A Study on the Electronic Effect of Reactions of π-Allylpalladiums Using 2-Arylsulfonyloxy-3-chloropropenes with Ethyl Malonate and Their Synthetic Utilization

Kohei Gotoh, Yasutaka Matsuura, Fuminori Hatanaka, Setsuko Sato, Shinzoh Kagabu, and Mitsuhiro Yoshimatsu*
Department of Chemistry, Faculty of Education, Gifu University, Yanagido 1-1, Gifu 501-1193

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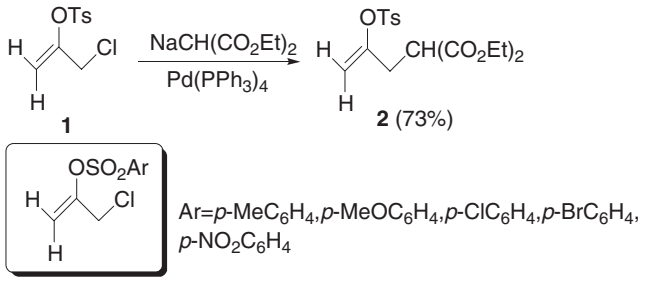
We have studied in detail the electronic effect on the reactions of π-allylpalladium with nucleophiles during the reactions of 2-arylsulfonyloxy-3-chloroprop-1-ene with diethyl malonate. The reaction rates increase increasing with the electron-withdrawing effects. We have also shown some synthetic utilization using these 2-arylsulfonyloxyprop-1-enes.

Much attention has been paid to the π-allylpalladium-mediated functionalization due to the ease of activation of an allylic system by attack of a nucleophile.[1] The regio- and stereoselectivities on the C–C bond formation of the π-allylpalladium have been found to be affected by the functions of the nucleophile, the substitution on the allylic moiety and the nature of the ligands on the palladium.[2] π-Allylpalladiums bearing various functional groups have been reported; however, an analysis of the electronic factors does not offer an obvious explanation because it is difficult to separate the electronic effect from the steric factors. It is of great significance to clarify the effect of the electronic factors on the π-allylpalladiums because of their wide utility in regio- and stereoselective functionalization.[3]

Recently, Buchwald et al. used arylsulfonates in the fields of palladium- or nickel-catalyzed synthetic organic chemistry with aryl and vinyl tosylates to produce C–C bonds[4] and C–N bonds.[5] The arylsulfonates are less reactive than the usual triflates;[6] however, they are less expensive, thermally stable and easy to handle. Therefore, they are extensively utilized for the biologically active compounds such as novobiocin I and 2′-deoxyguanosines.[7–10] We are also very interested in new 2-arylsulfonyloxypropenes as a good substrate for either clarifying the electronic factors on the π-allylpalladiums or for possible utilization in the Suzuki-type cross-coupling reactions using the simple $Pd(PPh_3)_4$. Herein, we report the findings regarding the electronic factor of the π-allylpalladiums and their synthetic utilization using 2-arylsulfonyloxypropenes and their coupling products.

We first selected 3-chloro-2-tosyloxypropene **1** as the representative substrate of the palladium-catalyzed coupling reactions with diethyl malonate/NaH in THF (Scheme 1). The alkylated product **2** was obtained in 73% yield, accompanied by a small amount of the dialkylated product. The reactions without a catalyst did not proceed and the propene **1** was mostly recovered. Next, we prepared various 2-arylsulfonyloxy-3-chloropropenes bearing some substituents such as chloro, bromo, methoxy, and nitro groups on the 4-position of the arylsulfonyl group and performed the coupling reaction of the 2-arylsulfonyloxyprop-1-enes with diethyl malonate in the presence of 5 mol % of tetrakis(triphenylphosphine)palladium at room temperature. The yields of the coupled products are plotted in Figure 1 for reaction times of 1–10 h.



Scheme 1. Preliminary study of palladium-catalyzed cross-coupling reaction of 2-tosyloxypropene **1** with diethyl malonate.

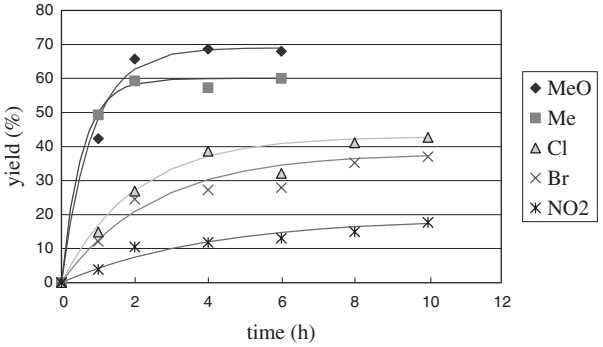
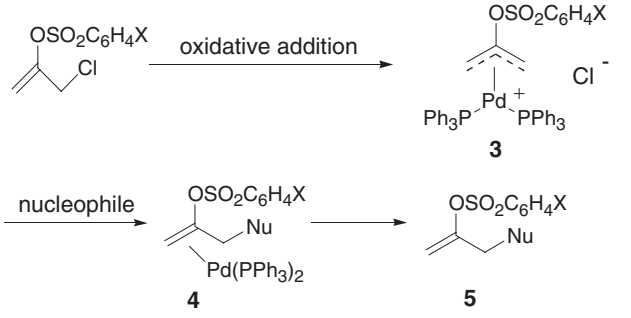


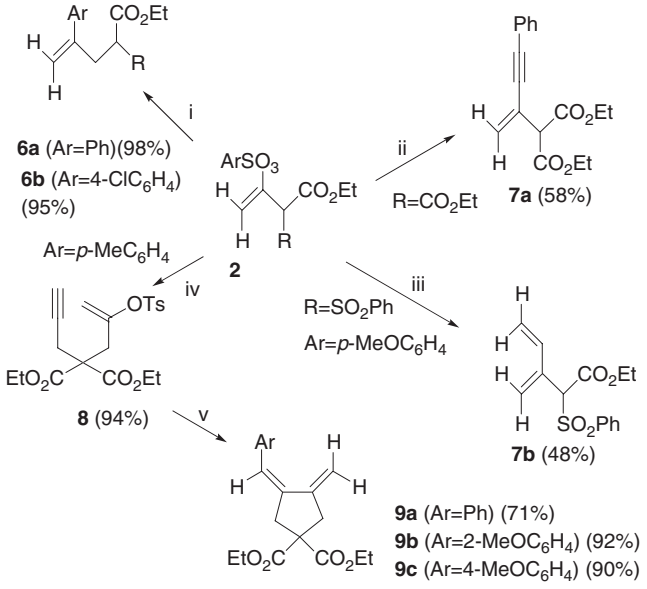
Figure 1. Rates of palladium-catalyzed cross coupling reactions of 2-arylsulfonyloxypropenes.

In Figure 1, the change in the yield vs time shows plateaus at about 65% for the compound bearing MeO and Me substituents, and at about 40% for the Cl and Br substituents. In these regions, the reactions might have been determined by the activity of the Pd-catalysts. According to previous investigations, we have shown the plausible mechanisms and considered the electronic factors in the palladium-catalyzed cross-coupling reactions of the 2-arylsulfonyloxypropenes. A reasonable reaction intermediate might be considered to be the cationic bisphosphine complex **3**, which is attacked by a highly acidic carbon nucleophile on the allylic ligand to give the intermediate **4** (Scheme 2). The rates for the formations of the products were found to be strongly acceralated by the electron-donating ability of the aromatic substituent X. This is attributed to the assumption that the reductive elimination of the intermediate **3** having the electron-donating substituents would be faster than that having the electron-withdrawing groups. Recently, Mayr et al. reported a new methodology for characterizing the electrophiles by two parameters,[11] which are very useful for predicting the rates of the reactions of nucleophiles and electrophiles, the inter- or intramolecular selectivities

and the reaction mechanisms. However, there are few examples of π-allylpalladiums bearing different substituents. We could use the novel allylic palladium intermediates, which are good candidates to compare the electrophilicities of the allylic cations without the any steric factors.



Scheme 2.



Scheme 3. Synthetic utilizations of 2-arylsulfonyloxypropenes, Reagents: (i) $ArB(OH)_2$/5 mol % $Pd(PPh_3)_4$/EtOH–benzene; (ii) phenylacetylene/$Pd(PPh_3)_4$/CuI/benzene/rt; (iii) vinyltributyltin/$Pd(PPh_3)_4$/LiBr; (iv) proparyl bromide/NaH/DMF/0 °C; v, $ArB(OH)_2$/5 mol % $PdCl_2/PPh_3/Na_2CO_3$aq/EtOH–toluene (1:1)/reflux/30 min.

Next, our attention focused on the synthetic utility based on the cross-coupling reaction at the enol carbon of 3-chloro-2-*p*-toluenesulfonyloxyprop-1-ene **2** with various nucleophiles in the presence of tetrakis(triphenylphosphine)palladium. First, we showed the reactions with arylboronic acids as described in Scheme 3. The reactions cleanly occurred and afforded the arylated products **6a**, **6b** in excellent yields. These results indicate that the 3-chloro-2-tosyloxyprop-1-ene is a good tool for the three component coupling reactions. Therefore, we further investigated the one-pot alkylation–arylation reaction of the selected 2-tosylate **1** with $CH_2(CO_2Et)_2$/NaH/$PhB(OH)_2$/Na_2CO_3aq. The reaction conditions were investigated in detail and the product **6a** was obtained in 80% yield. We further performed some transformations into more useful compounds. The palladium-catalyzed Sonogashira and Stille coupling reactions[12] of the 2-*p*-methoxyphenylsulfonyloxypropene **2** produced the enyne **7a** and diene **7b** in good yields, respectively. The intramolecular cyclization-coupling reactions of the 2-tosyloxy-1,6-enynes prepared from **2** were examined. The yields and stereoselectivities of the dienes **9b**, **9c** are excellent and no other isomers were observed; however, **9a** was contaminated with the *Z*-isomer (10%).

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