Mechanism of the Palladium Dichloride Catalyzed Cope Rearrangement of Acyclic Dienes. A Substituent Effect Study[1a]

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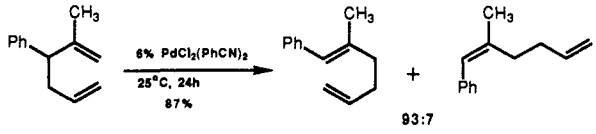
Abstract: The $PdCl_2$-catalyzed Cope rearrangement of eight 2-aryl-1,5-hexadienes was studied. No simple substituent effect relationship was found, since the catalyzed-rearrangement rate was decreased by introducing both electron-withdrawing and electron-donating substituents. The rates of rearrangement of the four most electron-deficient dienes (X = *p*-CF_3, *m*-CF_3, *m*-Br, *m*-F) showed good correlation ($\rho = -2.0$) with σ^+. This correlation provides the first direct evidence for the development of significant electron deficiency at C-2 in the transition state and is fully consistent with a cyclization-induced rearrangement mechanism in which the rate-limiting step involves cyclization of $PdCl_2$ alkene complex **5** to form the 4-palladacyclohexyl cation intermediate **6**. The fact that electron-donating substituents also decrease the rate of the catalyzed rearrangement is attributed to nonproductive binding of the $PdCl_2$ catalyst with the styrene unit. In support of this suggestion, *p*-methoxystyrene and 1-methyl-*p*-methoxystyrene are effective inhibitors of the $PdCl_2$-catalyzed rearrangement of dienes **3c** (X = H), **3b** (X = *m*-CF_3), and **3g** (X = *p*-CF_3), whereas 1-methyl-*p*-(trifluoromethyl)styrene is not.

The first reports of metal-promoted Cope rearrangements[2] were the stoichiometric reactions of *cis,trans*-1,5-cyclodecadienes and *cis*-1,2-divinylcyclobutanes with $[PdCl_2(PhCN)_2]$ to produce $PdCl_2$–diene complexes of 1,2-divinylcyclohexanes[3] and 1,5-cyclooctadienes,[4] respectively. The related stoichiometric conversion of divinylcyclobutanes to Ni(II) complexes of 1,5-cyclooctadienes has also been detailed.[5] In 1980 we reported for the first time that Cope rearrangements of acyclic 1,5-dienes could be conducted *catalytically* by using $[PdCl_2(RCN)_2]$ (e.g., eq 1).[6]

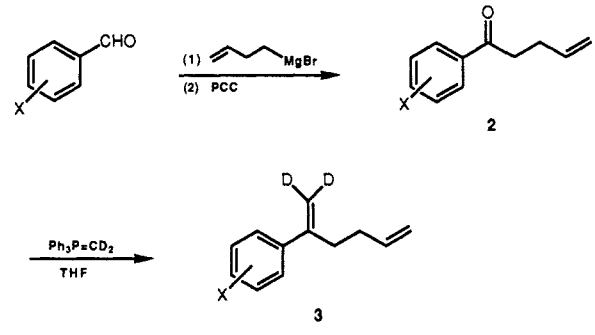


(1)

These catalyzed acyclic rearrangements occur at room temperature with rate accelerations on the order of 10^{10} (1 M $PdCl_2$) and with stereoselectivities that exceed their thermal counterparts.[6,7] We also demonstrated that $PdCl_2$-catalyzed Cope rearrangements occur with virtually complete transfer of chirality in a chair topographic sense similar to that observed for thermal Cope rearrangements of acyclic 1,5-dienes.[8,9] The extension of palladium dichloride catalysis to oxy Cope rearrangements has also been described.[10]

A variety of mechanisms has been considered for palladium(II)-catalyzed Cope rearrangements, although experimental investigations have been few.[1,6,8,11] The chirality-transfer investigations of Overman and Jacobsen unambiguously rule out mechanisms involving suprafacial formation and then fragmentation of metallocyclopentane (palladabicyclo[2.2.1]heptane) intermediates.[8] The absence of products of [1,3]-rearrangement[12] and the strict chair topography of the $PdCl_2$-catalyzed rearrangement of (3*R*,5*E*)-2,3-dimethyl-3-phenyl-1,5-heptadiene[8] argue against mechanisms[11] involving oxidative addition of the allylic C–C bond to form a bis(η^3-allyl)palladium(IV) intermediate. As we first suggested in 1980, the strict structural requirements of the $PdCl_2$-catalyzed Cope rearrangement of acyclic 1,5-dienes are well-rationalized by a cyclization-induced rearrangement mechanism as depicted in Figure 1.[1,6] Specifically, the requirement[1] that either C-2 or C-5 of a 1,5-hexadiene must be substituted with an electron-releasing substituent is consistent with the development of a positive charge at this site during the catalytic cycle. The failure of dienes substituted at *both* C-2 and C-5 to rearrange is explained in this context by a reluctance of the bulky metal catalyst to be σ-bonded to a tertiary carbon center.

Scheme I



a	*m*-OMe	d	*p*-Me	g	p-CF_3
b	*m*-CF_3	e	*m*-Br	h	p-Cl
c	H	f	*m*-F		

The central feature of a cyclization-induced rearrangement mechanism is the intervention of a metal-bound six-membered carbenium ion intermediate **1**. Besides the evidence for the intervention of **1** already noted, the formation of cyclohexyl products from the reaction of some 1,5-dienes with $PdCl_2$ provides indirect

(1) (a) Catalyzed Sigmatropic Rearrangements, 10. For part 9, see: Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579. (b) Current address: IBM Corporation, E-88/142, 5600 Cottle Rd., San Jose, CA 95123.

(2) For recent reviews, see: Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205 and reference 1.

(3) Trebellas, J. C.; Olechowski, J. R.; Jonassen, H. B. *J. Organomet. Chem.* **1966**, *6*, 412. Heimbach, P.; Molin, M. *Ibid.* **1973**, *49*, 477.

(4) Heimbach, P.; Molin, M. *J. Organomet. Chem.* **1973**, *49*, 483.

(5) Heimbach, P.; Brenner, W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 800.

(6) Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865.

(7) Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett.* **1983**, *24*, 3757.

(8) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225.

(9) As we discussed in more detail elsewhere,[1] the stereochemical outcome and reactivity patterns of the stoichiometric reactions of cyclic 1,5-dienes with $PdCl_2$ can be quite different.

(10) Bluthe, N.; Malacria, M.; Gore, J. *Tetrahedron Lett.* **1983**, *24*, 1157.

(11) (a) Heck, R. F. *Organotransition Metal Chemistry. A Mechanistic Approach*; Academic Press: New York, 1974; p 114. (b) Hamilton, R.; Mitchell, T. R. B.; Rooney, J. J. *J. Chem. Soc., Chem. Commun.* **1981**, 456.

(12) Products of competing [1,3]-rearrangement are often seen in transition metal-catalyzed [3,3]-rearrangements that are believed to proceed via η^3-allyl intermediates.[2,13]

(13) See, inter alia: Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058. Auburn, P.; Whelan, J.; Bosnich, B. *Organometallics* **1986**, *5*, 1533.

(14) Henry, P. M. *J. Am. Chem. Soc.* **1972**, *94*, 5200.

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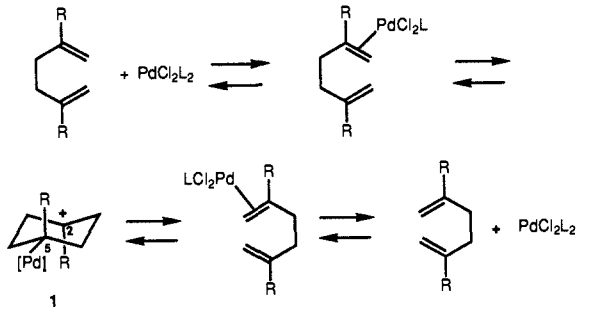


Figure 1. Proposed cyclization-induced rearrangement mechanism for $PdCl_2$ catalysis.

Table I. Preparation of 1-Aryl-4-penten-1-ones

X	yield, % Grignard addn	yield, % oxid	IR (film), cm^{-1}	^1H NMR[a]
m-OMe	29	71	1691	7.53 (7, 2), 7.37 (t, 1), 7.10 (d, 1)
m-CF_3	76	77	1696	8.23 (s, 1), 8.15 (d, 1), 7.82 (d, 1), 7.61 (t, 1)
m-Br	60	86	1680	8.08 (s, 1), 7.88 (d, 1), 7.69 (d, 1), 7.32 (t, 1)
m-F	50	87	1686	7.74 (d, 1), 7.65 (d, 1), 7.45 (m, 1), 7.26 (t, 1)

[a] In $CDCl_3$ at 250 MHz; δ (apparent major multiplicity, number of hydrogens); aromatic signals only.

support for the intervention of a palladacyclohexane intermediate.[1,15,16] It is important to stress, however, that this key intermediate has never been directly observed. Thus, we felt it was important to further investigate the proposed intervention of **1** in $PdCl_2$-catalyzed Cope rearrangements and in particular to probe the carbenium ion character at C-2 of such an intermediate. In this paper we report the results of our investigations of the $PdCl_2$-catalyzed rearrangement of deuterium-labeled 2-aryl-1,5-hexadienes, where the aryl substituent provides a classical Hammett probe of the transition-state environment of C-2. An earlier study of the thermal Cope rearrangement of 2-aryl-1,5-hexadienes by Marvell and Li[17] found very small effects for para substituents [k_X/k_H = 0.45 (Me), 1.17 (OMe), 1.16 (Cl)] in this pericyclic transformation[18] and provides an initial point of calibration for our studies.

Results

Preparation of Labeled Dienes. The three-step sequence shown in Scheme I was employed.[19] Addition of 3-butenylmagnesium bromide to the appropriate substituted benzaldehyde followed by oxidation of the benzylic alcohol product with pyridinium chlorochromate (PCC)[20] provided the required 1-aryl-4-penten-1-ones **2**. Table I summarizes this simple chemistry for the previously unknown members of this set. The remaining carbon and the deuterium label were cleanly introduced by reaction of **2** in THF (−78 → 23 °C) with the Wittig reagent prepared from commercially available (methyl-d_3)triphenylphosphonium iodide. The 1,1-dideuterio-2-aryl-1,5-dienes formed in this way contained 95–98% of the expected deuterium content by mass spectrometric analysis. Similar measures of deuterium content were obtained by 250-MHz ^1H NMR analysis, which also confirmed that within the limits of detection the label resided solely at C-1 (see Table II).

Table II. Preparation of [1-(Dideuteriomethylene)-4-pentenyl]arenes

X	yield, %	*d* content ^1H NMR[a]	*d* content MS[b]	^1H NMR[c]
m-OMe	40	1.90	1.94	7.24 (t, 1), 6.9–7.0 (m, 2), 6.82 (d, 1)
m-CF_3	43	1.94	1.94	7.4–7.7 (m, 4)
H	33	1.94	1.92	7.2–7.45 (m, 5)
p-Me	58	1.90	1.90	7.30 (d, 2), 7.13 (d, 2)
m-Br	57	1.96	1.98	7.53 (s, 1), 7.41 (d, 1), 7.15–7.35 (m, 2)
m-F	34	1.94	1.92	6.9–7.3 (m, 4)
p-CF_3	38	1.90	1.94	7.58 (d, 2), 7.49 (d, 2)
p-Cl	74	1.94	1.96	7.2–7.4 (m, 4)

[a] From integration of the terminal methylene signals of the d_0 and d_1 dienes which occur at ~δ 5.1 and 5.3. [b] EI (70 eV). [c] In $CDCl_3$ at 250 MHz; δ (apparent major multiplicity, number of hydrogens); aromatic signals only.

Table III. Bimolecular Rate Constants

diene	X	$[Pd(C_6H_{11})_2Cl_2]$, M × 10^3	no. of runs	k (1σ), L mol^{-1} min^{-1}[a]	σ^+[b]
3f	*m*-F	0.67–2.0	8	3.14 (0.30)	0.352
3h	*p*-Cl	0.67–2.0	7	2.03 (0.35)	0.035
3e	*m*-Br	1.0–2.0	6	2.00 (0.29)	0.40
3a	*m*-OMe	2.0	3	1.89 (0.15)	0.047
3c	H	0.67–2.0	7	1.89 (0.19)	0
3b	*m*-CF_3	1.0–2.0	8	1.32 (0.24)	0.52
3g	*p*-CF_3	1.0–2.0	7	0.99 (0.11)	0.582
3d	*p*-Me	4.0–8.0	7	0.61 (0.03)	−0.256

[a] At 25 ± 2 °C in $CDCl_3$. [b] Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1957**, *79*, 1913.

Substrates with the phenyl ring substituted with amine, nitrile, or amide functionality were not prepared, since these substituents had previously been shown to interfere with $PdCl_2$-catalyzed Cope rearrangements.[7] A nitro substituent was also not included, since the Wittig reaction of 1-(*m*-nitrophenyl)-4-penten-1-one with (methylene-d_2)triphenylphosphorane failed to produce 1,1-dideuterio-2-(*m*-nitrophenyl)-1,5-hexadiene.

Kinetic Studies. Catalyzed Cope rearrangements were carried out in $CDCl_3$ at ambient temperature (25 °C) in the probe of a Bruker WM-250 spectrometer at a substrate concentration of 0.10 M. The highly soluble catalyst, bis(hexanenitrile)palladium dichloride, was employed over a concentration range of 0.00067–0.008 M. Reactions were followed by measuring the appearance of the terminal methylene hydrogens at δ 5.0–5.3, allowance being made for the few percent of incomplete deuteration present in the starting diene. Isotope effects on the equilibrium constant were neglected in calculating pseudo-first-order rate constants: $k_{obsd} = k_1 + k_{-1}$ with $k_1 = k_{-1}$. This assumption is well-warranted since both we and Marvell[17] failed to detect by ^1H NMR spectroscopy a measurable variation from an equilibrium constant of 1.00. Pseudo-first-order rate constants were obtained from the integrated rate equation (correlation coefficients were ≥0.988) with the use of data taken during the first half-life only. At later stages of the reaction the rate was found to level off in an irreproducible fashion. We attribute this effect to slow destruction of the catalyst; this complication is not surprising, considering the low catalyst concentrations employed.

Pseudo-first-order rate constants were measured at three different concentrations of $[PdCl_2(C_5H_{11}CN)_2]$ and second-order rate constants were calculated from the equation $k_2 = k_1/[PdCl_2]$. The second-order rate constants are summarized in Table III, and the error limits indicate that these are of moderate precision only. The second-order rate constants vary by a factor of five as a function of the aryl substituents. Strongly electron-withdrawing substituents caused a decrease in the rate of rearrangement as did electron donors.

Inhibition Studies. The decrease in the second-order rate constants observed with electron-donating substituents suggested that competitive binding of $PdCl_2$ might be occurring at the styrene

(15) Overman, L. E.; Renaldo, A. F. *Tetrahedron Lett.* **1984**, *24*, 2235.
(16) See also: Julia, M.; Fourneron, J.-D. *J. Chem. Res., Miniprint* **1978**, 5401. Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. *J. Am. Chem. Soc.* **1979**, *101*, 494. Heumann, A.; Reglier, M.; Waegell, B. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 867. Kende, A. S.; Wustrow, D. J. *Tetrahedron Lett.* **1985**, *26*, 5411.
(17) Marvell, E. N.; Li, T. H.-C. *J. Am. Chem. Soc.* **1978**, *100*, 883.
(18) For a recent discussion of the mechanism of the thermal Cope rearrangement and leading references, see: Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1987**, *109*, 5893.
(19) In our hands this sequence was more efficient and convenient than the preparation of dienes **3** from the corresponding substituted acetophenones.[17]
(20) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

Table IV. Inhibition of the $PdCl_2$-Catalyzed Cope Rearrangement by Styrene Additives

diene	X	inhibitor, M × 10^1	$k_2 \times 10^{-1}$, M^{-1} min^{-1} [a]
3c	H	*p*-methoxystyrene, 2.81	1.38
		1-methyl-*p*-methoxystyrene, 3.00	*b*
		1-methyl-*p*-(trifluoromethyl)styrene-*2,2*-d_2, 3.00	2.05
		none	2.22[c]
3b	*m*-CF_3	*p*-methoxystyrene, 2.81	*b*
		1-methyl-*p*-methoxystyrene, 3.00	*b*
		none	1.58[c]
3g	*p*-CF_3	1-methyl-*p*-(trifluoromethyl)styrene-*2,2*-d_2, 3.00	0.76
		none	1.22[c]

[a] The concentration of dichlorobis(hexanenitrile)palladium(II) was 2.00×10^{-3} M, while the diene concentration was 0.10 M. [b] No rearrangement was detected over 24 h by 250-MHz ^1H NMR analysis. [c] This second-order rate constant (in the absence of inhibitor) was determined with the use of the same batch of diene and catalyst.

double bond. To probe this possibility, $PdCl_2$-catalyzed Cope rearrangements were conducted in the presence of styrene additives. A 3-fold excess of the styrene derivative (relative to the hexadiene) was utilized in these experiments, which employed 2 mol percent (0.002 M) of $[PdCl_2(C_5H_{11}CN)_2]$. As is apparent in Table IV the catalyzed rearrangement was substantially retarded in the presence of electron-rich styrene additives. The complete inhibition of the rearrangement of **3b** (*m*-CF_3) and **3c** (H) in the presence of 1-methyl-*p*-methoxystyrene is striking. In contrast, addition of 1-methyl-*p*-(trifluoromethyl)styrene showed no detectable inhibitory effect on the rearrangement of 2-phenyl-1,5-hexadiene (**3c**) and only ~30% inhibition of the rearrangement of **3g** (*p*-CF_3).

Discussion

No simple relationship exists between the electronic nature of the aryl substituent and the rate of the $PdCl_2$-catalyzed Cope rearrangement of 2-aryl-1,5-hexadienes, since the reaction rate was decreased by the introduction of both electron-donating and electron-withdrawing substituents. The rates of rearrangement of the four most electron-deficient dienes (X = *p*-CF_3, *m*-CF_3, *m*-Cl, *m*-F) exhibit fair Hammett correlations with σ ($\rho = -2.40$; correlation coefficient 0.945) and better correlation with σ^+ ($\rho = -2.03$, correlation coefficient 0.983). The σ^+ correlation is shown in Figure 2.

Before discussing the significance of these results we need briefly consider what is known about the thermodynamics of palladium(II) alkene π-complexation. Limited equilibria data is available for monoalkene complexes of palladium(II) which are either anionic, $[PdCl_3(alkene)]^-$,[21] cationic, $[Pd(C_5H_5)(PR_3)(alkene)]^+$,[22] or neutral, $[PdCl_2(pyridine)(alkene)]$[23] and **4**.[24,25] Steric effects are quite important and π-complex formation constants decrease with increasing substitution on the alkene.[21-26] The importance of electronic effects is seen in the complexation affinities of palladium(II) species for aryl-substituted styrenes,[22,24,26] which

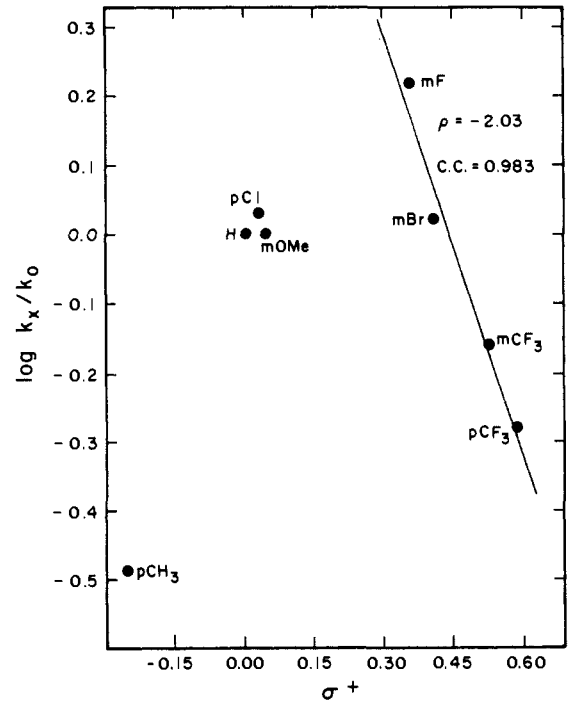
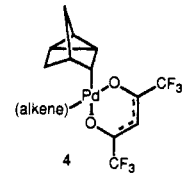


Figure 2. Log k_x/k_o vs σ^+ for $PdCl_2$-catalyzed rearrangement of 2-aryl-1,5-hexadienes.

are facilitated by electron donation [e.g., $\rho = -0.54$ (vs σ^+) in forming **4**].[24]



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A detailed mechanistic scheme for Cope rearrangement of **3** by a cyclization-induced rearrangement pathway is outlined in Scheme II. Intramolecular addition of the styrene π-nucleophile to the palladium(II)–alkene complex **5** would lead to the key cyclic intermediate **6**. Since **6** would surely be less stable than other intermediates depicted in Scheme II, k_2 should be rate-limiting and the rate of the catalyzed rearrangement thus facilitated by electron release from the aryl substituent. Complexation at the styrene π-bond to form **7** should be nonproductive, since this complex would not be expected to cyclize to the high-energy cyclic σ-alkyl palladium intermediate **8**.

The experimental results of our investigation are in full accord with the mechanism depicted in Scheme II. With strongly electron-deficient styrenes, nonproductive complexation to form **7** should not be competitive with the formation of the productive $PdCl_2$–alkene complex **5** (i.e., $k_1/k_{-1} \gg k_3/k_{-3}$). Thus, a simple Hammett relationship exists in forming **6** from this latter complex. The sign and magnitude of ρ, as well as the somewhat better correlation with σ^+ than σ, are all consistent with the formation of the benzylic cation **6** in the rate-limiting step of the rearrangement of these electron-deficient substrates. The value of ρ (−2.0) should be compared with the ρ of other reactions of substituted styrenes that are believed to have a high density of positive charge located on the benzylic carbon in the transition state. For example, the hydration of para-substituted styrenes correlates well with σ^+ constants with a slope (ρ) of ~−3.5.[27] A somewhat better comparison is hydration of aryl-substituted 1-methylstyrenes which correlates with σ^+ with a ρ of −3.2.[28]

(21) Hartley, F. R. *Chem. Rev.* **1973**, *73*, 163.
(22) Kurosawa, H.; Majima, T.; Asada, N. *J. Am. Chem. Soc.* **1980**, *102*, 6996. Miki, K.; Shiotani, O.; Kai, Y.; Kasai, N.; Kanatani, H.; Kurosawa, H. *Organometallics* **1983**, *2*, 585.
(23) Partenheimer, W.; Durham, B. *J. Am. Chem. Soc.* **1974**, *96*, 3800.
(24) Ban, E. M.; Hughes, R. P.; Powell, J. *J. Organomet. Chem.* **1974**, *69*, 455. Ban, E.; Hughes, R. P.; Powell, J. *J. Chem. Soc., Chem. Commun.* **1973**, 591.
(25) To the best of our knowledge, thermochemical data of this type on less stable $[PdCl_2(RCN)(alkene)]$ complexes is not available. Unfortunately, the study of $[PdCl_2(py)(alkene)]$ complexes by Partenheimer and Durham[23] included only three acyclic alkenes. In this study styrene and ethylene were found to have identical enthalpies for displacement by pyridine. A more extensive recent study of $[PtCl_2(pyridine)(alkene)]$ complex stabilities found that the equilibrium constant for styrene binding was 100× less than that of propene.[26]
(26) Kurosawa, H.; Erabe, A.; Emoto, M. *J. Chem. Soc., Dalton Trans.* **1986**, 891.
(27) Durand, J.-P.; Davidson, M.; Hellin, M.; Coussemant, F. *Bull. Chim. Soc. Fr.* **1966**, 52. Schubert, W. M.; Keefe, J. R. *J. Am. Chem. Soc.* **1971**, *94*, 559. Koshy, K. M.; Roy, D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 357.

The leveling off of the $PdCl_2$-catalyzed Cope rearrangement rate when X = *p*-Cl, *m*-OCH_3, or H and the marked decrease when X = *p*-Me is attributed to increasing nonproductive binding of the catalyst to the more electron-rich styrene double bond of these substrates (i.e., $k_3/k_{-3} \geq k_1/k_{-1}$). The rate of the $PdCl_2$-catalyzed Cope rearrangement is therefore diminished, since the concentration of the productive complex **5** is reduced. In this scenario, for example, all that would be required to observe a rate decrease in going from X = *m*-F to *p*-CH_3 is for the concentration of the productive complex **5** to decrease more than k_2 increases. The limited inhibition experiments carried out are consistent with this interpretation. Thus, although addition of 3 equiv of the electron-deficient styrene 1-methyl-*p*-(trifluoromethyl)styrene had only a small inhibitory effect on the $PdCl_2$-catalyzed rearrangements of **3b** (*m*-CF_3) and **3g** (*p*-CF_3), addition of 3 equiv of the electron-rich styrene 1-methyl-*p*-methoxystyrene totally inhibited rearrangements of **3b** (*m*-CF_3) and **3c** (H).

Could the unusual substituent effects we observe be equally well-rationalized by a mechanism involving the intervention of a bis(η^3-allyl)palladium(IV) intermediate? Since η^3-allyls of this type have only been proposed as reaction intermediates and never isolated or studied, an unequivocable answer to this question cannot be provided. However, we see no reason to anticipate a negative ρ of the magnitude we observe in a process involving, in the slow step, oxidative addition of the allylic bond of **3** to the palladium catalyst.

Conclusion

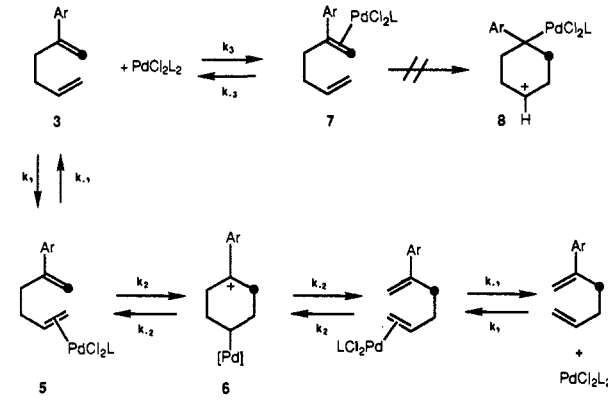
The rate of the thermal Cope rearrangement of a limited set of 2-aryl-1,5-hexadienes shows little sensitivity to the electronic nature of the aryl group. In contrast, the rate of the $PdCl_2$-catalyzed Cope rearrangement of electron-deficient 2-aryl-1,5-hexadienes correlates with σ^+ substituent constants and yields a large negative $\rho(-2.0)$. This result provides the first direct experimental evidence for the development of significant electron deficiency at C-2 in the transition state of the $PdCl_2$-catalyzed Cope rearrangement and is fully consistent with a cyclization-induced rearrangement mechanism in which the rate-limiting step involves formation of a 4-palladacyclohexyl cation intermediate.

Experimental Section[29]

Preparation of 1-Aryl-4-penten-1-ones. These intermediates were prepared by reaction of the appropriate substituent benzaldehyde with the Grignard reagent formed from 4-bromo-1-butene, followed by oxidation of the benzylic alcohol with pyridinium chlorochromate (PCC).[20] Ketones **1c**,[17] **2d**,[17] **2g**,[17] and **2h**[31] have been previously reported. Results are summarized in Table I. A representative procedure follows.

1-(3-Fluorophenyl)-4-penten-1-ol. 4-Bromo-1-butene (2.2 mL, 22 mmol) was slowly added dropwise to a mixture of magnesium ribbon (freshly etched, 0.6 g, 25 mmol) and THF (15 mL). The rate of addition was controlled to maintain a gentle reflux. The reaction mixture was then diluted with additional THF (25 mL) and heated to reflux for 1 h.

Scheme II[a]



[a] ● = CD_2.

After the Grignard reagent was allowed to cool to room temperature, a solution of 3-fluorobenzaldehyde (2.2 mL, 20 mmol) and THF (8 mL) was added dropwise over 10 min. After an additional 5 h at 23 °C, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous NH_4Cl, and diluted with hexane (20 mL). The organic layer was separated, washed with NH_4Cl (3 × 20 mL), H_2O (2 × 20 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (silica gel, 9:1 hexane/ethyl acetate) gave 1.8 g (50%) of 1-(3-fluorophenyl)-4-penten-1-ol as a colorless liquid, which was 97% pure by GLC analysis:[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.25–7.31 (m, ArH, 1 H), 6.95–7.11 (m, ArH, 3 H) 5.78–5.88 (m, C*H*=CH_2), 4.97–5.08 (m, C=CH_2, 2 H), 4.69 (app t, J = 6.6 Hz, OCH), 2.03–2.14 (m, 2 H), 1.79–1.88 (m, 2 H); IR (film) 3200–3600, 3078, 2920, 1578, 1442, 1243, 1134, 1055, 910 cm^{-1}; MS (EI, 20 eV) *m/e* (relative percent, 5% cutoff) 180 (M, 5), 162 (9), 151 (12), 138 (88), 125 (100), 122 (28), 121 (21), 97 (12); high-resolution MS 180.0938 (180.0950 calcd for $C_{11}H_{13}FO$).

1-(4-Fluorophenyl)-4-penten-1-one (2f). A mixture of PCC (1.8 g, 8.3 mmol) and CH_2Cl_2 (15 mL) was added at room temperature to a solution of 1-(4-fluorophenyl)-4-penten-1-ol (1.0 g, 5.6 mmol) and CH_2Cl_2 (40 mL).[20] After 4 h at 23 °C, Celite (2 g) was added and the reaction mixture was concentrated to a dry powder. The powder was applied to a column containing neutral alumina, and the column was eluted with CH_2Cl_2 (100 mL). Concentration and radial chromatography of the residue (4-mm silica gel plate, 95:5 hexane/ethyl acetate) gave 0.86 g (86%) of **2f** as a colorless liquid, which was 96% pure by GC analysis:[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.73 (app d, J = 7 Hz, ArH, 1 H), 7.65 (broadened d, J = 7 Hz, ArH, 1 H), 7.43–7.47 (m, ArH, 1 H), 7.25–7.27 (broadened t, J = 7 Hz, ArH, 1 H), 5.84–5.95 (m, C*H*=CH_2), 5.00–5.13 (m, C=CH_2, 2 H), 3.06 (t, J = 7.1 Hz, CH_2CO), 2.48–2.54 (m, C=CCH_2); IR (film) 3070, 2920, 1686, 1587, 1440, 1252, 1149, 989, 908, 872, 773 cm^{-1}; MS (EI, 20 eV) *m/e* (relative percent, 5% cutoff) 178 (M, 6), 124 (9), 123 (100), 121 (6), 119 (9); high-resolution MS 178.0810 (178.0794 calcd for $C_{11}H_{11}FO$).

Preparation of [1-(Dideuteriomethylene)-4-pentenyl]arenes. These were prepared by treatment of 1-aryl-4-penten-1-ones with excess of the Wittig reagent prepared from (methyl-d_3)triphenylphosphonium iodide. Yields, key characterization data, and deuterium content measurements are summarized in Table II. A representative procedure follows.

1-(Trifluoromethyl)-4-[1-(dideuteriomethylene)-4-pentenyl]benzene (3g). *n*-Butyllithium (1.8 mL of a 2.3 M solution in hexane, 4.1 mmol) was added dropwise to a stirring slurry of (methyl-d_3)triphenylphosphonium iodide (1.8 g, 4.4 mmol, 99 atom % d) and THF (35 mL) at −78 °C under an argon atmosphere. The resulting solution was stirred at 23 °C for 0.5 h and then recooled to −78 °C. A solution of ketone **2g** (0.48 g, 2.1 mmol) and THF (3 mL) was then added dropwise over 5 min. The reaction mixture was stirred for an additional 0.5 h at −78 °C and then allowed to warm to 23 °C. After an additional 8 h at 23 °C, the reaction mixture was quenched with 5 mL of saturated aqueous NH_4Cl and diluted with hexane (20 mL). The organic layer was separated and washed with NH_4Cl (3 × 20 mL), H_2O (3 × 20 mL), and brine (30 mL). Drying ($MgSO_4$) and concentration gave the crude diene, which was contaminated with triphenylphosphine oxide. Filtration and radial chromatography of the residue (4-mm silica gel plate, 98:2 hexane/ethyl acetate) gave 0.18 g (38%) of **3g**, which was 94% pure by GLC analysis:[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.58 (app d, J = 8.2 Hz, ArH, 2 H) 7.49 (app d, J = 8.1 Hz, ArH, 2 H), 5.77–5.88 (m, C*H*=

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(29) General experimental details: Tetrahydrofuran (THF) was distilled from Na and benzophenone and CH_2Cl_2 from CaH_2 prior to use. The molarities indicated for *n*-BuLi were established by titration with 2,5-dimethoxybenzyl alcohol.[30] ^{1}H NMR spectra were measured at 250 MHz with a Bruker WM-250 spectrometer. The kinetic micro-program in the Bruker ASPECT 2000 NMR software manual was employed for kinetic experiments. The parameters were as follows: pulse width (PW) = 1 μs; relaxation delay (RD) = 1 s; delay between the recording of each spectra (DP) = 1 s; total number of spectra recorded for each experiment (NE) = 12. ^{1}H NMR chemical shifts are reported as δ values in ppm relative to TMS. ^{1}H NMR coupling constants are reported in hertz and refer to apparent multiplicities and not true coupling constants. Multiplicity is indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); app d (apparent doublet); etc. High-resolution mass spectra were measured on a VG Analytical 7070E spectrometer. Low-resolution mass spectra were measured on a Finnigan 4000 GC/MS/DS spectrometer. Infrared spectra were recorded with a Perkin-Elmer 283 spectrometer. TLC and column chromatography were conducted with the use of E. Merck silica gel. Radial chromatography was done with a Harrison Research Chromatotron.

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(31) Alexander, E. C.; Uliana, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 5644.

(32) This analysis was done on a 25-m, 5% methylsilicon fused quartz capillary column.

CH_2), 4.96-5.05 (m, C=CH_2, 2 H), 2.57-2.63 (m, C=CCH_2), 2.19-2.25 (m, C=CCH_2); IR (film) 3083, 2929, 2859, 1644, 1618, 1444, 1408, 1327, 1168, 1117, 1067, 1014, 913, 844, 724 cm^{-1}; MS (EI, 70 eV) *m/e* (relative percent) 228 (M, 100), 213 (73), 173 (32), 167 (44), 159 (61), 131 (73), 117 (48). Integration of the small apparent singlets at δ 5.15 and 5.32 (due to the terminal methylene group of d_0 and d_1 diene) relative to the two hydrogen signal at 4.96-5.05 for the terminal vinyl group showed that the deuterium content was 1.94.

Preparation of Bis(hexanenitrile)palladium Dichloride. Palladium dichloride (5.0 g, 28 mmol) was added to freshly distilled hexanenitrile (30 mL), and the resulting mixture was stirred overnight under an argon atmosphere. The resulting orange mixture was filtered through glass wool, and the filtrate was treated with pentane (200 mL). The resulting yellow precipitate was filtered with use of a Schlenk apparatus and washed with pentane (2 × 100 mL). The orange-yellow crystals were dried under vacuum (2 mm, 2 h) to give 8.9 g (85%) of the bis(hexanenitrile) complex.

Kinetic Studies. Rearrangements were carried out at ambient temperature in the probe of a Bruker WM-250 spectrometer. The probe temperature was 25 ± 2 °C ($HOCH_2CH_2OH$). NMR tubes were charged with the starting diene in $CDCl_3$ (ca. 0.4 mL) then 3-40 μL of $[PdCl_2(C_5H_{11}CN)_2]$ solution (0.09 M in $CDCl_3$ with 1% TMS) was added to give a final diene concentration of 0.10 M. The ratio of the vinylic hydrogen at δ 5.7-5.9 to the terminal methylene hydrogens which appeared at δ 5.1-5.3 was determined by integration. Rate constants were obtained by least-squares analysis of $\ln [A_e - A_o]/[A_t - A_e] = -kt$, where A_e was assumed to be $^1/_2A_o$. Duplicate runs were conducted at three concentrations of $PdCl_2$. Pseudo-first-order plots were linear over one half-life and were considered acceptable if the correlation coefficient was ≥0.988. A typical example of the NMR traces, raw data, and first-order plots is provided as supplementary material as is a listing of the pseudo-first-order rate constants measured at all the $PdCl_2$ concentrations investigated.

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Registry No. 2a, 125996-98-7; **2b**, 125996-99-8; **2c**, 3240-29-7; **2d**, 26954-31-4; **2e**, 125997-00-4; **2f**, 125997-01-5; **2g**, 53342-47-5; **2h**, 35204-91-2; **3a**, 125997-02-6; **3b**, 125997-03-7; **3c**, 125997-04-8; **3d**, 125997-05-9; **3e**, 125997-06-0; **3f**, 125997-07-1; **3g**, 125997-08-2; **3h**, 125997-09-3; $MeOC_6H_4$-*m*-CHO, 591-31-1; $F_3CC_6H_4$-*m*-CHO, 454-89-7; PhCHO, 100-52-7; MeC_6H_4-*p*-CHO, 104-87-0; BrC_6H_4-*m*-CHO, 3132-99-8; FC_6H_4-*m*-CHO, 456-48-4; $F_3CC_6H_4$-*p*-CHO, 455-19-6; ClC_6H_4-*p*-CHO, 104-88-1; $H_2C{=}CH(CH_2)_2MgBr$, 7103-09-5; $H_2C{=}CH(CH_2)_2CHOHC_6H_4$-*m*-OMe, 125997-10-6; $H_2C{=}CH(CH_2)_2CHOHC_6H_4$-*m*-$CF_3$, 125997-11-7; $H_2C{=}CH(CH_2)_2CHOHPh$, 54525-86-9; $H_2C{=}CH(CH_2)_2CHOHC_6H_4$-*p*-Me, 125997-12-8; $H_2C{=}CH(CH_2)_2CHOHC_6H_4$-*m*-Br, 125997-13-9; $H_2C{=}CH(CH_2)_2CHOHC_6H_4$-*m*-F, 125997-14-0; $H_2C{=}CH(CH_2)_2CHOHC_6H_4$-*p*-$CF_3$, 125997-15-1; $H_2C{=}CH(CH_2)_2CHOHC_6H_4$-*p*-Cl, 102058-50-4; $MeOC_6H_4$-*p*-$CH{=}CH_2$, 637-69-4; $H_2C{=}C(p\text{-}MeOC_6H_4)Me$, 1712-69-2; $D_2C{=}C(p\text{-}F_3CC_6H_4)Me$, 125997-16-2; $PdCl_2$, 7647-10-1; $PdCl_2(C_5H_{11}CN)_2$, 87370-16-9; $H_3C(CH_2)_4CN$, 628-73-9.

Supplementary Material Available: ^1H NMR traces, raw data, and pseudo-first-order kinetic plot for the rearrangement of diene **3e** and a complete summary of second-order rate constants for $PdCl_2$-catalyzed rearrangements of dienes **3a-h** (7 pages). Ordering information is given on any current masthead page.

Catalytic Asymmetric Glyoxylate-Ene Reaction: A Practical Access to α-Hydroxy Esters in High Enantiomeric Purities

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Abstract: An efficient asymmetric catalysis is developed for the glyoxylate-ene reaction to afford the α-hydroxy esters of biological and synthetic importance. The key to the success is the use of the chiral titanium complex prepared in situ from $(i\text{-}PrO)_2TiX_2$ (X = Cl or Br) and the (*R*)- or (*S*)-binaphthol in the presence of molecular sieves (MS 4A). The presence of the molecular sieves (zeolite) is clarified to facilitate the alkoxy-ligand exchange reaction. Thus, the use of MS is shown to be essential for the in situ preparation step of the chiral catalyst and not for the ene reaction step. The present catalytic process is applicable to various 1,1-disubstituted olefins by the judicious choice of the dichloro or dibromo catalyst.

The development of asymmetric catalysis, for C-C bond-forming reactions in particular, is the most challenging and formidable endeavor in organic synthesis.[1] Recently impressive progress has been made on catalytic asymmetric aldol[2] and Diels-Alder reactions.[3] However, the catalytic asymmetric ene reaction with prochiral glyoxylate, which is potentially useful for the asymmetric synthesis of α-hydroxy esters of biological and synthetic importance,[4] has never been developed,[5,6] while Yamamoto has recently reported the first example of a catalytic ene reaction with halogenated aldehydes by using the modified binaphthol-derived aluminum reagent.[7a] In this paper we wish to describe a full account of the asymmetric glyoxylate-ene reaction[8] catalyzed by the chiral titanium complex of type (*R*)-**1a**[9] prepared in situ from $(i\text{-}PrO)_2TiX_2$[10] and the optically pure binaphthol

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