Phosphine-dependent Stereoselective Nucleophilic Reaction to Bicyclic Bis-μ-dichloro-η^3-allylpalladium Complexes

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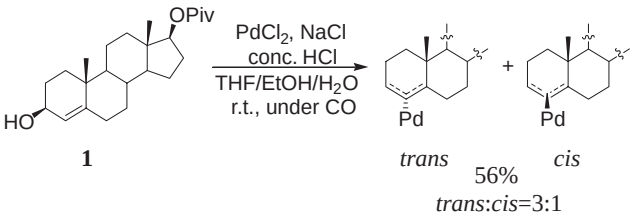
The effects on ligands in nucleophilic reaction of η^3-allylpalladium chloride dimers were studied. Reaction of steroid **1** with Na_2PdCl_4 in concentrated HCl under CO gave the *cis*,*trans*-bis-μ-dichloro-η^3-allylpalladium complex **2** after recrystallization. Reaction of **2** with malonate anion in the presence of PPh_3 afforded *trans*-**3** in 65% yield. When Dppe was used, *cis*-**3** was obtained as the major product. In nucleophilic reactions of bicyclic η^3-allylpalladium chloride complex **4a** or **4b** with PPh_3, *cis*-**5** was the major product. However, the reaction with Dppe gave *trans*-**5** predominantly. The stereochemistry in the nucleophilic reaction of η^3-allylpalladium chloride dimer is dependent on the added phosphines.

Strategies for organic synthesis that take advantage of η^3-allylpalladium chemistry have evolved remarkably since the discovery of the reaction with soft carbon nucleophiles almost forty years ago.[1] In a typical reaction, nucleophiles such as malonate anions attack a carbon atom of the η^3-allylpalladium complex in an S_N2 manner from the side opposite to the palladium atom. A carbon–carbon bond forms with inversion of stereochemistry. In palladium-catalyzed reactions of allylic compounds, Pd^0 species attack the allylic moiety to form an η^3-allylpalladium intermediate. Then, nucleophilic attack with inversion results in overall retention of stereochemistry.[2] In an effort to control the stereochemistry of bicyclic allylic compounds by palladium catalysis, we found that phosphine ligands are critically important for the nucleophilic reaction of bis-μ-dichloro-η^3-allylpalladium complexes.[3]

To analyze the stereochemistry of the nucleophilic reaction, we obtained the steroidal η^3-allylpalladium chloride complex **2** in 56% yield as a yellow solid from the steroid derivative **1** by the method of Bosnich et al. (Scheme 1).[4] A ^{1}H NMR spectrum of the solid **2** indicated the presence of isomeric *cis*-3–5η- and *trans*-3–5η-allylpalladium structures in a 1:3 ratio.[5] The finding suggested that palladium atoms bonded to the diastereomeric β-face as well as the α-face of the steroid. The allylic proton signal of the *cis*-3–5η-allyl moiety appeared at 4.28 ppm (br), and vinylic proton were at 5.14 ppm (d, $J = 6.6$ Hz). Those of the *trans*-3–5η-allyl moiety appeared at 4.88 ppm (br) and 5.30 ppm (d, $J = 6.4$ Hz).[6] The soluble *trans*,*trans*-**2** was washed from the yellow solid with ether. The ethereal elute was condensed and the residue was recrystallized from hexane–CH_2Cl_2. Interestingly, X-ray crystallography of the yellow crystals revealed the *cis*,*trans*-**2** (Figure 1).[7] The crystals stacked more closely with *cis*,*trans*-**2** after isomerization during recrystallization.



Scheme 1. Preparation of steroidal η^3-allylpalladium chloride dimer **2**.[5]

Then, the reaction of *cis*,*trans*-**2** with sodium dimethyl malonate was studied using various phophines in THF at room temperature. The cis/trans ratio of **3** was determined by ^{1}H NMR spectroscopy. The α-methyne proton signal of the malonate *cis*-**3** appeared at 3.19 ppm (d, $J = 9.3$ Hz), and the vinylic proton signal appeared at 5.08 ppm (s). Those of *trans*-**3** were at 3.33 ppm (d, $J = 10.6$ Hz) and 5.22 ppm (d, $J = 4.3$ Hz). The results of the nucleophilic reaction are summarized in Table 1. The reaction with PPh_3 gave the *trans*-**3** isomer in 65% yield. Only a trace of the corresponding cis isomer appeared in the NMR spectrum. A similar result was obtained with *n*-Bu_3P. When the bidentate ligands, Dppp and Dppb were used, selectivity for the trans isomer decreased. With Dppe, the *cis*-**3** isomer was obtained as the major product.[8] These results suggest phosphines control the stereochemistry of the nucleophilic reaction.

Isomeric bicyclic η^3-allylpalladium chloride complexes **4a** and **4b** were prepared to study the profound effects of ligands on the stereoselectivity of the reaction. The cis,cis isomer **4a** was prepared as a major product by the method of Trost, which converts olefins into η^3-allylpalladium chloride complexes.[9] On the contrary, the method of Bosnich from the corresponding allylic alcohol yielded the trans,trans isomer **4b** predominantly.[3] The complexes **4** were subjected to the nucleophilic reactions with sodium dimethyl malonate in the presence of PPh_3 or Dppe and the cis/trans ratio of **5** was determined by ^{1}H NMR. The α-methyne proton signal of the malonate of *cis*-**5** appeared at 3.21 ppm (d, $J = 9.4$ Hz), and the vinylic proton signal was at 5.08 ppm. Those of *trans*-**5** were at 3.33 ppm (d, $J = 10.2$ Hz)

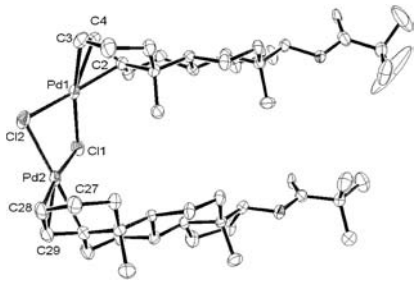
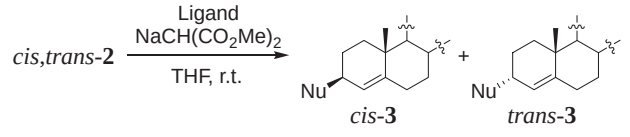


Figure 1. ORTEP drawing of steroidal α,β-bis-μ-dichloro-η^3-allylpalladium dimer **2**.[7]

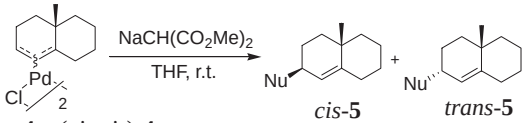
Table 1. Effects on ligands in nucleophilic reaction of steroidal η^3-allylpalladium chloride dimer **2**



Entry	Ligand (equiv.)	% Yield[a]	cis/trans[b]
1	PPh_3 (4)	65	1:99<
2	*n*-Bu_3P (4)	64	1:99<
3	Dppe (2)	38	4.1:1
4	Dppp (2)	94	1:3.1
5	Dppb (2)	87	1:5.3

[a]Isolated yield. [b]The ratio of the cis/trans isomer was determined by ^{1}H NMR analysis.

Table 2. Effects of ligands in nucleophilic reaction of bicyclic η^3-allylpalladium chloride dimers **4a** and **4b**



4a: (*cis*,*cis*)-**4**
4b: (*trans*,*trans*)-**4**

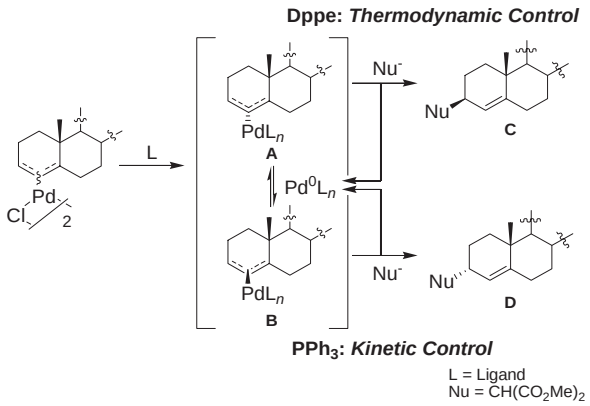
Entry	**4a**/**4b**	Ligand	Yield/%[a]	cis/trans[b]
1[c]	1:9	PPh_3	20	1:5.2
2	5:1	PPh_3	65	1:99<
3	1:8	Dppe	68	4.1:1
4	5:1	Dppe	69	6.2:1

[a]Isolated yield. [b]The ratio of the cis/trans isomer was determind by ^{1}H NMR analysis. [c]1,3-Dienes were formed.

and 5.17 ppm (d, $J = 2.0$ Hz). The signal from the angular methyl proton of *cis*-**5** appeared at 1.052 ppm, while that of *trans*-**5** was at 1.045 ppm. Table 2 depicts the slow nucleophilic reaction of **4b** (**4a**/**4b** 1:9) with PPh_3 resulting in the trans isomer as the major product (trans/cis = 5.2:1) while 1,3-dienes were formed by elimination in considerable yield (Entry 1). The reaction of a 5:1 mixture of **4a** and **4b** with PPh_3 proceeded rapidly to give the trans product (Entry 2). Reactions with PPh_3 produced *trans*-**5** independent of the ratio of **4a**/**4b**. By contrast, reactions with Dppe complex gave mostly the cis product (Entries 3 and 4).

To examine the effects of ligands on the stereochemistry in solution, η^3-allylpalladium–phosphine complexes were prepared in situ by treatment of **4** with PPh_3 or Dppe in $CDCl_3$. The cis/trans ratio of these complexes was determined by ^{1}H NMR spectra.[10] The stereochemistry of the PPh_3 complexes had a cis/trans ratio of 8.2:1. With Dppe as the ligand a cis/trans ratio was 1:7.4.

Scheme 2 presents a mechanism to explain these results. For the reaction with PPh_3 the intermediates **B** react faster than the isomers **A**. The nucleophilic attack on isomers **A** is so slow that epimerization to isomers **B** by Pd^0 species, generated after nucleophilic attack, occurs before the nucleophilic attack to **A**.[11] Thus, trans isomers **D** are the major products irrespectively. On the contrary, in the case of Dppe cis isomers **C** are obtained from both cis and trans complexes, because the isomers **B** with Dppe react more slowly than the trans isomers **A**.



Scheme 2. Plausible mechanism of the nucleophilic reaction with η^3-allylpalladium chloride dimers and phosphine.

In conclusion, the stereochemistry in the nucleophilic reaction of steroidal and bicyclic η^3-allylpalladium complexes is controlled by the added phosphines.

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