Unprecedented Ligand Dependent S_N2' Mechanism on the Palladium-catalyzed Nucleophilic Substitution to Bicyclic Dienyl Acetates

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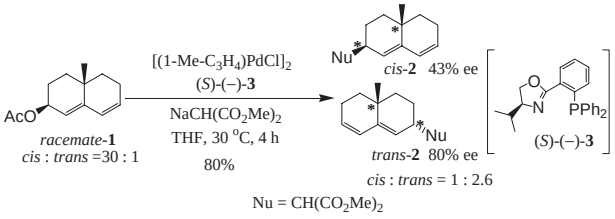
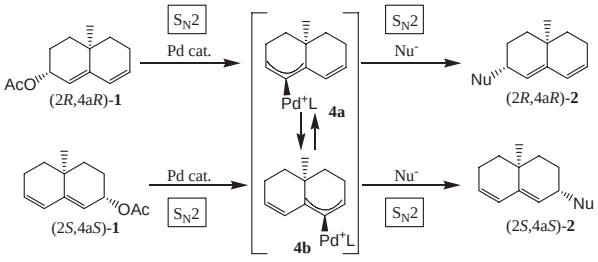
Palladium-catalyzed nucleophilic reaction to bicyclic dienyl acetates **1** was studied with both optically active substrates and deuterium labeled substrates in order to clarify regioselectivity of the reaction. The regioselectivity depended on phosphine ligands. Thus, S_N2 type reaction was observed using PPh_3. Whereas, unprecedented S_N2' type reaction proceeded in high yields using DPPP and DPPB, which is applicable to a remote nucleophilic substitution.

Catalytic enantioselective reactions have attracted considerable attention, and various practical asymmetric synthetic methods are now available.[1] Among them the palladium-catalyzed asymmetric nucleophilic reactions via symmetrical 1,3-disubstituted π-allylpalladium intermediates have been realized with high enantioselectivity using various chiral ligands.[2] However, only a limited number of nucleophilic reactions with conjugated dienyl compounds have been reported.[3] The palladium-catalyzed nucleophilic reaction with conjugated dienyl compounds is considered to involve η^3-η^1-$\eta^{3'}$ isomerization of alkenyl π-allylpalladium intermediates, which indicates the possibility to asymmetric reaction. Previously we realized the enantioselective nucleophlic reaction using a bicyclic dienyl acetate **1** on the basis of these concepts (Scheme 1).[4]



Scheme 1.

A plausible mechanism of the enantioselective reaction is illustrated in Scheme 2. Oxidative addition of dienyl acetate (2*R*,4a*R*)-**1** to Pd(0) species gives the η^3-pentadienylpalladium intermediate **4a** as S_N2 manner. The intermediate **4a** reacts with the nucleophile at less hindered C2 position of the hydronaphthalene **4a** as S_N2 mannar to give the *cis* product (2*R*,4a*R*)-**2**. Similarly, reaction of (2*S*,4a*S*)-**1**, the enantiomer of (2*R*,4a*R*)-**1**, gives (2*S*,4a*S*)-**2**. If interconversion between the π-allylpalladium intermediate **4a** and **4b** is possible and the optically active catalysts can control the equilibration, the reaction takes place in an enantioselective manner. The rate of the interconversion has to be much faster than the nucleophilic reaction for the high enantioselectivity. In order to clarify the fact and to elucidate precise mechanism of η^3-η^1-$\eta^{3'}$ isomerization of alkenyl π-allylpalladium intermediates, we have studied the nucleophilic reaction of optically active acetate (2*R*,4a*R*)-**1** with achiral phosphine, expecting racemization. If the equilibrium takes place rapidly, racemization of chiral substrate (2*R*,4a*R*)-**1** to (2*R*,4a*R*)-**2** and (2*S*,4a*S*)-**2** would be observed with achiral catalyst. On the other hand when the equilibrium between **4a** and **4b** is slow, optically active (2*R*,4a*R*)-**2** would be obtained.



Scheme 2.

Palladium-catalyzed nucleophilic reactions of dimethyl 2-methyl-2-sodiomalonate were carried out using 86% enantiomeric excess of (2*R*,4a*R*)-**1** in the presence of achiral phosphines and the results are shown in Table 1.

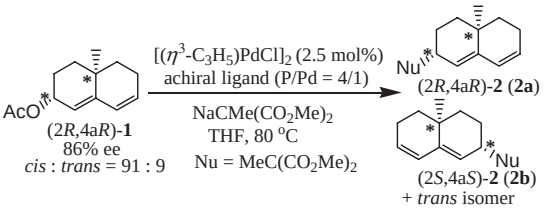


Table 1. Pd-catalyzed nucleophilic reaction of optically active dienyl acetate with achiral phosphines[a]

Run	Ligand	Yield[b]/%	*cis*:*trans*[c]	ee[c]/% (**2a**:**2b**)
1	PPh_3	30	85:15	+32 (63:34)
2	DPPE	90	82:18	−6 (47:53)
3	DPPP	93	76:24	−54 (23:77)
4	DPPB	93	93:7	−34 (33:67)

[a]Dimethyl-2-methylmalonate (2.0 equiv.) was used. [b]Isolated yields as a mixture of *cis* and *trans* isomers after column chromatography. [c]Determined by GLC.

The reaction with PPh_3 was slow, and the enantiomeric excess of the major *cis* product **2** was decreased to 32% ee (Run 1). On the other hand, almost racemization was observed with DPPE (Run 2). Surprisingly, the reaction with DPPP and DPPB proceeded smoothly to give the opposite stereoisomer **2** to that in the case of PPh_3 with considerable enantiomeric excesses (Runs 3 and 4).

Similarly, to confirm this ligand dependent regioselectivity, the 2-deuterio dienyl acetate **1** was used (Runs 1–4 in Table 2).

The results are in accordance with those of the reaction using optically active substrates (2*R*,4a*R*)-**1**. Thus, retention of stereochemistry in the reaction was observed with PPh_3, disproportionation reaction was observed with DPPE, and the remote conjugate substitution took place to give the 7-deuterio-**2** as a major product with DPPP and DPPB.

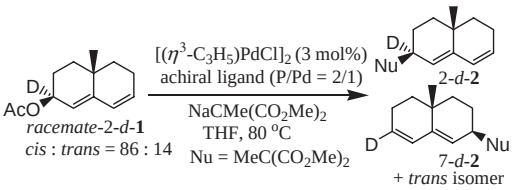


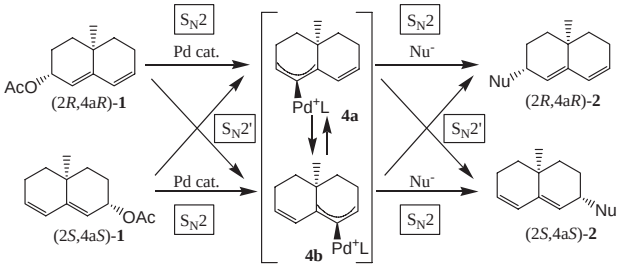
Table 2. Pd-catalyzed nucleophilic reaction of 2-deuterium labeled dienyl acetate with achiral phosphines[a]

Run	Ligand	Yield[b]/%	*cis*:*trans*[c]	2-*d*-**2**:7-*d*-**2**[c]
1	PPh_3	17	93:7	73:27
2	DPPE	50	83:17	54:46
3	DPPP	90	88:12	31:69
4	DPPB	99	94:6	35:65
5[d]	DPPP	45	75:25	48:52

[a]Dimethyl-2-methylmalonate (2.5 equiv.) was used. [b]Isolated yields as a mixture of *cis* and *trans* isomers after column chromatography. [c]Determined by ^{1}H NMR. [d]*n*-Bu_4NBr (4.2 equiv.) was added.

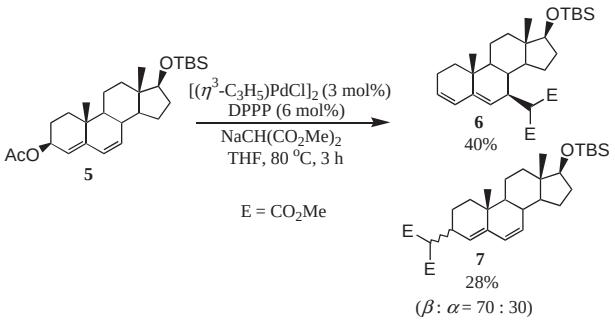
The facts that remote conjugate substitution took place predominantly with DPPP and DPPB can be explained by the mechanism in Scheme 3. The involvement of S_N2' direct attack without η^3-η^1-$\eta^{3'}$ interconversion of alkenyl π-allylpalladium intermediates is plausible. Thus the nucleophilic reaction to **4a** takes place as S_N2' manner directly to give (2*S*,4a*S*)-**2**. Similarly, a mechanism that oxidative addition of Pd(0) species to (2*R*,4a*R*)-**1** to form **4b** as S_N2' manner is also considerable.

It is noteworthy that the S_N2' reaction in the formation of the π-allylpalladium **4** by nucleophilic attack of Pd(0) species or nucleophlic reaction to **4** to give **2** proceeded with *anti* stereochemistry.[5]



Scheme 3.

It is reported that addition of bulky ammonium salts retards the nucleophilic reaction to palladium intermediates, which increases the relative rate of η^3-η^1-$\eta^{3'}$ interconversion against that of nucleophilic reaction.[3e] Actually, palladium-catalyzed nucleophilic reaction of 2-*d*-**1** in the presence of *n*-Bu_4NBr proceeded



Scheme 4.

to give the nearly 1:1 products 2-*d*-**2** and 7-*d*-**2** (Runs 5 in Table 2). Thus, this result strongly suggests that the rate of S_N2' type nucleophilic attack is faster than that of η^3-η^1-$\eta^{3'}$ interconversion in the reaction of the bicyclic dienyl acetates **1** in the absence of the ammonium salt.

The interesting observation of S_N2' mechanism is applicable to a remote nucleophilic substitution. Nucleophilic reaction to the bicyclic dienyl acetate **5** derived from a natural steroid using Pd-DPPP catalyst with dimethyl 2-sodiomalonate proceeded to give **6** in 40% yield with **7** in 28% yield (Scheme 4). Against large steric hindrance, the π-allylpalladium template controls the nucleophilic attack at C7 position regio- and stereoselectively to give **6**.

In conclusion, the ligand dependent regioselectivity and involvment of S_N2' mechanism with DPPP and DPPB were observed in the palladium-catalyzed nucleophilic reaction of **1**. The template effect of π-allylpalladium enables the remote nucleophilic reaction of **5** to give **6** in a considerable yield.

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