Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 46 (2005) 1631–1634

Tetrahedron Letters

Isotope effects and the mechanism of palladium-catalyzed allylic alkylation

Daniel A. Singleton* and Chad F. Christian

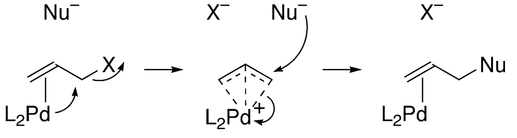
Department of Chemistry, Texas A&M University, PO Box 30012, College Station, Texas 77842, USA

Received 8 November 2004; accepted 18 January 2005

Abstract—The palladium-catalyzed allylic alkylation reaction of 1,1-dimethylallyl acetate with dimethyl malonate is studied by a combination of isotope effects and theoretical calculations. A large ^{13}C isotope effect of ≈1.037 is observed at the tertiary carbon, while small isotope effects are observed at the olefinic carbons. These results support rate-limiting ionization of a η^2-Pd complex. The observed isotope effects are compared with predictions from calculational models employing either solvent models or ionization of an amidinium ion. The calculated transition structures are notably η^2 in character, and the implications of this observation are discussed.

Many palladium complexes catalyze the reaction of nucleophiles with allylic functionalities such as allylic esters.[1] The mildness of the allylic alkylation reaction conditions and their broad chemoselectivity has allowed the application of these reactions to diverse complex structures.[2] Highly enantioselective allylations have now emerged as a powerful tool in the synthesis of optically active products.[3]

Much is known in general terms about the mechanism of Pd-catalyzed allylations. Under most reaction conditions, the products are the result of a double-inversion process, consistent with an S_N2-like nucleophilic displacement of the leaving group by Pd, followed by a second displacement of Pd by an incoming nucleophile. The support for initial formation of a η^2-Pd complex **1** and the intermediacy of a η^3-Pd complex **2** is extensive. However, a more detailed knowledge of the selectivity-determining transition states would aid in addressing subtle selectivity issues, as would allow, for example, the design of new ligands for enantioselective reactions. The theoretical study of these reactions can in principle provide such detail.[4] However, this is a challenging reaction for theory, as most experimental reactions involve key steps that either generate or annihilate ions. This problem has been addressed using both solvent models and neutral nucleophiles/leaving groups,[4] but the experimental relevance of the results is often difficult to judge.



1 **2** **3**

We describe here the study of a Pd-catalyzed allylic alkylation reaction by a combination of theoretical calculations and experimental kinetic isotope effects (KIEs). The KIEs not only provide a qualitative view of the rate-limiting transition state but also allow us to assess the accuracy of calculational models. The combination of theory and experiment supports a transition state that is η^2-like and S_N1-like in character, providing insight into the nature of selectivity in these reactions.

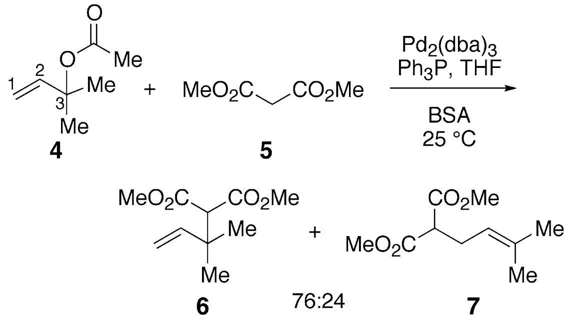
The allylic alkylation reaction of dimethylallyl acetate (**4**) with dimethyl malonate (**5**) was chosen for study because it is a prototypical example and allylations via the intermediate 3-methylbutenyl palladium complexes have been well-studied previously.[5] The reaction of **4** with **5** at 25 °C in THF was catalyzed by a combination of $Pd_2(dba)_3$ and triphenylphosphine (≈3 equiv phosphine per Pd), using *O*,*N*-bis(trimethylsilyl)acetamide (BSA)

Keywords: Isotope effects; Mechanism; Allylic alkylation; Allylation; Palladium.

* Corresponding author. Tel.: +1 979 845 9166; fax: +1 979 845 4719; e-mail: singleton@mail.chem.tamu.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.088

as base. Under these conditions, a 76:24 mixture of substitution products **6** and **7** is formed in nearly quantitative yield over the course of a few hours. The preference for nucleophilic attack at the more substituted allylic carbon in this particular reaction is in line with most previous observations.[5] Andersson and Bäckvall have reported that these products can equilibrate under certain conditions,[5e] but no significant equilibration could be observed under the mild conditions here. Allylic isomerization of **4** to afford 1-acetoxy-3-methyl-2-butene was observable but it was very slow (≈2.5% in recovered **4** after 71% conversion).



The ^{13}C KIEs in **4** were determined by NMR methodology at natural abundance.[6] Two reactions of **4** at 25 °C were taken to 71% and 75% conversion, and the starting **4** was recovered by an extractive workup followed by fractional distillation. The recovered **4** was analyzed by ^{13}C NMR along with standard samples that had not been subjected to the reaction conditions. The change in isotopic composition in each position was determined relative to the methyl carbons of the dimethylallyl group, with the assumption that isotopic fractionation in these carbons was negligible. From the changes in isotopic composition, the KIEs were calculated as previously described.[6]

The results from six separate determinations on the two independent reactions are summarized in Figure 1. A very large ^{13}C KIE of ≈1.037 was observed at the tertiary carbon C3 of **4**, indicative of this carbon undergoing a substantial bonding change in the transition state for the rate limiting step. Very small normal isotope ^{13}C KIEs were observed at C1 and C2. These small KIEs are consistent with π-complexation to the olefin during the rate-limiting step, but suggest that these carbons are not undergoing a significant bonding change. Overall, the KIEs appear qualitatively consistent with rate-limiting C–O bond cleavage ionizing the acetoxy group in a η^2-Pd complex.

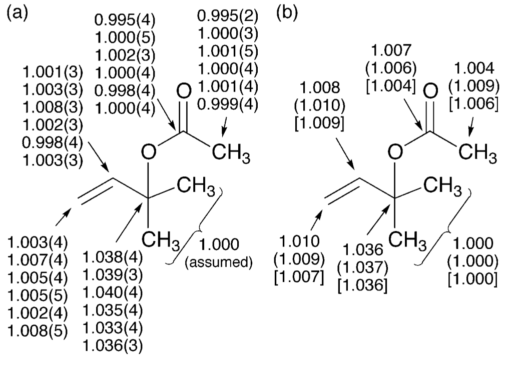


Figure 1. (a) Experimental ^{13}C KIEs (k_{12C}/k_{13C}) for the allylic alkylation reaction of **4** with **5** at 25 °C. The top three KIEs in each group arise from the 75%-conversion reaction. Standard deviations ($n = 6$) are shown in parentheses. (b) Predicted ^{13}C KIEs for three calculational models. Plain numbers are based on transition structure **10**, numbers in parentheses are based on transition structure **12**, and numbers in brackets are based on transition structure **13**.

If ionization of the acetoxy group were reversible, followed by rate-limiting nucleophilic attack on the η^3-Pd complex, then the isotope effects at C3 versus C1 would reflect the 76:24 product mixture. The low KIE averaging 1.005 at C1 does not seem consistent with this scenario. Together with the low amount of allylic isomerization of **4** observed, the results do not support reversibility of ionization as the major mechanistic pathway.

Theoretical calculations were used to interpret the isotope effects in greater detail. As introduced above, the challenge in studying these reactions theoretically is the formation of ionic intermediates from a neutral η^2-Pd complex. In the gas phase, the ionization of a complex of **4** with $Pd(PMe_3)_2$ into separate acetate anion and η^3-Pd cation is uphill by ≈70 kcal/mol. The high-energy ionization is accordingly disdained in favor of processes affording neutral products, such as elimination of a molecule of acetic acid.

To circumvent this problem, three distinct approaches to calculationally modeling this reaction were explored. The first was to study the reaction of the amidinium ion **8**. With **8**, the neutral acetamidine is the leaving group and the 'ionization' process in the gas phase is not dominated by Coulombic effects. A drawback is that the energetics for ionization of **8** are unlikely to match those for ionization of **4** in solution, except by accident. However, this approach is straightforward, making practical the use of a relatively complete theoretical model including two $PHPh_2$ ligands. In the event, transition structure **10** and intermediates **9** and **11** were located in B3LYP/BS1[7] calculations (Fig. 2).

The second approach used an implicit solvent model. Transition structure **12** (Fig. 3) for the ionization of **4** mediated by $Pd(PMe_3)_2$ was located using B3LYP/BS2[7] calculations and an Onsager solvent model for THF. (See Supplementary data for calculational procedures.)

The third theoretical model used explicit solvent molecules. It is normally difficult to use enough solvent molecules to sufficiently stabilize ion formation. Our strategy to attack this problem used 6 discrete HCN molecules. HCN was chosen because it is small, has a large dipole moment, and does not strongly interact with itself. As a result, a relatively small number of HCN molecules can greatly stabilize ionization. Transition structure **13** was located for the ionization of **4** mediated by $Pd(PH_3)_2$ in B3LYP/BS2[7] calculations. Many arrangements of the HCN molecules are possible and