Abstract: (1R*,4S*,4aR*,9aS*,10S*)-10-Hydroxy-10-phenyl-1,4a,9a,10-tetrahydro-1,4-
methanoanthracen-9(4H)-one (1c) was prepared for the elucidation of the reaction
mechanism of intramolecular hydroalkoxylation of alkenes catalyzed by gold nanoclusters
stabilized by a hydrophilic polymer, poly(N-vinyl-2-pyrrolidone) (Au:PVP). It was found
that the reaction proceeded via anti-addition of alcohol to the alkene assisted by
\( \pi \)-activation of the gold clusters, which is the same mechanism as the hydroamination by
toluenesulfonamides.

Keywords: gold nanoclusters; hydroalkoxylation; anti-addition; \( \pi \)-activation

1. Introduction

Since the discovery of Haruta’s CO oxidation reaction [1], aerobic oxidation reactions have been a
central issue in nanogold chemistry in contrast to the chemistry of cationic gold(I) complexes, where
the focus has been on their behavior as soft Lewis acid catalysts [2–6]. On the contrary, we have
demonstrated that quasi-homogeneous nanogold protected by hydrophilic polymer, poly(N-vinyl-2-
pyrrolidone) (Au:PVP), exhibits a formal “Lewis acid” activity and promotes intramolecular
heterocyclization of \( \gamma \)-hydroxyalkenes and \( \gamma \)-aminoalkenes [7–12]. The success of the reaction depends
on the choice of the sacrificial reductant (solvent) because the redox reaction between \( O_2 \) and the
solvent takes place behind the main (Lewis acidic) addition reaction. For example, DMF is found to be
a good co-solvent with H2O in the reaction of hydroalkoxylation but EtOH or EtOH-H2O are more suitable in the case of hydroamination. Scheme 1 shows the proposed mechanism of the **Au:PVP**-catalyzed hydroalkoxylation. The reaction is initiated by the formation of key intermediate **A**, which possesses an electron-deficient site generated by adsorption of O2 onto the surface of the Au. Species **A** acts as a Lewis acid, activating both alkoxide and alkene by adsorption onto the surface (**B**), and giving **C** by either the insertion of an alkene into O-Au bond or the external attack of oxygen to the alkene adsorbed on Au. From this C-Au intermediate, neither β-elimination (Wacker-type process: 3 or 4), O2 insertion (oxygenation: 5), nor protonation proceeds; only DMF acts as a hydrogen source to afforded 2 accompanied by the regeneration of free Au clusters.

**Scheme 1.** Possible mechanism of **Au:PVP**-catalyzed hydroalkoxylation of γ-hydroxyalkenes (1).

Among these intramolecular heterocyclizations, the reaction of toluenesulfonamides is well studied due to their high reactivity including the mechanism at the cyclization process [8,11]. Two main pathways are possible in the cyclization process, which may occur together: amine activation and alkene activation [13–16]. In one pathway, a metal amide is formed via amine activation by N-H oxidative addition, which then allows insertion of the alkene into the M-N bond (Scheme 2). These pathways have been proposed for organolanthanide [17], group IV [18–21], or Cu(II) complex [22] catalyst systems. An alternative mechanism involves olefin activation via a transition metal complex similar to cationic Au(I) complexes [23–26]. Finally it was elucidated that the reaction proceeds via anti-addition of the toluenesulfonamide followed by π-activation even under basic and protic solution conditions (Equation 1) [8,11].
To be honest, the result was different from our hypothesis. One reason is that the reaction was carried out under the basic conditions. In general, the \textit{anti}-addition mechanism has been observed under (Lewis) acidic conditions \cite{23,24}. Another is that adsorption of nitrogen or oxygen, equal to gold-nitrogen or gold-oxygen bond formation, is believed to be essential for this reaction by the analogy of the mechanism of alcohol oxidation. We have elucidated that the co-adsorption process of molecular oxygen and the alkoxide, generated by the deprotonation by the base, is facile and promotes the aerobic alcohol oxidation on the surface of Au$_{20}$ clusters, a model for Au:PVP \cite{27–29}. However, the result of Equation (1) suggested that the adsorbed alkoxide (Au-O) does not attack to the alkenes but the external (non-adsorbed) alcohol would attack to the alkenes adsorbed on the Au surface if the same reaction mechanism is adapted to the hydroalkoxylation. Such confusion motivated us to investigate the same mechanistic study in the case of hydroalkoxylation.

2. Results and Discussion

However, upon investigation a severe problem becomes evident. It has been reported that the hydroalkoxylation reactivity is highly susceptible to steric effects, especially at the substituents on alkene in comparison with hydroamination \cite{9}. Indeed, the reaction of the alcohol 1b did not give the cyclized product but rather a complex mixture including alcohol oxidation products (Equation 2). Therefore a new model compound, (1$R^*$,4$S^*$,4a$R^*$,9a$S^*$,10$S^*$)-10-hydroxy-10-phenyl-1,4a,9a,10-
tetrahydro-1,4-methanoanthracen-9(4H)-one (1c), was designed based on the following two features. One is that 1c possesses a norbornene moiety, which might be highly reactive towards the addition reaction [13–15]. Also, we chose a α,α-diaryl tertiary alcohol like 1c according to our previous results [9].

The precursor of 1c (compound 6) was prepared by the Diels-Alder reaction of 1,4-naphthoquinone with cyclopentadiene according to the literature [30]. Phenyl Grignard reagent attacked one of the carbonyl groups selectively from the exo side to afford the endo tertially alcohol in 86% yield (Scheme 3).

**Scheme 3. Preparation of γ-hydroxyalkene 1c.**

The first concern was the poor reactivity of 1c. Indeed, no reaction was observed under the previously reported conditions (10 atom% Au:PVP, 200 mol% DBU, DMF/H2O, 50 °C). The cycloaddition took place when the temperature was increased to 80 °C, and 2c(H) was obtained in 64% yield after 23 h (Scheme 4, Equation 3). A second concern was that a very large kinetic isotope effect has been observed in many case of the Au:PVP-catalyzed reactions [7–12,31]. Thus, the reaction proceeded very slowly when the solvent was replaced to DMF-d7/H2O in order to confirm the stereoselectivity. Finally the amount of Au:PVP was increased to 25 atom% to afford 2c(D) in 37% yield after 58 h at 80°C (Scheme 4, Equation 4).

**Scheme 4. Anti-Addition mechanism in the Au:PVP-catalyzed hydroalkoxylation.**
Judging from the mass spectrum, only one deuterium was introduced in this reaction with 77% D yield, similar to the previous result [8,9]. 2H-NMR showed a singlet peak at 1.59 ppm assignable to the exo position. Introduction of the D at the exo position was further confirmed by the coupling with adjacent exo proton (α position of the tetrahydrofuran ring). The proton in 2c(II) was observed at 3.02 ppm as ddd (J = 2.0, 4.2, 10.4 Hz), but the smallest coupling (J = 2.0 Hz) corresponding to the vicinal exo-exo coupling disappeared in 2c(D). Although it is difficult to exclude the formation of the trace amount of the endo-D isomer under these experimental conditions, it can be concluded that exo-D should be the major product, which indicates that the hydroalkoxylation is also followed by the anti-addition mechanism as same as the reaction with toluenesulphonamide (Scheme 4).

Finally, some comments on the role of the base in this reaction are warranted because basic conditions are indispensable for the hydroalkoxylation. The present results reveal that adsorption of I through the deprotonated alkoxide is not required for promoting the reaction. In other words, the base should play an important role in a different process. The most probable step might be the hydrogen transfer process from the formyl group of DMF (D in Scheme 1). Under the basic conditions, DMF is easily adsorbed on the surface of gold via its hemiacetal form, from which a β-hydrogen might be released. The similar effect has also been proposed in the formylation of amine catalyzed by Au:PVP under basic conditions [32].

3. Experimental Section

Melting points were determined on a Yanaco HK-10D and were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT IR-4100 spectrometer. 1H- and 13C-NMR spectra were measured on a JEOL JMN LAMBDA 400 spectrometer at 23 °C at 400 and 100 MHz, respectively. CDCl3 was used as a solvent and the residual solvent peaks were used as an internal standard (1H-NMR: 7.26 ppm; 13C-NMR: 77.00 ppm). 2H-NMR spectra were measured on JEOL JNM LAMBDA 500 spectrometer (500 MHz) in CHCl3. Silica gel chromatography was performed on Kanto 60N, Wako Wakosil C-300, or Yamazen Hi-Flash column using a Yamazen YFLC purification system. TLC analysis was performed using Merck Silica gel 60 F254 and preparative TLC was conducted using Wako Wakogel B-5F. Au:PVP was prepared according to the literature [34]. Other reagents and solvents were commercially purchased and further purified according to the standard methods, if necessary.

3.1. Preparation of (1R*,4S*,4aR*,9aS*,10S*)-10-Hydroxy-10-phenyl-1,4a,9a,10-tetrahydro-1,4-methanoanthracen-9(4H)-one (1c)

To a solution of 6 (224 mg, 1 mmol) in THF (25 mL) at −10 °C under argon atmosphere was slowly added 1 M PhMgBr (5 mL, 5 mmol) and the mixture was stirred at −10 °C for 3 h then at room temperature overnight. The reaction was quenched with H2O and the aqueous phase was extracted with EtOAc (3 × 20 mL) and then the combined organic layers were washed with H2O and brine, dried over Na2SO4, and concentrated in vacuo. The crude product was purified by silica gel chromatography (10–20% EtOAc/Hexane) to afford 1c (259.3 mg, 86%). Pale yellow solid; mp 44–45 °C; IR (KBr) 3488, 2920, 1661 cm−1; 1H-NMR (CDCl3): δ 1.45–1.50 (m, 2H), 2.45 (s, 1H), 3.28–3.36 (m, 3H), 3.41 (s, 1H), 5.54 (dd, J = 2.4, 5.6 Hz, 1H), 5.76 (dd, J = 2.8, 5.6 Hz, 1H), 7.14–7.33 (m, 6H), 7.52–7.61 (m, 2H), 7.68–7.70 (m, 1H); 13C-NMR: δ 200.95, 149.56, 145.80, 134.85, 134.55, 134.12,
3.2. Procedure for the Hydroalkoxylation

All the reactions were carried out using an EYELA PPS-2510 organic synthesizer. A test tube (φ = 30 mm) was placed with 1c (0.1 mmol), DBU (30 µL, 200 mol%), and dried Au:PVP (86 mg = 10 atom%). Water (20 mL) and DMF (or DMF-d7) (10 mL) were added and the reaction mixture was stirred vigorously (1,300 rpm) at 80 °C for the time specified. The reaction mixture was extracted with ethyl acetate (3 × 20 mL), and then the combined organic layers were washed with water and brine, dried over Na2SO4, and concentrated in vacuo. Purification of the product 2c was carried out by PTLC.

(2a'R*,4aS*,9bS*)-9b-phenyl-2a,2a1,3,4,4a,9b-hexahydro-2,4-methanobenzo[5,6]indenono[7,1-bc]furan-5(2H)-one [2c(H)]: Colorless solid; mp 160–161 °C; IR (KBr) 2921, 1678, 1102, 1037 cm⁻¹; 1H-NMR (CDCl3): δ 1.44–1.50 (m, 2H), 1.55–1.61 (m, 1H), 1.67–1.70 (m, 1H), 3.02 (dd, J = 2.0, 4.2, 10.4 Hz, 1H), 3.13 (dd, J = 4.3, 10.4 Hz, 1H), 4.64 (dd, J = 6.1, 6.1 Hz, 1H), 6.71–6.76 (m, 1H), 7.09 (br, 1H), 7.32–7.41 (m, 5H), 7.82 (br, 1H), 8.03–8.07 (m, 1H); 13C-NMR: δ 199.54, 145.46, 144.74, 133.61, 133.17, 129.48, 128.29, 127.97, 127.19, 127.10, 126.78, 83.75, 80.33, 50.66, 49.18, 48.01, 39.39, 38.03, 36.99; HRMS m/z Calcd for C21H18O2: 302.1307. Found: 302.1310.

(2a'R*,4aS*,9bS*)-10-deuterio-9b-phenyl-2a,2a1,3,4,4a,9b-hexahydro-2,4-methanobenzo[5,6]indenono[7,1-bc]furan-5(2H)-one [2c(D)]: 1H-NMR (CDCl3): δ 1.44–1.47 (m, 2H), 1.67–1.70 (m, 1H), 2.81–2.84 (m, 1H), 2.92 (d, J = 3.4 Hz, 1H), 3.02 (dd, J = 4.3, 10.4 Hz, 1H), 3.13 (dd, J = 4.2, 10.4 Hz), 4.63 (d, J = 5.1 Hz, 1H), 6.71–6.75 (m, 1H), 7.09 (br, 1H), 7.32–7.42 (m, 5H), 7.81 (br, 1H), 8.03–8.06 (m, 1H); 2H-NMR (CDCl3): δ 1.59 (s, 1D); HRMS m/z Calcd for C21H17DO2: 302.1370. Found: 302.1365.

4. Conclusions

In conclusion, the hydroalkoxylation catalyzed by Au:PVP proceeds via an anti-addition mechanism as same as hydroamination from toluenesulfoamidine. As a result, the formal behavior of Au:PVP resembles that of the cationic Au(I) complex catalyst, well-known to be a soft π-Lewis acid, even though Au:PVP is negatively charged and performs under basic conditions [33]. Therefore the Au:PVP catalyst system may be expected to be useful in new reactions, similar to those of cationic Au(I) catalysts, but which are only accessible under basic conditions.

Acknowledgements

Financial support from NEDO is gratefully acknowledged.

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