PALLADIUM CATALYSTS IN NATURAL PRODUCTS SYNTHESIS

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Abstract - Two important palladium catalyzed reactions, namely oxidation of olefins to methyl ketones with PdCl₂/CuCl/O₂ system, and telomerization of butadiene with nucleophiles catalyzed by Pd(OAc)₂/PPh₃ are used in key steps of natural products synthesis. Syntheses of Matsutake alcohol, lipoic acid, diplodialide, lasiodiplodin, zearalenone, l2-acetoxy-l,3-dodecadiene, cis-civetone, recifeiolide, royal jelly acid, 2,15-hexadecanedione are described.

INTRODUCTION

A variety of organic reactions promoted by palladium compounds have been discovered in the last decade, and palladium compounds play important roles in organic synthesis especially as catalysts. Among numerous reactions catalyzed by palladium compounds, two reactions are most important and useful in organic synthesis. The first one is the oxidation of olefins to carbonyl compounds. The original reaction is well-known as the Wacker reaction and actually acetaldehyde is produced in an industrial scale from ethylene and oxygen by using PdCl2/CuCl2 as a catalyst system (1). Application of this oxidation method to higher 1-olefins affords methyl ketones selectively (2). We use PdCl2/CuCl system, rather than PdCl2/CuCl2, in DMF or methanol for the oxidation of 1-olefins to methyl ketones (3). This reaction is very useful synthetic method, but no application to natural product synthesis has been reported before.

$$RCH=CH_2 + O_2 \xrightarrow{PdCl_2/CuCl} \xrightarrow{R-C-CH_3}$$

The second reaction is the telomerization of butadiene catalyzed by $Pd(OAc)_2/PPh_3$ system (4). In this telomerization, dimerization of butadiene with incorporation of various nucleophiles takes place to give the following telomers in high yields.

Nucleophiles such as water, carboxylic acids, ammonia, amines, enamines, nitroalkanes, and active methylene compounds participate in the telomerization. We have found that these trifunctional telomers are extremely useful starting materials for simple synthesis of various natural products. In this paper, synthsis of natural products carried out in our laboratories, using the butadiene telomers as starting materials are presented. Also in these syntheses, the Wacker type oxidation reaction is applied in key steps.

Acetoxyoctadienes

Butadiene reacts with acetic acid to give two acetoxyoctadienes $\underline{1}$ and $\underline{2}$ in high yields (5).

$$1 + ACOH$$
 OAC OAC OAC OAC OAC OAC

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The simplest natural product prepared from the telomer $\underline{2}$ is Matsutake alcohol $\underline{4}$, a fragrant compound contained in a Japanese mushroom (6). The synthesis was achieved by highly selective reduction of one of the terminal double bonds at C_7 without attacking the other one at C_1 . Hydroalumination catalyzed by a titanium compound was used for the selective reduction (7). Formation of alkoxyaluminum compound $\underline{5}$ by the treatment of 1,7-octadien-3-ol $\underline{3}$ with one mole of dibutylaluminum hydride protects the hydroxy group and also gives steric hindrance to the neighbouring double bond. Addition of LiAlH4 in the presence of a catalytic amount of Cp_2TiCl_2 caused the selective hydroalmination of the terminal olefin. The hydrolysis afforded 1-octen-3-ol (Matsutake alcohol 4) in a high yield with 90% selectivity.

The alcohol 3 is a good starting material for the synthesis of lipoic acid $\underline{10}$ without changing carbon numbers (8). Hydroboration of the two double bonds produced the triol $\underline{6}$. The 1,3-diol system was protected by acetal formation $\underline{7}$ and the terminal free alcohol was oxidized to the carboxylic acid $\underline{8}$. The conversion of the 1,3-diol to 1,3-dithiol is a known reaction. The oxidation of the dithiol 9 catalyzed by FeCl₃ afforded lipoic acid $\underline{10}$.

We have explored a method for macrolide synthesis based on intramolecular carbon-carbon bond formation using butadiene telomers as starting materials. The acetate 1 has a suitable functionality for the synthesis of diplodialide B $\underline{14}$ (9). At first the acetate was converted to tetrahydropyranyl ether, and the terminal olefin was oxidized to the methyl ketone $\underline{11}$ with PdCl₂/CuCl/O₂ and then reduced to alcohol. The bromoacetate $\underline{12}$ was formed by the reaction of the alcohol with bromoacetyl bromide. The tetrahydropyranyl ether was removed and the alcohol was oxidized with CrO₃ to the aldehyde $\underline{13}$ in 60% yield (10). The final step is the intramolecular Reformatsky reaction to form diplodialide B $\underline{14}$ in 45% yield. The cyclization was promoted by Zn in the presence of AlEt₂Cl as an activator (11). In this reaction, aluminum protects the hydroxy group formed by the reaction from dehydration.

The ring chain of the ten-membered lactones can be conveniently prepared from the acetate $\underline{1}$ (12). Again the terminal double bond was oxidized to the methyl ketone $\underline{15}$ and then reduced to the alcohol. The allylic acetate was converted, after hydrolysis, to the allylic chloride $\underline{16}$ by the treatment with $CC1_4/PPh_3$. The ester $\underline{17}$ was prepared by the reaction of phenylthioacetyl chloride. The intramolecular alkylation of the anion generated by KN(SiMe₃)₂ as a base afforded the unsaturated lactone $\underline{18}$ in 71% yield. The saturated and unsaturated lactones 19 and 20 were prepared from 18.

The ring chain of lasiodiplodin $\underline{24}$ can be conveniently derived from the allylic chloride $\underline{16}$ (13). The ester $\underline{22}$ was prepared from $\underline{16}$ and $\underline{21}$ and the intramolecular alkylation of the anion generated by KN(SiMe3)2 afforded the unsaturated lactone $\underline{23}$ in 40% yield. The reduction of the double bond and removal of the phenylthio group were achieved by the treatment with Raney nickel to give the methyl derivative of lasiodiplodin $\underline{24}$.

Zearalenone is another type of orsellinic acid type macrolide and its ring chain was prepared easily from the acetate $\underline{2}$ by the following sequence of reaction (13). The allylic alcohol $\underline{25}$ was oxidized to the enone $\underline{26}$, which underwent Michael reaction with malonate to give the diester $\underline{27}$ in 70% yield. One of the ester was removed by heating in HMPA and the ketone was protected to give $\underline{28}$. The ester was reduced to the alcohol and converted to tosylate. The terminal olefin was oxidized with $PdCl_2/CuCl/O_2$ to give the methyl ketone $\underline{29}$. The tosylate was converted to the iodide and the ketone was reduced to the alcohol $\underline{30}$, which was esterified with $\underline{21}$ to give the ester $\underline{31}$. The cyclization was carried out as before to give the lactone $\underline{32}$ in $\underline{50}\%$ yield. Oxidative removal of the phenylthio group and deketalization produced dimethyl ether of zearalenone $\underline{33}$.

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Elimination reactions of allylic acetates and phenyl ethers

We found that allylic acetates and allylic phenyl ethers can be converted to conjugated dienes by the treatment with a catalyst system of Pd(OAc)₂/PPh₃ at 100° with expulsion of acetic acid and phenol (14).

$$R$$
 OR'
 $Pd(OAc)_2/PPh_3$
 $R' = CH_3CO, Ph$

When these allylic compounds were treated with alkylammonium formate in the presence of $Pd(OAc)_2/PPh_3$ as the catalyst, reductive elimination of acetic acid and phenol took place to give olefins (15). Interestingly, the olefins produced from both isomeric 1- and 3-oxyallylic compounds, were predominantly terminal olefins.

The above shown catalytic reaction was applied to the synthesis of 12-acetoxy-1,3-dodecadiene 39, a pheromone of Diparopsis castanea (16). Starting from 8-phenoxy-1,6-octadiene 34, easily prepared by the reaction of butadiene and phenol, a four carbon unit was added. The alcohol 35a was formed by selective hydroboration of the terminal double bond and tosylated. The tosylate was converted to iodide 35b with sodium iodide. The iodide 35b was coupled in 80% yield with the Grignard reagent 36 prepared from THF using CuI/bipyr as a catalyst system. Then the phenyl ether 37 was converted to the diene 38 with Pd(OAc)₂/PPh₃ in 71% yield. The acetylation completes the synthesis \overline{of} the pheromone 39.

Telomers of nitroalkanes

Active hydrogens of nitroalkanes are displaced in a stepwise-manner with the octadienyl chain by the catalysis of $Pd(OAc)_2/PPh_3$ at room temperature to give long chain unsaturated nitro compounds (17).

The telomer of nitroethane $\underline{40}$ was used for the synthesis of Recifeiolide $\underline{44}$, a naturally occurring 12-membered lactone (12, 18). The usefulness of the compound $\underline{40}$ is apparent by the comparison of $\underline{40}$ with $\underline{44}$. The internal double bond of $\underline{40}$ is at the right position with the trans configuration, and the nitro group can be converted to ketone easily. The nitro group was converted to the ketone by Nef reaction (MeONa/TiCl₄) and protected by ketal formation. The terminal double bond was selectively hydroaluminated with LiAlH₄ using TiCl₄ and quenched with iodine to give the iodide. The protected ketone was liberated and reduced to the alcohol $\underline{41}$. The phenylthioacetate $\underline{42}$ was prepared by the treatment of the alcohol $\underline{41}$ with phenylthioacetyl chloride. The intramolecular alkylation of $\underline{42}$ using $\overline{KN}(\text{SiMe}_3)_2$ afforded the lactone $\underline{43}$ in 75% yield. The phenylthio group was removed with deactivated Raney nickel to give Recifeiolide $\underline{44}$ in 80% yield.

$$+ NO_{2} \xrightarrow{Pd (OAc)_{2}} = NO_{2}$$

$$\frac{40}{2 \cdot H^{+}}$$

$$3 \cdot NaBH_{4}$$

$$\frac{KN(SiMe_{3})_{2}}{SPh}$$

$$\frac{41}{3}$$

$$\frac{41}{3}$$

$$\frac{41}{3}$$

$$\frac{41}{3}$$

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9-Nitro-1,6,11,16-heptadecatetraene <u>45</u> is one of the telomerization product of butadiene and nitromethane. The telomer <u>45</u> has a linear 17 carbon chain and the nitro group at the center of the carbon chain. Civetonedicarboxylic acid <u>46</u>, a precursor of civetone, was prepared by the following scheme without changing the carbon numbers.

The nitro group was converted to ketone by the Nef reaction (MeONa/ H_2SO_4) and protected as a ketal. The terminal double bonds were selectively hydroborated with 9-BBN and the internal double bonds were hydrogenated. Then the terminal alcohols were oxidized to carboxylic acids to afford civetone-dicarboxylic acid $\underline{46}$. Civetonedicarboxylate was cyclized by acyloin condensation to give the acyloin $\underline{47}$ in 65% yield. The ketol was oxidized to α -diketone and then converted to dihydrazone $\underline{48}$, which was oxidized to the acetylene $\underline{49}$ with CuCl in pyridine. The hydrogenation catalyzed by Lindler catalyst afforded cis-civetone $\underline{50}$ (19).

3,8-Nonadienoate

Carbonylation of butadiene in alcohol catalyzed by $Pd(OAc)_2/PPh_3$ affords 3,8-nonadienoate 51 in a high yield (20).

+ CO + ROH
$$\frac{\text{Pd (OAc)}_2/\text{PPh}_3}{51}$$
 CO_2R

Synthesis of 2-decenedioic acid 53 (royal jelly acid) was carried out by the carbonylation of 51 and the double bond migration (21). Co₂(CO)₈/pyridine was used as a catalyst, and the linear diester 52 was obtained as a main product. The hydrolysis and double bond migration were achieved by the treatment of the diester with strong alcoholic KOH to give royal jelly acid 53 as a crystalline compound.

$$\frac{51}{6} + CO + ROH \xrightarrow{CO_2(CO)_8} RO_2^C \xrightarrow{CO_2^R}$$

$$\frac{KOH}{6} + ROH \xrightarrow{CO_2(CO)_8} RO_2^C \xrightarrow{CO_2^R}$$

The terminal double bond of 51 was oxidized with PdCl₂/CuCl/O₂ to the methyl ketone 54 and the double bond was hydrogenated. Hydrolysis of the ester afforded 8-oxononanoic acid 55, which was subjected to Kolbe electrolysis. By this way, 1,15-hexadecanedione 56 was obtained in a high yield (22). Cyclization of this dione and hydrogenation produced muscone 57.

Synthesis of Brevicomin from 51 has been reported (23).

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