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Metal catalyzed allylic alkylation: its development in the Trost laboratories

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Contents

1. Introduction

I am highly honored to be the co-recipient of the Tetrahedron Prize for 2014 with Professor Jiro Tsuji for our work on metal catalyzed allylic alkylation, notably that using palladium. In the context of this award, this report deals only with the evolution of our work. Nevertheless, it is important to note that innumerable groups around the world have and are playing essential roles in metal catalyzed allylic alkylations. The reader can find citations to such work in the references to our work that appears in this report. My involvement with this field derived from work in my laboratory dealing with the structure determination and synthesis of the insect juvenile hormone.[1] The juvenile hormone is one of three hormones that control the stages of insect development from the pupae to the larvae and finally to the adult. Thus, these hormones, most notably the juvenile hormone that prevented molting was targeted as a potentially more environmentally benign insecticide. The structural relationship of the insect juvenile hormone and methyl farnesoate suggests a possible biosynthetic pathway may be involving the homologation of two of the olefinic methyl groups to

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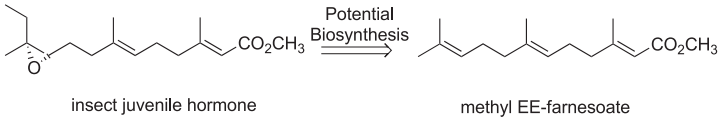
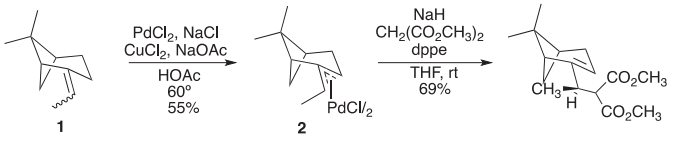
ethyl groups (see Scheme 1). Such an approach, if feasible, would be very attractive, short, and potentially very practical. Unfortunately, such a synthetic protocol did not exist—a fact that intrigued me. While the reactions of the oxygen analog wherein alkylation at the carbon adjacent to the π-unsaturated carbonyl group is one of the most important synthetic reactions, the inability of the all carbon analog to undergo a similar transformation was very attractive.



Scheme 1. Structure and potential biosynthesis of insect juvenile hormone.

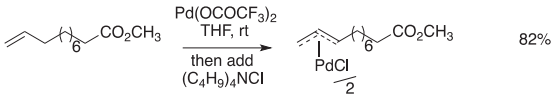
2. Methodology of palladium processes

We initiated studies by dividing the objective of allylic alkylation into two stages—the first involving the cleavage of the allylic C–H bond and the second being the C–C bond forming step.[2,3] Treatment of an olefin such as 2-ethylidenenopinane **1**, which was a mixture of geometric isomers, gave



(1)

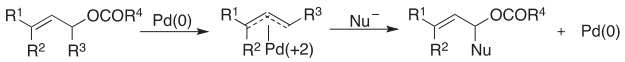
a single π-allylpalladium complex **2** (Eq. 1).[4] A broad range of di- and tri-substituted olefins reacted well. Most interestingly, the presence of a carbonyl group in the substrate did not interfere. Mono-substituted double bonds are apparently not nucleophilic enough, a fact that led to poor reactivity with palladium chloride. Using a more electrophilic palladium salt such as palladium trifluoroacetate allowed the reaction to proceed under much milder conditions and in higher yields.[5] Furthermore,



82% (2)

monosubstituted alkenes reacted well too (Eq. 2). We observed that the alkylation step did not proceed upon addition of a nucleophile. This lack of reactivity was overcome by the addition of a phosphine wherein a much more electrophilic cationic π-allylpalladium complex forms in situ and can now readily react with appropriate nucleophiles.[2] The stereochemistry of the alkylation step was established to occur with inversion of configuration wherein the nucleophile attacked the π-allylpalladium species on the face opposite from where the palladium resided as shown in Eq. 1.[4]

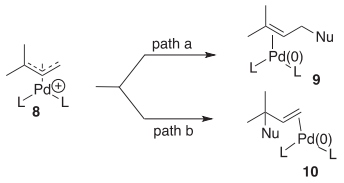
This new concept of allylic alkylation led to the creation of a prenylation protocol as shown in Scheme 2 for the prenylation of methyl farnesoate to geranylgeraniol.[6,7] The chemoselectivity of the palladation reaction is noteworthy. Use of methyl phenylsulfinylacetate as nucleophile led to a one pot synthesis of dienoates (Scheme 3).[7] The overall sequence is an alkene version of an allylic olefination. Since Pd(0) is the product of the alkylation reaction but Pd (+2) is required for the formation of the π-allylpalladium species, a catalytic version requires an oxidation of Pd(0) to Pd(+2) under the reaction conditions. On the other hand, an alternative method to generate π-allylpalladium intermediates is the oxidative addition of an allylic ester with a Pd(0) complex. The advantage of this approach is that Pd(0)



(3)

both initiates ionization and is the product of the alkylation, thus being catalytic in palladium.[8] We therefore turned our attention to the development of this catalytic allylic alkylation. Olefination ofestrone methyl ether generates the ethylidene product **3** with high Z-alkene selectivity (see Scheme 4). Using the stoichiometric allylic alkylation protocol, the angular methyl substituent directs the metal to the face of the alkene anti to the methyl group to give π-allylpalladium complex **4**. The approach of the nucleophile on the face distal to the metal then generates **5**. On the other hand, epoxidation of the same alkene **6** followed by base promoted epoxide opening generates allylic ester diastereomer **6** selectively. Its alkylation leads to the diastereomeric product **7**. Thus, the stereochemistry of palladium catalyzed allylic substitution proceeds with overall net retention of configuration, a stereochemical complement to normal non-catalyzed substitution processes, which proceed with inversion. The unprecedented switch in stereochemistry led us to verify further this conclusion as shown in Scheme 5.[9] In each case, the product stereochemistry was the same as the stereochemistry of the starting material within experimental error. Given that the stereochemistry of the nucleophilic attack on the π-allylpalladium species occurred with inversion of configuration, the overall net retention of the process therefore stipulates that the ionization of the allylic ester also proceeds with inversion. Thus, the net retention must derive by a double inversion mechanism.

The regioselectivity proved to be much more complicated. The generalization that Pd promotes nucleophilic attack on the least hindered allyl terminus of an unsymmetrically substituted π-allylpalladium species (Eq. 4, path a) is an oversimplification. There are multiple factors that control the



(4)

regioselectivity. Considering the π-allyl intermediate **8**, steric factors favor attack at the less substituted terminus to give **9**. On the other hand, stability of the initially formed olefin-Pd(0) complexes favors the less substituted olefin **10** (Eq. 4, path b) due to its lower LUMO making back-bonding from Pd(0) to olefin more favorable. Thus, an early transition state especially with a more bulky nucleophile should favor path a of Eq. 4; whereas, a late transition state with not too sterically demanding nucleophile should favor path b of Eq. 4. In accord with this generalization, the product of the reaction of neryl acetate with malonate anion favors attack at the more