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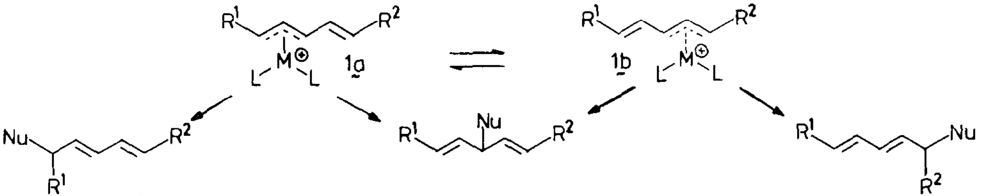
# Regiochemical Directing Effects in Palladium Catalyzed Alkylations with Polyene Electrophilic Partners

Barry M. Trost*, Christopher J. Urch, and
Ming-Hong Hung

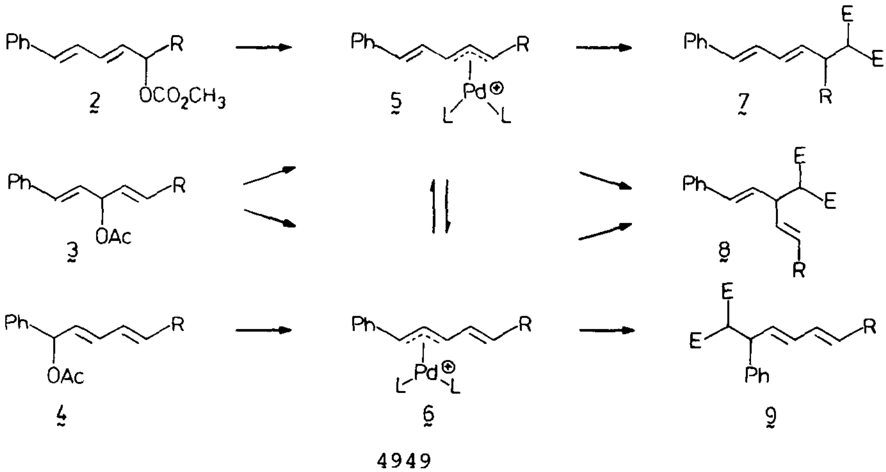
McElvain Laboratories of Organic Chemistry
Department of Chemistry
University of Wisconsin-Madison
Madison, Wisconsin 53706

**Summary:** Unusual regioselectivity in alkylations arise as a result of the dynamic behavior of trihapto pentadienyl metal complexes, a phenomenon previously studied from a theoretical point of view.



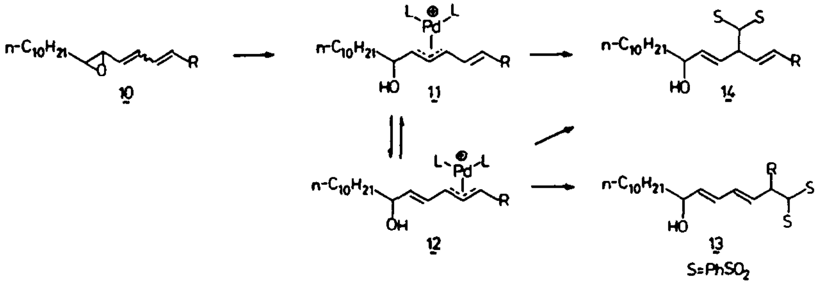
The dynamic behavior of pentadienyl metal complexes such as 1 has attracted interest from a theoretical point of view,[1] but there is sparse experimental information on the chemical consequences of such processes.[2,3] Consideration of these equilibria becomes particularly important in terms of the question of the regiochemistry of alkylation. In the case of tungsten catalyzed allylic alkylations, we noted that analogous equilibrations of the presumed octahedral complexes appeared to be slow compared to the rate of alkylations with soft carbon nucleophiles.[4] If the equilibration depicted in 1 can be made fast relative to alkylation, quite a different regiochemical outcome may arise. We wish to record an unusual, but predictable, sensitivity of the regiochemistry of attack on palladium complexes corresponding to 1 which may reflect the ability of palladium to migrate along the $\pi$ system in contradistinction to the molybdenum and tungsten catalyzed reactions.[5] A consequence of such a process is to permit metals to control new bond formation at sites quite distant from the original leaving group.

Consider the palladium catalyzed alkylation of the three dienyl carboxylates



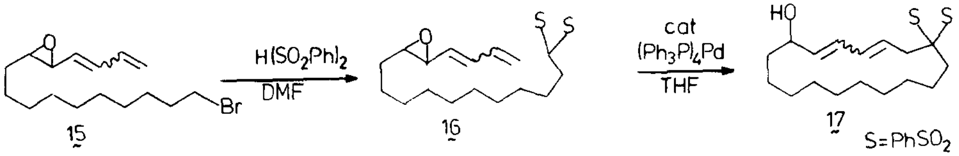
2-4. Kinetically, dienyl carboxylate 2 should generate complex 5 which can lead to alkylation products 7 and 8. The other terminal carboxylate should generate 6 initially which should produce 8 and 9. Since dienyl acetate 3 can generate both 5 and 6 kinetically, all three products may be seen. Experimentally 2 (R=H) gives an 84:13 mixture of 7[6] and 8[6] (77% yield); whereas 4 ($R=CH_3$) gives a 15:85 mixture of 7 and 8 (85% yield). Dienyl acetate 3 (R=H) produces a 56:44 mixture of 7 and 8 (73% yield). These results are best in accord with the notion that 5 and 6 equilibrate rather slowly relative to alkylation and that 5 leads predominantly to terminal attack generating 7 but 6 leads exclusively to central attack producing 8. The regioselectivity of alkylation can be understood on the basis of competing steric and electronic effects. Whereas steric effects dictate formation of 7, charge distribution dictates the formation 8.[5] The small amount of crossover in the reactions of 2 and 4 may result from a partial equilibration between 5 and 6 beginning to compete with alkylation.

If the latter interpretation is correct, we should enhance the formation of products like 7 in alkylations of 4 if we can slow the rate of alkylation of 6 compared to the rate of its equilibration to create 5. The presence of electron withdrawing groups in the proximity of the π-allyl fragment appear to slow alkylation proximal to such groups.[7,8] Thus, the intermediate 11 in the reaction of the dienyl epoxide 10 may equilibrate to 12 faster than it alkylates. For the case of 10 (R=H), steric considerations, which appear to dominate in palladium reactions,[9-11] predict



terminal attack should be preferred. Experimentally that is exactly what is observed; the sole product of palladium catalyzed alkylation of 10 (R=H) is 13[6] (R=H, 92% yield). Thus, the oxygen substituent serves as a regiochemical conductor in that it leads the nucleophile to attack as distal to this substituent as possible.

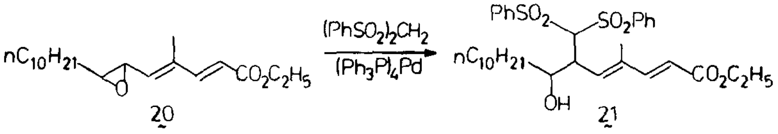
The effect of the oxygen substituent on regioselectivity of alkylations occurs in both intramolecular[12] as well as intermolecular reactions. Alkylation of the bromoepoxide 15 with sodium bis(benzenesulfonyl)methane produces the alkylation substrate 16 for the intramolecular test. Exposing 16 to a palladium(0) catalyst again leads only to the product arising by attack at the most remote end of the π-allyl unit 17[6] in 77% yield.



Placing a substituent at the terminus of 11 distal to the hydroxyl goup that inhibits terminal attack should steer the incoming nucleophile to the central position, thereby producing 14. It is known that reactions that proceed through

the complex 18 as an intermediate lead to the alkylation product (19) distal to the electron withdrawing group because of the dominance of electronic effects.[13] Indeed, alkylation of 10 ($R=CO_2C_2H_5$) produces only the central alkylation product 14[6] (R=55%). In this case, it is not necessary to consider equilibration of 11 ($R=CO_2C_2H_5$) and 12 ($R=CO_2C_2H_5$) since attack on either by the sulfone stabilized anion is predicted to generate 14.

The results reported herein demonstrate the ability to control regioselectivity of alkylation of polyene substrates in a predictable manner in palladium catalyzed reactions. In the absence of the domination of steric factors at the termini of pentadienyl systems, palladium catalysts steer the nucleophile to the carbon that is most distal to all electron withdrawing groups. Steric effects can overcome this electronic bias as in the case of 20 which leads to exclusive formation of 21.[6] The steric demands of a bulky nucleophile like bis(benzenesulfonyl) methyl carbanion



precludes attack at a tertiary carbon, which would have been the expected position of attack in analogy to the reaction of 10 ($R=CO_2C_2H_5$). The preferential formation of 21 rather than the product derived from attack alpha to the ester may be understood on the basis of the charge distribution in the hypothetical pentadienyl cation model. In the pentadienyl cation corresponding to 11 and 12 ($R=CO_2C_2H_5$), the electron deficiency predicts the positional selectivity of attack to be C(4) > C(6) > C(2). With C(4) being precluded because of steric effects in 21, charge distribution considerations lead to prediction of attack at C(6) as observed.

Of special importance in these reactions is the ability of oxygen in the case of the dienyl epoxides as substrates to direct reaction to the most distal carbon as in 10 (R=H) and 16 which has relevance in creating polyenes of interest in natural products. The simplest explanation for this regioselectivity is that it is a consequence of the dynamic properties of the pentadienyl metal complex intermediates.[14] The synthetic consequence of such an observation is to allow new bonds to form at a carbon quite distant from the position of the leaving group.

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14. The possibility that conjugate addition to 1a accounts for the regioselectivity cannot be dismissed. Such a process is unprecedented. It would not seem to account for the variable regioselectivity since it is difficult to see why the degree of conjugate addition should differ between 5 or 6 and 11.

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