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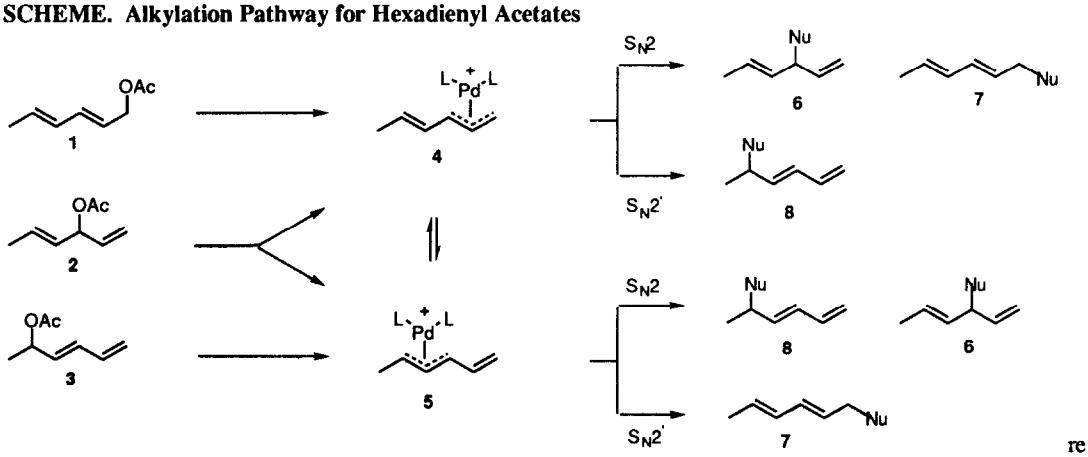
# ON THE NATURE OF THE ION PAIR AS A NUCLEOPHILE IN PD CATALYZED ALKYLATIONS WITH DIENYL CARBOXYLATES

Barry M. Trost and Richard C. Bunt
Department of Chemistry
Stanford Univeristy, Stanford, CA 94305-5080

**Summary**: The regioselectivity of nucleophilic attack on unsymmetrical dienyl acetates depends upon the nature of the nucleophile in which the use of the tetrahexylammonium salt decreases the rate of nucleophilic attack. Equilibration of the products does not occur to any significant extent under the conditions reported here.

The Pd catalyzed nucleophilic substitution of allylic leaving groups creates opportunities for chemo-, regio-, and diastereoselective elaboration of organic structures that are not available in non-metal catalyzed reactions.[1] Previous work established the general mechanistic features of the reaction with "soft" nucleophiles focusing on how the structure of the π-allyl unit influenced selectivity.[2] In conjunction with our program to develop asymmetric versions of this reaction,[3-5] we became interested in the question of how the structure of the nucleophile influenced selectivity. While relatively non-polar solvents like THF, dioxane, toluene etc. are frequently used for these reactions which involve charged intermediates, the question of the effect, if any, of ion pairing has not been addressed with respect to the charged nucleophiles illustrated by the common use of the sodium salts of malonate anions. Our interest in the question of how polyunsaturated allylic carboxylates participate in Pd catalyzed allylic alkylations suggested they may be a good testing ground to probe any subtle effects ion pairing may have on these reactions since the regioisomeric product mixture will be a fingerprint for the nature of the reactive intermediates. Consider the hexadienyl acetates **1-3**. Assuming that ionization occurs kinetically to the π-palladium complex incorporating the carbon bearing the leaving group, dienyl acetate **1** generates complex **4**. If it reacts only by an $S_N2$ mechanism, it will produce only **6** and **7**. If it

**SCHEME. Alkylation Pathway for Hexadienyl Acetates**

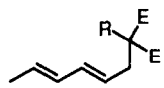
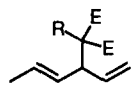
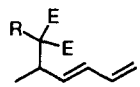
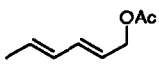
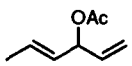
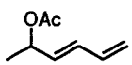
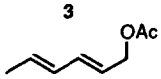
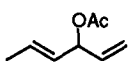
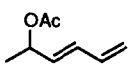



reacts only by an $S_N2'$ mechanism, it will generate **8**. On the other hand, the regioisomeric acetate **3** should produce the allylically related allyl complex **5** whose subsequent substitution by an $S_N2$ mechanism will produce only **6** and **8** and by an $S_N2'$ mechanism **7**. The final member of the trio, dienyl acetate **2**, may ionize

to a mixture of **4** and **5** from which the product ratio will depend upon this ratio. This whole picture becomes cloudier when we realize that interconversion of the two π-allyl complexes may occur. We wish to report that the nature of the malonate counterion has a significant effect on the selectivity of alkylations of dienyl carboxylates.

Table 1 summarizes the alkylation under quite standard conditions with dimethyl sodiomalonates in THF using 5 mol % $(Ph_3P)_4Pd$ as catalyst at reflux. Reactions went to completion in 1-3 h. It is immediately obvious that the ratio of alkylation products depends upon the regioisomeric nature of the starting material in which steric effects play a prominent role. Thus, dienyl acetate **1** preferentially alkylates at the primary carbon with this preference increasing as the steric demands of the nucleophile increases (cf entries 1 and 4). At the other extreme, dienyl acetate **3** reacts to form all three possible products with that derived from attack at the primary carbon (i.e., **9**) increasing with steric hindrance of the nucleophile (cf entries 3 and 6).

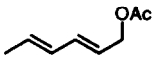
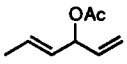
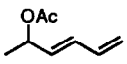
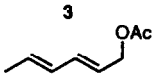
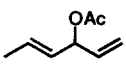
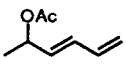
**TABLE 1. Alkylation of Hexadienyl Acetates with Dimethyl Sodiomalonates**[a,b]

| | |  **9** |  **10** |  **11** | Entry |
|---|---|---|---|---|---|
|  **1** | a) R = H | 67 | 33 | trace | 1 |
|  **2** | a) R = H | 51 | 49 | trace | 2 |
|  **3** | a) R = H | 37 | 49 | 14 | 3 |
|  **1** | b) R = $PhCH_2$ | 78.5 | 20 | 1.5 | 4 |
|  **2** | b) R = $PhCH_2$ | 70 | 28 | 2 | 5 |
|  **3** | b) R = $PhCH_2$ | 57 | 33 | 10 | 6 |

a) E = $CO_2CH_3$. b) All yields were determined by gas chromatography using a flame ionization detector with a 25m x 0.25mm capillary polydimethylsiloxane column.

A dramatic effect on the product distribution occurs upon using the tetrahexylammonium salt of the malonate formed *in situ* by adding tetrahexylammonium bromide to the sodium salt (see Table 2). In contrast to the use of the sodium salt, *these ratios are within experimental error independent of the regioisomeric nature of the starting material.* Increasing the steric hindrance of the nucleophile by switching from malonate anion to benzylmalonate anion increases the propensity for attack at the primary carbon to give alkylated product **9**.

**TABLE 2. Alkylation of Hexadienyl Acetates with Dimethyl Tetrahexylammonium Malonates[a,b]**

| | | 9 | 10 | 11 | Entry |
|---|---|---|---|---|---|
|  1 | a) R = H | 57.2 | 34.2 | 8.6 | 1 |
|  2 | a) R = H | 55.0 | 38.9 | 6.1 | 2 |
|  3 | a) R = H | 58.1 | 33.4 | 8.5 | 3 |
|  1 | b) R = $PhCH_2$ | 75.8 | 21.3 | 2.9 | 4 |
|  2 | b) R = $PhCH_2$ | 72.0 | 25.2 | 2.8 | 5 |
|  3 | b) R = $PhCH_2$ | 76.8 | 20.0 | 3.2 | 6 |

a) E = $CO_2CH_3$. b) All yields were determined by gas chromatography using a flame ionization detector with a 25m x 0.25mm capillary polydimethylsiloxane column..

While many complicated scenarios invoking different mixes of $S_N2$ and $S_N2'$ attack may be envisioned, the most straightforward explanation accommodates all our observations. First, consider the cases of alkylations with the sodium salts of the malonates. Complex **4** generated from **1** shows a strong preference for attack at the primary carbon to give **7** -- a preference which increases with the steric demands of the attacking nucleophile. Complex **5** generated kinetically from **3** shows a strong preference for attack at the central carbon of the pentadienyl unit to favor formation of **6**. However, in this case, significant isomerization of **5** to **4** competes with alkylation -- an interpretation that accounts for production of products of type **7**. As the steric demands of the nucleophile increases, this competitive isomerization increases -- an observation that suggests that benzylmalonate anion reacts at a *slower* rate than malonate anion. The production of quantifiable amounts of alkylated product **11** from dienyl acetate **1** with benzylmalonate anion indicates that equilibration of **4** with **5** begins to occur even in this case. In contrast to this conclusion, in the reaction of simple enolates with alkyl halides, the more substituted enolate reacts *faster*.[8] Dienyl acetate **2** kinetically partitions to both **4** and **5** strongly favoring the former -- presumably reflecting preferential coordination of palladium(0) to the less substituted olefin for both steric and electronic reasons.[1,2]

The identical product distribution independent of starting material by switching the counterion of the nucleophile to the tetrahexylammonium cation indicates that equilibration of the two π-allylpalladium intermediates **4** and **5** is fast relative to alkylation under these conditions. Two explanations can be profferred for such a change in relative rates. In the first, the absolute rates of equilibration have increased while the rate of nucleophilic attack has not. However, it is not obvious how introduction of a tetrahexylammonium ion

would have such an effect. In the second, the absolute rates of equilibration remain unaffected but the rate of nucleophilic attack has decreased. Since in solvents like THF, strong ion pairing is expected,[6] change of the nature of this ion pair would be anticipated to have an effect on alkylation rates. Curiously, the conclusion for this scenario must be that introduction of the tetrahexylammonium salts *decreases* the rate of alkylation in contrast to the normally expected role of such salts.[9]

Subsequent to submission of this paper, it has been suggested that the products of these alkylations may equilibrate.[10] Contrary to that claim, we have found that under conditions reported herein and normally used in all of our previous work[7] which restricts reaction times and temperatures and only employed triphenylphosphine as ligand, equilibration does not occur to any significant extent. Prolonged reaction times (24 h at reflux) under our conditions lead to equilibration of only product **10** wherein its yield tended towards zero with no evidence that either **9** or **11** reacts further.

Thus, selectivity in palladium catalyzed alkylations may be modified not only by variation of ligands and solvent, but also by the nature of the ion pair. Introduction of tetrahexylammonium cation allows equilibration of the π-allylpalladium intermediate to dominate -- an observation that may provide a complementary selectivity than might otherwise be observed. Such effects also will have importance with respect to asymmetric induction in which the enantiodiscriminating step involves nucleophilic attack on the π-allylpalladium unit.

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10. Nilsson, Y.I.M.; Andersson, P.G.; Bäckvall, J.E. *J. Am. Chem. Soc.* **1993**, *115*, 6609. This paper incorrectly infers that our previously reported ratios (ref. 7) reflect equilibration of products. While equilibration may occur under certain circumstances with some products, it does not commonly occur if reactions are properly monitored. A more detailed discussion of this point will appear in our full account of this work.

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