Enantioselective Nucleophilic Substitution of a 6,6-Bicyclic Dienyl Acetate by Palladium-Chiral Phosphine Catalyst

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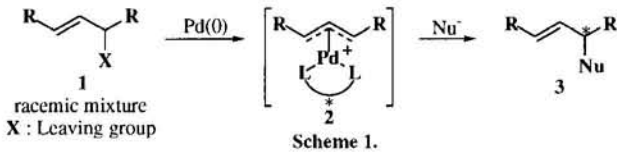
The enantioselective nucleophilic substitution of (±)-2β-acetoxy-4aβ-methyl-2,3,4,4a,5,6-hexahydronaphthalene with dimethyl malonate anion was performed in the presence of palladium-chiral ligand catalysts to give optically active 2-di(methoxycarbonyl)methyl-4a-methyl-2,3,4,4a,5,6-hexahydronaphthalenes.

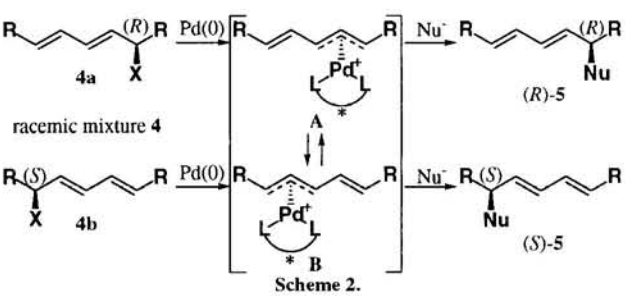
Catalytic enantioselective reactions have attracted considerable attention, and various practical asymmetric synthetic methods are now available.[1] Nucleophilic reactions *via* symmetrical 1,3-disubstituted η^3-allylpalladium complexes have been realized with high enantioselectivity by using various chiral ligands (Scheme 1).[2] The enantioselectivity in these reactions arises from discrimination of the nucleophilic attack on the 1- or 3-position of allylic groups under the influence of the coordinated chiral ligands.



Scheme 1.

We describe here a new type of enantioselective control by chiral ligands in the regioselective nucleophilic attack on vinyl η^3-allylpalladium intermediate as represented in Scheme 2. When a racemate of **4** reacts with a Pd(0) complex, the enantiomeric isomers **4a** and **4b** would form the η^3-allylpalladium complexes **A** and **B**, respectively. The enantiomeric intermediates **A** and **B** are supposed to be in equilibrium by transfer of the palladium entity.[3] If this equilibrium process or subsequent nucleophilic attack on the intermediates **A** and **B** can be controlled by chiral ligands on palladium catalyst, enantioselective synthesis of **5** should be realized. On the basis of the concept, we have studied the asymmetric synthesis of bicyclo[4.4.0]decane derivatives starting with a racemic (±)-2β-acetoxy-4aβ-methyl-2,3,4,4a,5,6-hexahydronaphthalene (**6**)[4] as a source of the alkenyl η^3-allylpalladium intermediates.

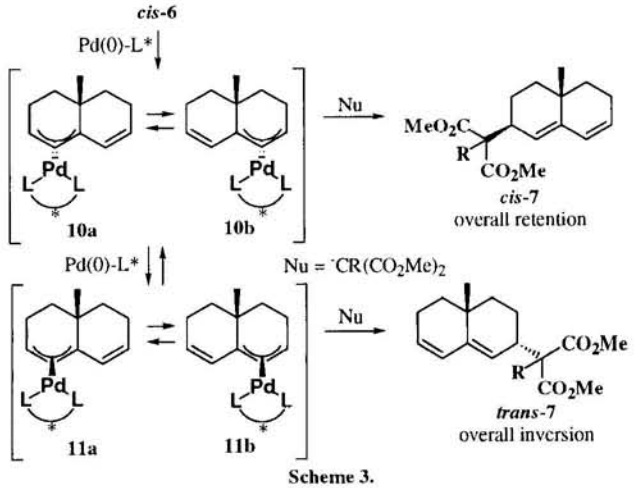
First, reaction of ***rac*-6** with dimethyl sodiomalonate was carried out in the presence of $[(1\text{-Me-}C_3H_4)PdCl]_2$ with several chiral ligands. The results are summarized in Table 1. The reaction with Pd-(-)-BINAP catalyst scarcely proceeded in THF at 30 °C. However, the reaction proceeded at 80 °C in 86% yield to give ***cis*-7a** with a small amount of ***trans*-7a** (*cis* / *trans* = 20:1). Similar results were obtained with bidentate bisphosphines, (-)-Chiraphos and (-)-DIOP. Enantiomeric excess in the reactions with bisphosphines, however, was unsatisfactory (Runs 1-3).[6]



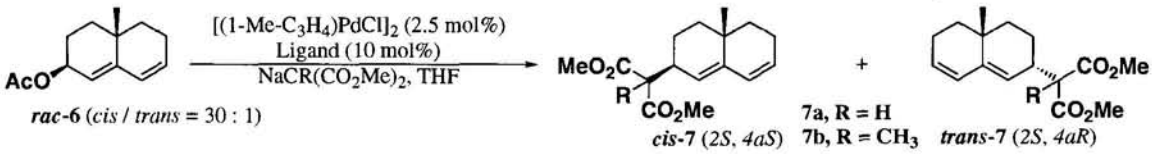
Scheme 2.

The reaction with an arylphosphine containing an oxazoline ligand **8** proceeded smoothly at 30 °C to give a mixture of ***cis*-7a** and ***trans*-7a** in good yields. Enantioselectivities of both ***cis*-7a** and ***trans*-7a** were moderate (40-58%, Runs 4 and 5).[7] The enantioselective nucleophilic reaction with dimethyl sodiomethylmalonate was also carried out similarly to give corresponding esters, ***cis*-7b** and ***trans*-7b** (Runs 6-8). When the reaction was carried out with **9** instead of **8** as a ligand, the trans isomer was obtained as a major product with the enantioselectivity similar to the reaction with **8** (Run 9 and 11). The enantiomeric excess of ***trans*-7b** was observed to increase to 70% when $[(2\text{-Me-}C_3H_4)PdCl]_2$ and the ligand **8** were used as a catalyst (Run 10).

Palladium-catalyzed alkylation of allylic acetates with active methylene compounds are known to proceed with retention of stereochemistry.[8] The reaction of the dienyl acetate **6** using palladium-diphosphine catalyst gave the *cis* product with retention. However, inversion of stereochemistry was also observed in employing **8** as the ligand. The formation of ***trans*-7** is explained by the isomerization of the η^3-allylpalladium complexes **10** to intermediate **11** caused by attack of other Pd(0) complexes prior to attack of malonate anion (Scheme 3).[9,10] Actually, when the reaction was carried out with stoichiometric amounts of the palladium complexes, isomerization *via* the η^3-allylpalladium intermediate proceeded more rapidly to give a 1:2.6 mixture of ***cis*-7a** and ***trans*-7a**. Furthermore higher enantiomeric excesses of the products were obtained (***cis*-7a**,



Scheme 3.

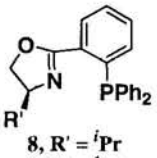


rac-**6** (*cis* / *trans* = 30 : 1)

cis-**7** (2*S*, 4*aS*) **7a**, R = H **7b**, R = CH_3 *trans*-**7** (2*S*, 4*aR*)

Table 1. Nucleophilic substitution of ***rac*-6** with palladium catalyst and dimethyl malonate anion

Run	Ligand	R	Temp. / °C	Time / h	Yield[c] / %	*cis* / *trans*[d]	% ee[d] (Config.) *cis*-7	% ee[d] (Config.) *trans*-7
1	(-)-BINAP	H	80	2	86	20 : 1	16 (2*S*, 4*aS*)	0
2	(-)-Chiraphos	H	80	2	93	6 : 1	6 (2*R*, 4*aR*)	10 (2*R*, 4*aS*)
3	(-)-DIOP	H	80	2	97	21 : 1	2 (2*S*, 4*aS*)	4 (2*R*, 4*aS*)
4	**8**	H	80	4	86	1.2 : 1	40 (2*S*, 4*aS*)	52 (2*S*, 4*aR*)
5	**8**	H	30	4	89	1 : 1.2	44 (2*S*, 4*aS*)	58 (2*S*, 4*aR*)
6	(-)-BINAP	CH_3	80	2	88	20 : 1	2 (2*S*, 4*aS*)	8 (2*S*, 4*aR*)
7	**8**	CH_3	80	2	87	1.3 : 1	46 (2*S*, 4*aS*)	58 (2*S*, 4*aR*)
8	**8**	CH_3	20	4	87	1.3 : 1	44 (2*S*, 4*aS*)	62 (2*S*, 4*aR*)
9	**9**	CH_3	20	4	84	1 : 1.5	50 (2*S*, 4*aS*)	56 (2*S*, 4*aR*)
10[a]	**8**	CH_3	20	4	88	1.2 : 1	44 (2*S*, 4*aS*)	70 (2*S*, 4*aR*)
11[a]	**9**	CH_3	20	4	81	1 : 1.5	46 (2*S*, 4*aS*)	62 (2*S*, 4*aR*)
12[b]	**8**	H	30	4	80	1 : 2.6	43 (2*S*, 4*aS*)	80 (2*S*, 4*aR*)



8, R' = ^{i}Pr
9, R' = ^{t}Bu

[a] $[(2\text{-Me-}C_3H_4)PdCl]_2$ (2.5 mol%) as a palladium catalyst was used. [b] $[(1\text{-Me-}C_3H_4)PdCl]_2$ (0.5 eq.) and ligand (2.0 eq.) were used. [c] Isolated yield as a mixture of *cis* and *trans* isomers after column chromatography. [d] Determined by GLC.

43% and ***trans*-7a**, 80%, Run 12 in Table 1). On the contrary, in the case of palladium-diphosphine ligand, nucleophilic attack of malonate anions is very fast, resulting in the almost retention of stereochemistry.[11]

In conclusion, we presented here a first example of enantioselective reaction involving η^3- η^1- $\eta^{3'}$ isomerization of η^3-allylpalladium from a dienyl compound. The present method will provide a new approach to synthesis of optically active compounds. Further synthetic applications and mechanistic studies are in progress.

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4 Racemic **6** was synthesized from 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone (**12**) in 4 steps. Thus, reaction of **12** and Ac_2O with TMSCl at 100 °C gave dienol acetate **13**. Oxidation of **13** with $Pd(OAc)_2$, $MeOSnBu_3$, and allyl methyl carbonate[5] gave 4,4a,5,6-tetrahydro-4a-methyl-2(3H)-naphthalenone (**14**), and the subsequent reduction of **14** with $LiAlH_4$ provided alcohol **15**. Then treatment of **15** with Ac_2O and pyridine afforded **6** in 34% from **12**.

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6 The product was isolated as a mixture of ***cis*-7** and ***trans*-7**. The stereoselectivity and enantioselectivity were determined by GLC using Chirasil Dex CB (25 m X 0.25 mm from CHROMPACK) and TC-1 (30 m x 0.25 mm from GL Science INC.). The absolute configuration was determined after hydrogenation of the $\Delta^{7,8}$ double bond by referring to the optically active authentic naphthalene derivative, which was prepared in 3 steps from the commercially available (*S*)- 4,4a,5,6,7,8-hexahydro-4a-methyl-2(3H)-naphthalenone.

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11 We confirmed that the isomerization of ***cis*-7** to ***trans*-7** did not take place under similar reaction conditions. Thus, by monitoring the process of the reaction with GLC, the remaining starting material, ***rac*-6**, was found to be completely racemic, and the enantiomeric excesses of the products, ***cis*-7** and ***trans*-7**, were constant during the reaction, the fact indicating that neither kinetic resolution nor product equilibration processes are involved.