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Palladium-catalyzed allylic sulfinylation and the Mislow-Braverman- Evans rearrangement

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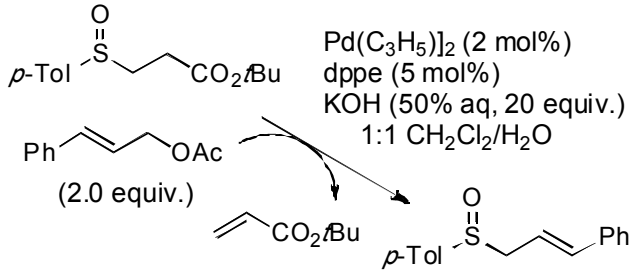
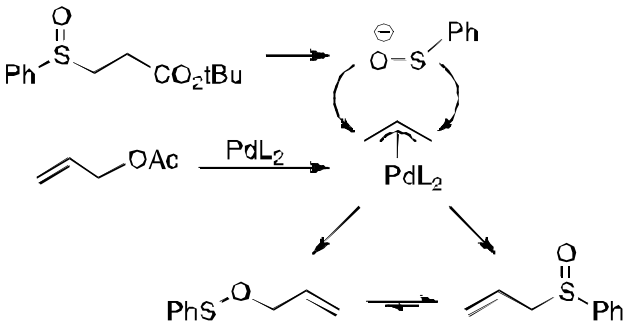
Sulfoxides play important roles in organic and medicinal chemistry, as chiral handles,[1] ligands,[2] or bioisosteres.[3] The most common method for sulfoxide preparation is controlled sulfide oxidation,[4] but a more convergent approach would be to make them by formation of the C-S bond. Poli and Madec recently disclosed a method for direct sulfoxide formation involving a Pd-catalyzed allylation or arylation of an intermediate sulfenate anion.[5] This strategy is illustrated by the reaction between *t*-butyl 3-*p*-tolyosylfinylpropionate and cinnamyl acetate, which gave the cinnamyl *p*-tolyl sulfoxide. In this reaction, the sulfenate anion and η^3-allyl complex are generated *in situ* and react with each other to afford the final product. In here, we disclose our theoretical results for the formation of the allyl sulfoxides (Scheme 1).



Scheme 1. Generation of sulfoxides *via* sulfenates.

A simplified mechanistic scheme for formation of phenyl allyl sulfoxide is shown in Scheme 2. Sulfenate anion and η^3-allyl Pd complexes are formed *in situ* and react by nucleophilic displacement. However, it is not *a priori* clear whether initial attack occurs from the formally anionic oxygen or formally neutral sulfur. The observed product is the allyl sulfoxide, but this would be expected to be formed also from a rapid Mislow-Braverman-Evans (MBE) rearrangement[6] even if the allyl sulfenate would be the initially formed product. Since the two mechanisms are closely linked, we initiated our investigation by a detailed computational study of the MBE rearrangement.



Scheme 2. Sulfenate allylation mechanism.

Our standard workhorse for computational investigations of reaction mechanisms is DFT at the B3LYP level[7] with a polarized double-ζ basis set (6-31G*), augmented by vibrational corrections, ECP basis sets for heavy elements,[8] continuum solvation,[9] and dispersion corrections.[10] However, Jorgensen and coworkers showed that even though trends in the MBE rearrangement kinetics could be well reproduced by similar methods, the equilibrium was erroneously calculated to favor the sulfenate product, not the sulfoxide.[11] We could verify that the same problem exists also when applying our standard methods to methyl allyl sulfoxide. The correct preference for the sulfoxide could only be reproduced using large basis sets. The results seemed reasonably well converged at the cc-PVDZ level, but due to a slight shift in energy when going to the cc-PVTZ basis[12] we selected the latter basis set for further studies. Geometries were well converged already at the 6-31G* level, as evidenced by small differences in energy between cc-PVTZ and cc-PVTZ//6-31G* calculations. Single point cc-PVTZ calculations at 6-31G*-derived IRC points also revealed that the transition state of the rearrangement shifted by less than 0.1 Å with the larger basis set. Details of these investigations can be found in supporting information. In conclusion, to ensure proper energetics in our studies of the Pd-catalyzed process, we performed geometry optimizations at the B3LYP level with the lacvp* basis set,[8] validated all stationary point by vibrational calculations, corrected to

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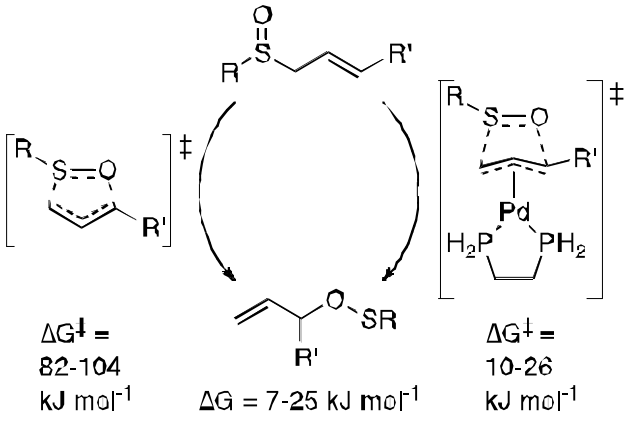
Supporting information for this article is available on the WWW

final free energies by adding contributions from vibrations, solvation, and basis set correction using cc-PVTZ basis set for the organic moieties and lacv3p*+ for Pd.

We next turned our attention to the reaction between sulfenate anion and η^3-allyl Pd complexes, for three model systems. The methyl allyl sulfoxide **1a** was retained as a simple model product, but we also investigated the reactions leading to the experimentally relevant phenyl allyl sulfoxide **1b** and phenyl cinnamyl sulfoxide **1c**. For all resulting MBE pairs, our selected computational methodology correctly identifies the sulfoxide **1a-c** as being preferred over the corresponding sulfenate **2a-c**, by 7-25 kJ mol^{-1}. Since the reaction center is remote from the ligand, we selected diphosphinoethane (DPE, $H_2PCH_2CH_2PH_2$) as a model for the experimentally competent DPPE-ligand.

Looking first at the MBE rearrangement from allyl sulfenate to sulfoxide for the three model systems, we see moderate barriers (82-104 kJ mol^{-1}) for the free substrates, reduced to only 10-26 kJ mol^{-1} in the presence of the Pd^0 DPE complex (Scheme 3). The low barrier is largely due to solvation; the free energy barrier in gas phase is >70 kJ mol^{-1}. As far as we know, the ability of Pd to increase the rate of the MBE rearrangement has previously not been shown, but Pd-catalysis of the closely related Overman rearrangement is well precedented.[13] A typical catalyzed MBE rearrangement transition state is depicted in Figure 1. The metal fragment is reminiscent of an (η^3-allyl)Pd complex, but with substantially longer distances from Pd to the terminal carbons.



Scheme 3 Uncatalyzed *vs* Pd-catalyzed MBE rearrangement.

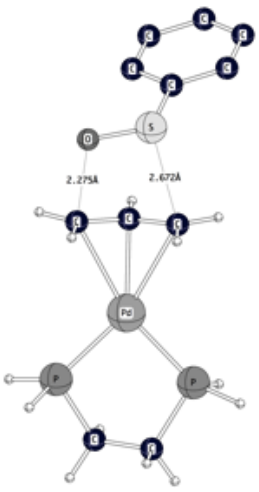


Figure 1 Typical TS for Pd-catalyzed MBE rearrangement

We next studied the O vs S nucleophilic trapping of the η^3-allyl complex. NBO analysis[14] of the sulfenate ions themselves reveal a full negative charge on oxygen, but the HOMO still has a significant component on sulfur. We therefore assumed that both O and S could be competent nucleophiles. As seen before for nucleophilic attack on η^3-allyl Pd complexes, the reaction in gas phase is monotonous, without a TS on the potential energy surface[15]. Location of TSs for this reaction thus required optimization in solvent. With our current resources, this excludes calculation of the vibrational free energy component, but for *relative* energies of competing transition states, the influence of this factor should be minor. All rotameric attack vectors utilizing either O or S as the nucleophile were considered. For the unsubstituted allyl, attack by either S or O were virtually isoergic, differing only by 1 kJ mol^{-1}. However, for this substrate, the product will undergo rapid MBE rearrangement and only the sulfoxide will be isolated (Scheme 2). The reaction surface is unusual; the addition TS does not lead directly to the product, but to another, lower saddle point that is also a TS for the MBE rearrangement (Figure 2). We note that care must be taken in the search for the nucleophilic attack TS, since the automatic search procedures more easily locate the lower energy TS for the MBE rearrangement (depicted in Figure 1). The latter TS can also be located *in vacuo*.

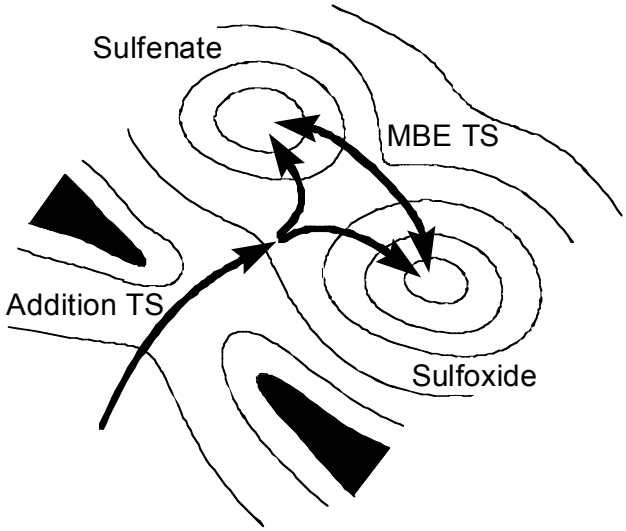
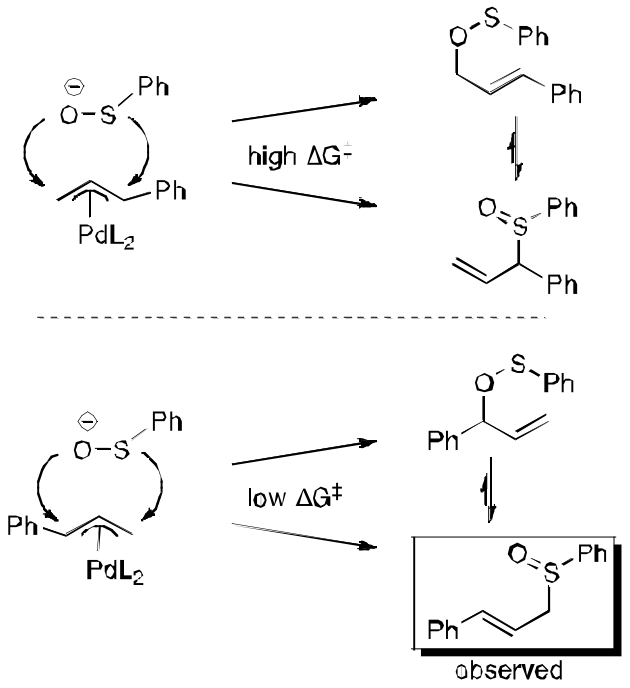


Figure 2 Potential energy surface for sulfenate attack on (η^3-allyl)Pd

Potential energy surfaces of the type depicted in **Figure 2** pose a particular problem in modeling. The standard procedure of following the minimum energy path from the TS to the minimum can only locate one possible product in such cases, but *ab initio* dynamics reveals that depending on the trajectory of attack, both products can be formed.[16] However, in the current case, the rapid equilibration of products over the very low second saddle point alleviates the need for these more complex computational treatments.

For the cinnamyl substrate, the situation is more complex. The four possible types of attack (each with several rotameric vectors) will lead to two manifolds of rapidly equilibrating products, of which only the sulfoxide will be observed (Scheme 4). The pathways leading to the manifold containing the observed sulfoxide product were indeed lowest in energy. Several different approach vectors were possible, and the one leading directly to the terminal sulfoxide was preferred, but interestingly the oxygen attack at the internal position was only 2 kJ mol^{-1} higher in energy. The paths

leading to the product manifold containing the internal sulfoxide were at least 12 kJ mol^{-1} higher in energy. Since the lowest energy paths all lead to the observed product (directly or through MBE rearrangement), the results are in excellent agreement with the experimental observation for the corresponding *p*-tolyl sulfenate. The results can be understood in terms of steric effects and charge distribution. The cationic charge is most highly concentrated at the benzylic position, the preferred site of attack for the formally anionic oxygen, whereas the formally neutral, larger sulfur atom preferentially attacks the sterically least hindered position.



Scheme 4 Cinnamyl sulfinylation pathways.

To summarize, the sulfenate has little difference in reactivity between the two potential nucleophilic sites, but since these two sites have opposite regiochemical preference, and the products are in rapid, catalyzed equilibrium, the reaction shows a strong preference for one of the two possible sulfoxide products. Furthermore, a catalytic effect of palladium on the MBE rearrangement has been indicated.

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A product quick-step

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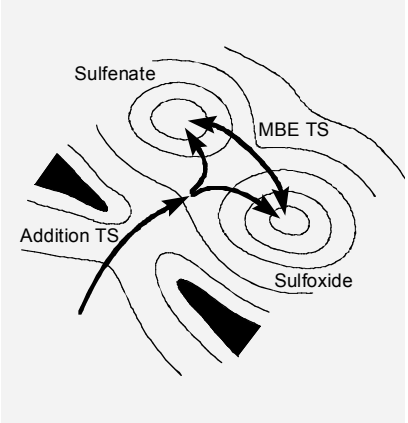
Palladium-catalyzed allylic sulfinylation and the Mislow-Braverman-Evans Rearrangement



The Mislow-Braverman-Evans rearrangement and the synthesis of sulfoxides through allylic sulfinylation have been studied. A viable DFT method for treatment of the sulfoxide-sulfenate equilibrium is presented and the ability of Pd to enhance the rate of the MBE rearrangement is shown. Of the four possible nucleophilic attacks, the two leading to the observed product are strongly preferred