was transferred to the bomb, the reaction was pressurized to 1450 psig of CO. The bomb was then placed in an oil bath preheated to 100 °C. The reaction was stirred at this temperature for 15 h and then cooled and depressurized. The contents of the bomb were analyzed by GC. **1** was produced in 75% yield, as determined by GC. **2a** and **2b** were produced in 5% yield, while **2c** was produced in 0.4% yield, as determined by GC. The 1-butanol was then removed under reduced pressure, and the crude oil was purified by flash chromatography. The column was eluted with hexanes (150 mL), followed by 15% ethyl acetate in hexanes. Isolation of the major fraction gave 3.318 g (70%) of a clear oil. ^{1}H NMR: δ (mixture of two diastereomers) 4.05−4.09 (m, 2H), 2.71−2.75 (m, 1H), 2.36−2.50 (m, 1H + 1H), 2.17−2.26 (m, 1H + 1H + 1H), 1.53−1.62(m, 2H + 1H), 1.33−1.42 (m, 2H + 1H), 1.12 (d, J = 6.78 Hz, 3H, major diastereomer), 1.08 (d, J = 7.36 Hz, 3H, minor diastereomer), 0.92 (t, J = 7.39, 7.39 Hz, 3H). Comparison of the peaks at 1.12 and 1.08 showed a 70:30 mixture of diastereomers. ^{13}C NMR: δ (major diastereomer) 220.5, 172.0, 64.4, 45.2, 43.6, 34.4, 30.6, 29.9, 27.4, 19.0, 14.4, 13.6; (minor diastereomer) 220.5, 172.0, 64.4, 44.5, 41.9, 34.6, 30.6, 28.6, 26.3, 19.0, 15.2, 13.6. FTIR: 2960.3, 1734.4, 1250.8, 1179.8 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.33; H, 9.88.

Butyl 2-(1,3-Dimethyl-2-oxocyclopentyl)acetate (3). 2-Methyl-1,5-hexadiene (2.142 g, 22.3 mmol) was carboxylated under 1200 psig of CO at 100 °C for 23 h. GC analysis of the reaction mixture showed a 6% yield of a mixture of monoester products and 8% yield of a mixture of diester products. The major cyclic product was isolated by flash chromatography to give 4.616 g (82%) of a clear oil. ^{1}H NMR: δ (mixture of diastereomers) 4.03 (m, 2H), 2.72 (d, J = 6.48 Hz, 1H), 2.37−2.56 (m, 2H), 2.10−2.25 (m, 1H), 1.95−2.06 (m, 2H), 1.74−1.79 (m, 1H), 1.50−1.62 (m, 3H), 1.11 (s, 3H, minor diastereomer), 1.00 (s, 3H, major diastereomer), 0.91−0.95 (m, 3H). Comparison of the relative integration areas of the peaks at 1.11 and 1.00 showed this to be a 60:40 mixture of diastereomers. ^{13}C NMR: δ (major diastereomer) 222.9, 171.5, 64.3, 46.2, 43.6, 42.2, 33.1, 30.7, 28.1, 19.1, 14.9, 13.6; (minor diastereomer) 223.1, 171.2, 64.3, 46.4, 41.9, 41.5, 33.1, 30.6, 24.5, 24.2, 19.1, 15.2, 13.6. FTIR: 2960.5, 1734.5, 1458.1, 1347.0, 1226.9, 1168.1, 1160.6 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 69.00; H, 9.80. Found: C, 69.16; H, 10.10.

Butyl 2-(2-Oxocyclopentyl)acetate (4). 1,4-Pentadiene (1.526 g, 22.3 mmol) was carboxylated under 1000 psig of CO at 100 °C for 23 h. GC analysis of the reaction mixture showed a mixture of a number of products. The crude material was flash chromatographed. Fractions 3−6 gave 857.8 mg (23%) of a clear oil, which was shown by ^{1}H NMR to be a mixture of ω-olefin esters. Integration of the α-methyl region showed that 86% of the total esters were branched. Fractions 7−10 gave 479.7 mg (8%) of oil, which was shown by ^{1}H NMR to be a mixture of diester products. Integration of the α-methyl region showed the mixture to be 45% branched. The desired cyclic product was isolated from fractions 11−15 to give 736.6 mg (17%) of a clear oil. ^{1}H NMR: δ 4.08 (t, J = 6.41, 6.72 Hz, 2H), 2.72 (m, 1H), 2.38−2.45 (m, 2H), 2.28−2.34 (m, 1H), 2.0−2.2 (m, 2H), 1.77−1.88 (m, 1H), 1.57−1.64 (m, 1H), 1.34−1.40 (m, 2H), 0.93 (t, J = 7.39, 7.02 Hz, 3H). ^{13}C NMR: δ 219.0, 172.1, 64.4, 45.5, 37.3, 33.9, 30.5, 29.2, 20.5, 19.0, 13.6. FTIR: 2960.4, 1774.8, 1735.0, 1262.3, 1181.1 cm^{-1}. Anal.

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Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.96; H, 9.15.

Butyl 2-(3-Methyl-2-oxocyclohexyl)acetate (5). 1,6-Heptadiene was carboxylated under 1300 psig of CO at 100 °C for 20 h. GC analysis of the reaction mixture showed a complex mixture of products. Only a small amount of monoester products were formed. GC yield was determined to be 6%. The crude material was flash chromatographed. Fractions 6−8 gave 3.011 g (45%) of a mixture of diesters. By ^{1}H NMR it was determined that 50% of the ester groups were branched. Fraction 9 gave 2.007 g (30%) of a mixture of diastereomeric cyclic products. ^{1}H NMR: δ (mixture of diastereomers) 4.11 (m, 2H), 2.78−2.90 (m, 2H), 2.48−2.62 (m, 2H), 2.12−2.35 (m, 3H), 1.82−1.91 (m, 1H), 1.59−1.67 (m, 3H), 1.35−1.45 (m, 4H), 1.23 (d, J = 7.32 Hz, 3H, minor diastereomer), 1.05 (d, J = 6.48 Hz, 3H, major diastereomer), 0.97 (t, J = 7.36, 6.60 Hz, 3H). ^{13}C NMR: δ (major diastereomer) 212.2, 172.7, 64.2, 47.1, 45.2, 37.0, 34.7, 34.4, 30.6, 25.3, 19.1, 14.4, 13.6; (minor diastereomer) 212.2, 172.7, 64.2, 47.1, 44.2, 38.8, 35.1, 33.7, 28.9, 22.3, 20.9, 13.9, 13.6.

Butyl Heptanoate and Butyl 2-Methylhexanoate (6a and 6b). 1-Hexene (1.8844 g, 22.4 mmol) was carboxylated under 1000 psig of CO at 100 °C for 25 h. GC analysis showed a 2:1 mixture of a linear to branched product. The crude product was flash chromatographed to give 2.919 g (70%) of a mixture of regioisomeric esters. The esters produced gave identical GC retention times and spectral data as authentic samples.

Preparation of *trans*-Bis(triphenylphosphine)-6-heptenoylpalladium Chloride (7). 7-Heptenoic acid (0.9 mL, 851.4 mg, 6.6 mmol) was converted to the acid chloride by refluxing with thionyl chloride (1.75 mL, 2.86 g, 24 mmol) in toluene (50 mL). Removal of the solvent left an oil, which was distilled at 30 mmHg. The product distilled at 82 °C to give 445.4 mg (46%) of the acid chloride. The acid chloride was oxidatively added to $(PPh_3)_4Pd$ in benzene by the method of Fitton.[19] The crude product was recrystallized from a methylene chloride/hexane mixture. The product was obtained as a pale orange powder (1.20 g, 52% yield). ^{1}H NMR: δ 7.73−7.81 (m, 12H), 7.35−7.50 (m, 18H), 5.51−5.62 (m, 1H), 4.79−4.86 (m, 2H), 1.90−1.96 (t, J = 7.12, 7.06 Hz, 2H), 1.54−1.62 (m, 2H), 0.54−0.63 (m, 2H), 0.38−0.49 (m, 2H). ^{13}C NMR: δ 235.8, 139.7, 135.2, 132.0 (t, ^1J_P = 21.4, 21.1 Hz), 130.9, 128.8, 114.3, 55.6 (t, J_P = 17.92, 17.31 Hz), 33.5, 28.4, 24.4. ^{31}P{^{1}H}: δ 21.4 (s). Anal. Calcd for $C_{43}H_{41}ClPd$: C, 66.42; H, 5.32. Found: C, 66.21; H, 5.29.

2-Methyl-5-hexenoyl Chloride (8a). 5-Hexen-2-one (12.7493 g, 0.130 mol) was reduced with lithium aluminum hydride (1.5397 g, 0.0406 mol) to give the alcohol (10.3662 g, 80%), which was converted to the mesylate with mesyl chloride (8.9 mL, 0.1149 mol) in pyridine (250 mL) at 0 °C. The crude mesylate was recovered in quantitative yield and used without purification. Displacement of the mesylate with sodium bromide (13.40 g, 0.130 mol) in DMSO (150 mL) overnight gave 5-bromo-1-hexene (5.5604 g, 33%). Treatment of this bromide with magnesium (1.1099 g, 0.474 mol) in ether, followed by an excess of solid CO_2, gave 2-methyl-5-hexenoic acid (1.2910 g, 30%). This was converted to the acid chloride by heating in thionyl chloride (1.1 mL, 0.015 mol) for 2 h. 2-Methyl-5-hexenoyl chloride was distilled off at 85 °C (30 mmHg). Recovered: 852.8 mg (58% yield).

Attempted Preparation of *trans*-Bis(triphenylphosphine)(2-methyl-5-hexenoyl)palladium Chloride (9a). $(PPh_3)_4Pd$ (117 mg, 0.101 mmol) was weighed in the drybox and suspended in C_6D_6. This was placed in an NMR tube and sealed with a rubber septum. The tube was removed from the drybox, and 2-methyl-5-hexenoyl chloride (15.2 mg, 0.0971 mmol) was added via syringe. The reaction was shaken periodically over 3 h and then an NMR spectrum was taken. ^{1}H NMR showed a large number of small peaks in the alkyl region that could not be assigned to a structure. No evidence of the desired product was observed.

Preparation of *trans*-Bis(triphenylphosphine)-5-hexenoylpalladium Chloride (9b). In the drybox, $(PPh_3)_4Pd$ (116 mg, 0.1 mmol) was weighed into a vial and suspended in C_6D_6. This suspension was transferred to an NMR tube and sealed with a septum. The NMR tube was brought out of the box, and 5-hexenoyl chloride (11.3 mg, 0.085 mmol) was added via syringe. The tube was shaken repeatedly, and periodic NMR spectra were taken. After 150 min, there was a 3:1 ratio of Pd−acyl:acyl chloride ratio. A spectrum taken of the same sample after 4 days showed complete loss of the Pd−acyl peaks. An attempt to prepare **9b** on a preparative scale was carried out as described for **6**. Only uncharacterized palladium−phosphine complexes were recovered.

Carboxylation of 7. **7** (246 mg, 0.316 mmol) was weighed into a schlenk tube in the drybox. Under Ar, butanol (2 mL) was added to give a suspension. The suspension was transferred via cannula to the bomb, which was under vacuum. The reaction was pressurized to 1500 psi CO and placed in a preheated oil bath at 100 °C. The reaction was stirred for 24 h. Upon cooling, the reaction pressure was 1400 psi. GC analysis of the reaction mixture showed a 4.5:2.2:1 mixture of **2a**:**2b**:**2c**.

Carboxylation of 1,5-Hexadiene with 7. The carboxylation was carried out as described above, but with 79 mg (0.10 mmol) of **7**. The reaction was carried out at 1500 psi and 100 °C for 24 h. Upon cooling, the reaction pressure was 1150 psi. GC analysis of reaction mixture showed 100% conversion of 1,5-hexadiene. **1** was produced in 73% yield, as determined by GC. **2a**, **2b**, and **2c** were produced as minor impurities. **2a** and **2b** were produced in 2.3% yield, and **2c** was produced in 0.4% yield, as determined by GC.

Carboxylation of 1,5-Hexadiene in 1-Butan(ol-*d*). 1,5-Hexadiene was carboxylated as described above, using 1-butan(ol-*d*) as the solvent. The carboxylation was carried out under 1500 psig of CO at 100 °C for 24 h. Flash chromatography of the crude material gave 4.0338 g (80%) of **1-*d***. The ^{1}H and ^{13}C NMR spectra of this material were similar to **1**. Deuterium incorporation was determined by careful integration of the ^{1}H NMR spectrum. Differences between the expected and integrated number of protons were used to determine the number of deuterium atoms at each peak. Integration of the ^{1}H NMR spectrum showed 26% D incorporation at H_1 (0.79 D/Me) and 67% combined incorporation at H_2 and H_5. ^{2}H NMR: δ 2.52 (H_2 minor diastereomer), 2.29 (H_2 major, H_5 minor), 2.09 (H_5 major), 1.04 (H_1). LRMS: calcd for $C_{12}H_{20}O_3$, 212; found, 212 (3.56%), 213 (20.4%), 214 (39.9%), 215 (29.6%), 216 (6.56%).

Low Conversion Carboxylation of 1,5-Hexadiene in 1-Butan-*d*-ol. The reaction was carried out as described above, but was stopped after 90 min by cooling and depressurizing the reaction bomb. GC analysis of the reaction mixture showed 62% conversion of 1,5-hexadiene and a 38% yield of **1-*d***. 1,5-Hexadiene was distilled from the reaction mixture. The hexadiene recovered was 98% pure, by GC, with the remainder being BuOD. ^{1}H NMR of the hexadiene matched authentic samples and showed no discrepancy in the integration areas. The trace of BuOD was also observed, and the ratio of hexadiene to BuOD was determined to be 19:1. ^{2}H NMR showed a small peak at 5.0 ppm, which corresponds to the terminal vinylic protons, plus a small peak for BuOD. The integrated ratio of these two peaks was 1:1.9 hexadiene:BuOD. The deuterium incorporation is thus 2.6%. The **1-*d*** was isolated in 34% yield from the reaction mixture as usual. The ^{1}H and ^{2}H NMR spectra were similar to the full conversion experiment. Deuterium incorporation was 33% for H_1 and 60% for H_2 and H_5, as determined from the proton integration.

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