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Tetrahedron Letters 46 (2005) 1631–1634
Tetrahedron Letters

Isotope effects and the mechanism of palladium-catalyzed allylic alkylation

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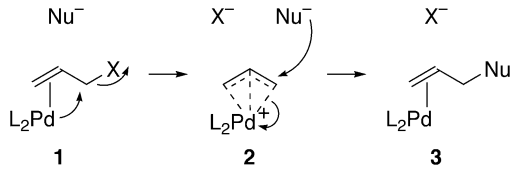
Received 8 November 2004; accepted 18 January 2005
Available online 1 February 2005

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.



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.
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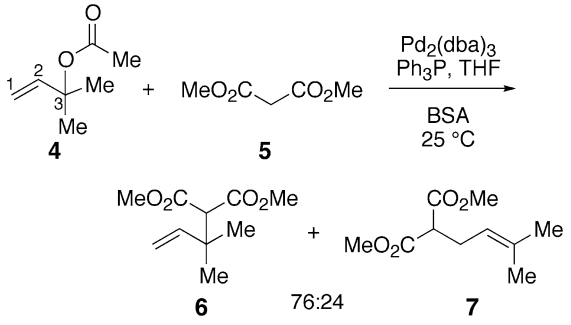
doi:10.1016/j.tetlet.2005.01.088

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.

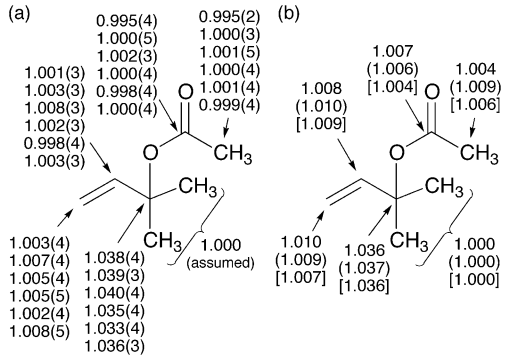


Figure 1. (a) Experimental ^{13}C KIEs (k_{12C}/k_{13C}) for the allylic alkylation reaction of **4** with **5** at 25 °C. The top three KIEs in each group arise from the 75%-conversion reaction. Standard deviations ($n = 6$) are shown in parentheses. (b) Predicted ^{13}C KIEs for three calculational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

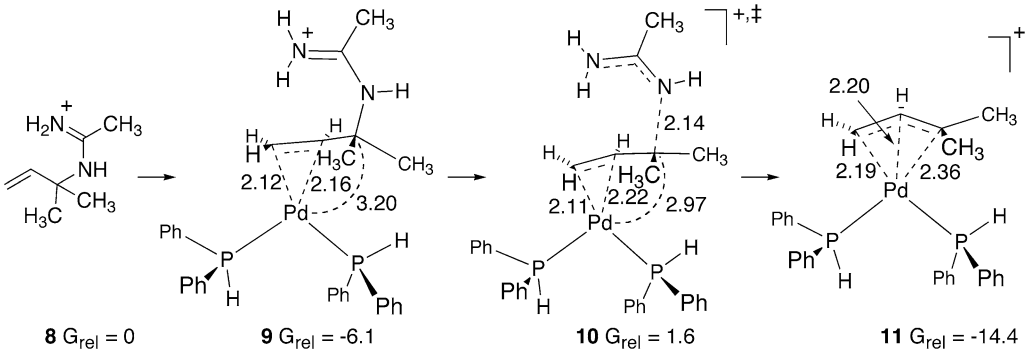


Figure 2. Calculated pathway (B3LYP/BS1[7]) for the ionization of **8** catalyzed by $Pd(PHPh_2)_2$. Free energies are relative to separate **8** and $Pd(PHPh_2)_2$ at standard state, based on unscaled harmonic frequencies at 25 °C, and are given in kcal/mol. Complete structures are given in Supplementary data.

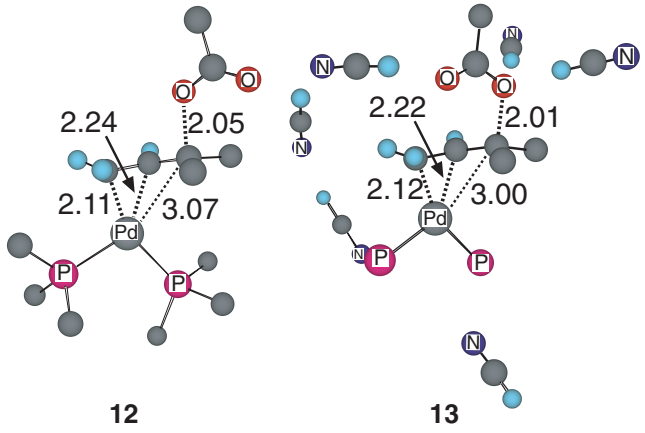


Figure 3. Transition structures for the ionization of **4** using solvent models. Structure **12** used an Onsager model for THF. Structure **13** used six HCN molecules. Most hydrogens have been removed for clarity.

no effort was made to find the global-optimum arrangement. The goal was to model ionization as an aid in the interpretation of the KIEs, and **13** may serve that purpose despite its limitations.

Theoretical KIEs were calculated based on each of the transition structures **10**, **12**, and **13**. The KIEs were predicted from the scaled theoretical vibrational frequencies[8] using conventional transition state theory by the method of Bigeleisen and Mayer.[9] Tunneling corrections were applied using an infinite parabolic barrier model.[10] The results are shown in Figure 1b.

In many reactions, KIE predictions have proven highly accurate, often within the uncertainty of the experimental measurement.[11] This is not true in the current case, and the difference between experiment and prediction may reflect the difficulty of modeling the ionization. The acetyl group carbons in particular exhibit experimental isotope effects near unity, but the predicted isotope effects are all in the 1.004–1.009 range. The predicted acetyl group KIEs in the three models are mainly the result of a mass effect on the moment of inertia,[9] not zero-point energy changes, and it is possible that this component of the isotope effect is not correctly predicted for an ionization in a solvent cage. Another issue is that the experimental KIEs assume that the dimethylallyl methyl carbons do not undergo isotopic fractionation—an error in this assumption would depress the KIEs, which are almost all smaller than predictions.

Within the dimethylallyl group, the experimental and predicted isotope effects are in qualitatively better accord. The predicted C3 KIEs fit perfectly with experiment. The calculations overestimate the olefinic carbon KIEs, though the scatter in the experimental results is large and the pattern of KIEs predicted for **10** appears to fit reasonably. As structural models for the ionization, **10**, **12**, and **13** are qualitatively supported, though the low experimental olefinic KIEs suggest that these carbons may be undergoing less bonding change in the actual transition state than in the calculated transition structures.

In calculations of nucleophilic attack on (allyl)-$Pd(NH_3)_2$, Norrby has previously noted that the transition structures are very product-like in character.[4a] This makes the transition structures resemble closely the corresponding η^2 complexes. Our KIEs and calculated structures support and amplify this idea. In **10**, **12**, and **13**, the Pd has not significantly begun to approach the ionizing carbon. The C2–C3 bond has shortened significantly at the transition structure (from 1.53 Å in **9** to 1.43 Å in **10**) and the Pd–C2–C3 angle bends downward (from 119.3° in **9** to 106.7° in **10**) as C3 becomes planar, and these changes have the effect of moving C3 toward the Pd atom, but the Pd coordination is still almost purely η^2. The Pd–C2 distance is greater at the transition structure than in the η^2 precursor, and the two phosphine ligands along with C1 and C2 are still nearly planar in their coordination of the Pd. In the ultimate η^3 structure **11**, the allyl moiety has twisted so that C1 and C3 are in the plane of the phosphines, but this process has not significantly commenced in the transition structures. There is no such twisting motion in the transition vectors associated with **10**, **12**, and **13**, and the slight approach of C3 and the Pd atom appears to be incidental. *The Pd atom is not carrying out an S_N2 displacement!*

How then is the Pd catalyzing the ionization? A clue comes from looking at the charge distribution in **11**

versus **12**. In the process of forming **12**, the acetamidine moiety transfers +0.28 *e* (Mulliken charges) to the remainder of the molecule. The dimethylallyl moiety gains +0.14 *e* between **11** and **12**, while the $Pd(PHPh_2)_2$ moiety gains +0.14 *e*. The $Pd(PHPh_2)_2$ moiety is thus serving to delocalize a large portion of the incipient positive charge. This stabilization does not require S_N2 character in the ionization; rather, the ionization seems best understood as S_N1 in character.

The results here have implications in understanding selectivity in palladium-catalyzed allylic alkylation reactions. Both the experimental isotope effects and the calculated structures suggest that the Pd center is not substantially migrating in the transition state. The transition state for ionization thus more closely resembles a η^2 complex than the ultimate η^3 intermediate. This idea may be useful in ligand design, for example, the effects of chiral ligands on the reactivity of enantiomeric allylic acetates should be reasonably understood from steric effects in the η^2 complex.

In many Pd-catalyzed allylations, the important selectivity issues arise at the stage of nucleophilic attack on the η^3 complex rather than initial ionization. However, the transition state for nucleophilic attack on the η^3 complex should be similar to that for ionization, and the Norrby observations[4a] are consistent with this idea. Nucleophilic attack on a η^3 intermediate should thus involve considerable reorganization of the allyl moiety toward a η^2 geometry. This would account for the often-observed attack of unhindered nucleophiles on the more substituted π-allyl carbon, as in the preferential formation of **6** from **5**. In considering enantioselective reactions, the twisting of the PdL_2 moiety between the η^3 intermediate and the η^2-like transition state provides a mechanism by which chiral ligands can induce enantioselective attack on a prochiral η^3 complex without directly interacting with the incoming nucleophile. A similar twisting has recently been invoked in Pd-catalyzed enantioselective hydroaminations.[12] All of these ideas suggest further investigations.

Acknowledgements

We thank NIH grant # GM-45617 and The Robert A. Welch Foundation for support of this research.

Supplementary data

Experimental procedures, NMR integration results, calculational procedures, and energies and geometries of all calculated structures. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.088.

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