Conversion of Allyl Alk-2-ynoates to Alk-2-ynoic Acids Using Morpholine and Palladium(0)-Bis(diphenylphosphino)alkane Catalyst; Synthesis of 2,2,3,3-Tetradehydro PGE_1

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Allyl alk-2-ynoates can be readily converted into alk-2-ynoic acids by the reaction with morpholine in the presence of a palladium-diphenylphosphinopropane catalyst, thus providing the chemical deprotection method of allyl ester of 2,2,3,3-tetradehydro PGE_1.

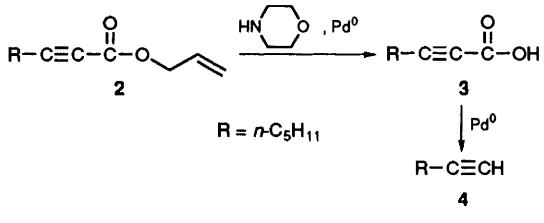
Nucleophilic substitution of allylic systems activated with Pd^0 catalyst affords an efficient method for deprotection of the ester functional group.[1–3] In connecting with our recent research project to make the two-component coupling synthesis of prostaglandins (PGs) as industrially viable process,[4] we have successfully applied this method to effect for the first time chemical deprotection of the ester functional group of PGEs as shown in eqn. (1).[4b] This reaction, however, could not be applied to the allyl ester of 2,2,3,3-tetradehydro-PGE_1 **1**[4a,b] which resulted in not only deallylation but also decarboxylation as shown in [eqn. (2)] .

This decarboxylation is not specific to **1**. Similar reaction occurred with allyl oct-2-ynoate **2** providing hept-1-yne **4** quantitatively (GC yield). We also found that oct-2-ynoic acid **3** was easily converted into **4** quantitatively by treatment with a catalytic amount of $Pd(PPh_3)_4$. Under the similar conditions phenylpropiolic acid was also converted into phenylacetylene in quantitative yield. This decarboxylation, however, is specific for alk-2-ynoic acids and no decarboxylation was observed for alkanoic acids and alk-2-enoic acids. These findings strongly indicate that the decarboxylation of **2** proceeds stepwise as shown in Scheme 1.

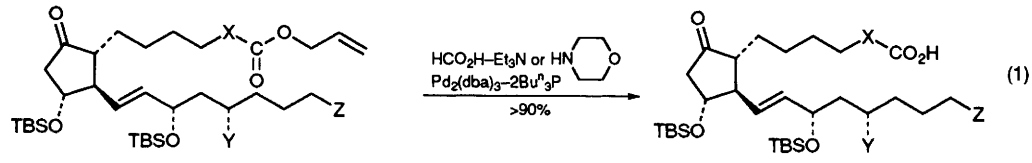
As a working hypothesis for the decarboxylation of alk-2-ynoic acids, we formulated a pathway involving initial oxidative addition leading to the Pd^{II} compound **A**, which undergoes decarboxylation affording the compound **C** *via* intermediate **B** and then undergoes reductive elimination (Scheme 2). We accordingly anticipated that use of a bidentate diphosphine ligand in place of a monodentate phosphine ligand would hinder the formation of the intermediate **B** due to the chelate stabilizing effect of a diphosphine and thus prevent the decarboxylation.

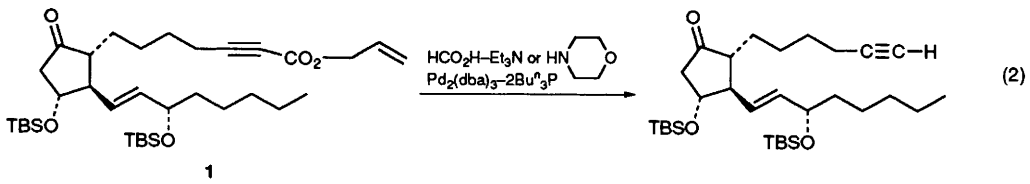
Actually the reaction of **2** with morpholine in the presence of $[Pd_2(dba)_3]$-dppe, -dppp or -dppb [dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane] catalyst afforded **3** quantitatively. Noteworthy also is the fact that use of HCO_2H–Et_3N in place of morpholine resulted in no reaction. These findings are understandable by the following reports that the Pd^0-catalysed deallylation of allylic esters proceeds by the formation of a π-allyl palladium complex followed by the nucleophilic substitution of the allylic system to afford the alkene and regenerate the Pd^0 compound and that nucleophiles with $pK_a < 20$ such as morpholine attack the allyl ligand directly whereas nucleophiles with $pK_a > 20$ such as ammonium formate attack *via* the palladium.[5] Since the intermediary π-allyl palladium complex formed in the present reaction is coordinatively saturated, it can not react with ammonium formate but can react with morpholine (Fig. 1).

With this result in hand we have carried out successfully the synthesis of 2,2,3,3-tetradehydro PGE_1 **6** from **1**. Thus, the reaction of **1** with morpholine in the presence of $[Pd_2(dba)_3]$-dppp in THF at 35 °C for 1 h provided 2,2,3,3-tetradehydro PGE_1 bissilyl ester **5** in 83% yield, which in turn was converted into **6** by treatment with aqueous HF in THF. ^1H NMR for **6**, ($[^2H_6]$DMSO 300 MHz) δ 0.86 (t, *J* 5.8 Hz, 3 H), 1.10–1.55 (m, 14 H), 1.94–2.18 (m, 1 H), 2.03 (dd, *J* 7.9, 17.6 Hz, 1 H), 2.13 (t, *J* 5.7 Hz, 2 H), 2.20–2.34 (m, 1 H), 2.56 (dd, *J* 17.6, 7.0 Hz, 1 H), 3.84–4.00 (m, 2 H), 5.44–5.60 (m, 2 H). In the inhibition of ADP induced platelet aggregation of

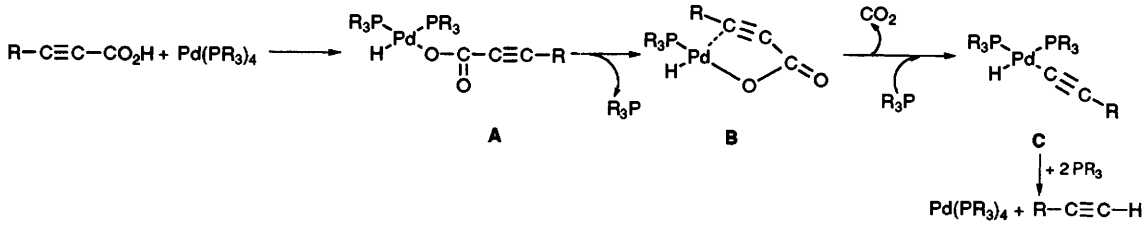


Scheme 1





1



Scheme 2

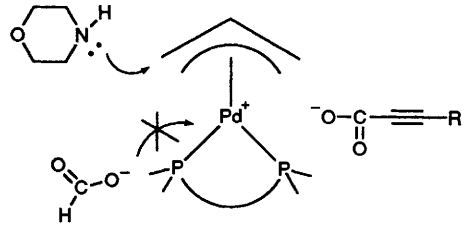
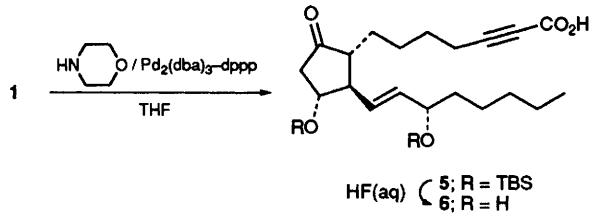


Fig. 1



Scheme 3

human platelet-rich plasma, **6** was one and a half times more potent than PGE_1.

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