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Reversal of Regioselectivity in Wacker-Type Oxidation of Simple Terminal Alkenes and Its Paired Interacting Orbitals (PIO) Analysis

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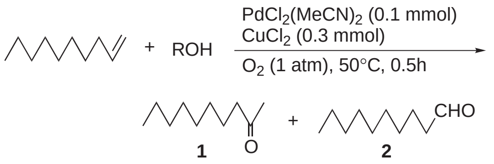
The trend of aldehyde selectivity observed in the oxidation of 1-decene with $PdCl_2(CH_3CN)_2/CuCl_2$ in alcohol (ROH) under O_2 can be evaluated by the overlap populations for Pd–C and C–OR bonds in the oxypalladation step with paired interacting orbitals (PIO) analysis. The use of *t*-BuOH affords decanal in 84% regioselectivity.

Simple terminal alkenes such as 1-decene, when treated with $PdCl_2$ in water under O_2, give methyl ketones.[1] No aldehydes are formed via the nucleophilic attack of H_2O at terminal olefinic carbon. To get aldehydes from non-branched 1-alkenes is a challenging subject in the chemistry of the Wacker reaction.[2] In 1993, Wenzel reported that 1-octene was oxidized to octanal in *t*-BuOH by a catalyst system of $PdCl_2(CH_3CN)_2$, $CuCl_2$, and LiCl, where the regioselectivity was 57% in 1% chemical yield.[3] This is the only document so far reported. Our present study shows that, under the conditions similar to those of Wenzel, the bulkiness of alcohols as the nucleophile is evidently responsible for the formation of aldehyde. However, a notion of alcohol bulkiness is one factor governing the regioselectivity. The other important one is the ease of Pd–C bond formation. We report here that this insight is given by the paired interacting orbitals (PIO) analysis, a simple device of molecular orbital calculation, which clarifies local characteristics of the bond-forming step.[4]

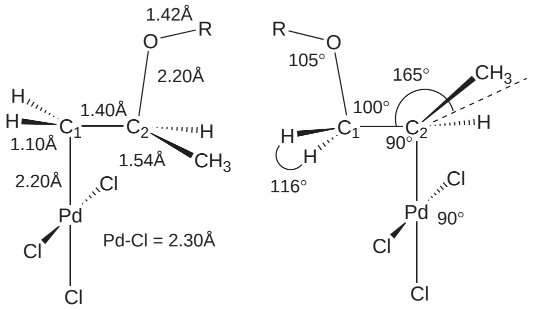
At first, we found that a higher aldehyde selectivity could be attained in *t*-BuOH by using a simple combination of $PdCl_2(CH_3CN)_2$ and $CuCl_2$ (1:3). The use of LiCl and/or CuCl reduced the regioselectivity. The experimental procedure is as follows. A suspension of $PdCl_2(CH_3CN)_2$ (0.1 mmol), $CuCl_2$ (0.3 mmol), and alcohol (1 mL) was stirred at room temperature for 0.5 h under O_2 (balloon), and then a solution of 1-decene (1 mmol) in alcohol (1 mL) was added. After the resulting solution was stirred at 50 °C for 0.5 h under O_2 (balloon), the reaction was stopped by adding hexane (1 mL) and ether (1 mL). The products were analyzed by GLC using tridecane as the internal standard. The results given in Scheme 1 show that increasing the bulkiness of alcohol increases the regioselectivity for aldehyde formation. In the case of MeOH, only a little decanal was formed, and the C=C bond isomerization of 1-decene occurred.[5] The use of *t*-BuOH gives decanal in 84% regioselectivity (0.5 h). In this case, virtually no C=C bond isomerization took place.



R	Yield / %	**1 : 2**
Me	26	97 : 3
Et	22	84 : 16
i-Pr	11	58 : 42
t-Bu	7	16 : 84

Scheme 1.

With these observations in hand, our attention was directed toward verifying the efficacy of PIO analysis developed by Fujimoto.[4] The PIO analysis is a method for unequivocally determining the orbitals which should play dominant roles in chemical interactions between two fragments A and B. This method provides not only visualization of bond-forming step as the orbital phase, but also the suitability of the bond formation is evaluated by the value of overlap population (OP). The PIO analysis based on the extended Hückel method can be readily carried out by software called LUMMOX™ recently developed by Sumitomo Chemical Co., Ltd in Japan.[4c,6] Among the studies of PIO analysis made by Fujimoto, fruitful insights have been given on the stereochemistry of the Wacker reaction, where the structural model was constructed by ethene, $PdCl_3^-$, and OH^-.[4a] For our present analysis, this Fujimoto model was slightly modified, as shown in Fig. 1. The modifications are as follows. (i) Propene was chosen instead of 1-decene for simplifying calculation. (ii) The bond length of newly formed C–OR bond was selected as 2.20 Å.[7] (iii) The bond lengths for propene C_2–CH_3 and O–C bond of alkoxy group (OR) are selected to be 1.54 and 1.42 Å, respectively, as the usual values. Other bond lengths and angles are taken from the values of Fujimoto model.[4a] Shown in Fig. 1 are the models for methyl ketone (model **1**) and aldehyde (model **2**), each of which corresponds to the reaction model



model **1** (ketone) model **2** (aldehyde)

Fig. 1. Reaction models for methyl ketone (model **1**) and aldehyde (model **2**).

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Table 1. Total Overlap Population (ΣOP) of All Paired Interacting Orbitals in Models **1** and **2**

	Model **1** (ketone)			Model **2** (aldehyde)		
	ΣOP			ΣOP		
R	Pd–C	C–OR	$\Sigma\Sigma$OP	Pd–C	C–OR	$\Sigma\Sigma$OP
Me	+0.112	−0.087	**+0.025**	+0.003	−0.028	−0.025
Et	+0.112	−0.088	**+0.024**	+0.003	−0.033	−0.030
i-Pr	+0.112	−0.105	**+0.007**	+0.003	−0.052	−0.049
t-Bu	+0.104	−0.669	−0.564	+0.003	−0.090	**−0.087**

for oxypalladation step. Subsequent Pd–H elimination leads to vinyl ether, which reacts with ROH to afford acetal.[8] The acetal or vinyl ether thus formed could be attacked by water generated in situ to yield methyl ketone or aldehyde.[3,8b,9] In any case, the regioselectivity is determined in the stage of oxypalladation.

Since the reaction occurs via the formation of two bonds of Pd–C and C–OR as depicted in Fig. 1, calculations were performed for two sets of A and B in each model, i.e., A/B = $PdCl_3$/remaining and OR/remaining for Pd–C and C–OR bond, respectively. The total overlap populations (ΣOP) of all PIOs deduced in each model are summarized in Table 1.[10] At first glance, one can see that ΣOP values for Pd–C are all positive, whereas all ΣOP values for C–OR are negative. Namely, the overlap interaction between Pd and C is favorable, whereas the C–OR bond is repulsive. In other words, the formation of Pd–C takes place effectively, but not for C–OR. The PIO analysis also shows that the negative value (overlap repulsion) for C–OR increases with increasing the steric hindrance of OR group toward propene moiety.

The overlap population of each PIOs reflects the extent of electron delocalization between two fragments of A and B. The larger the overlap population, the more smoothly the bond formation occurs. In the case of MeOH, the overlap population of C–OR in model **1** (ketone) is smaller than that in model **2** (aldehyde), indicating that the model **1** leading to methyl ketone is less likely. Thus, the preferential formation of methyl ketone observed is not justified by the value of C–OR. Compensation by the positive overlap population of Pd–C is required for it. The same trend is also seen with EtOH and *i*-PrOH. In the case of *t*-BuOH, inversely, the C–OR bond formation is important in determining the regioselectivity, because the very large negative value of C–OR is not compensated by the positive value of Pd–C. Obviously, model **1** is not preferable in this case. In short, the PIO analysis explicitly shows that the present reaction is controlled by the competitive nature of positive and negative overlap populations with revealing their characteristics.

The above considerations allow us to propose that the sum ($\Sigma\Sigma$OP) of ΣOP value for Pd–C and C–OR can formally serve as the indicator of the reaction pathway. Since $\Sigma\Sigma$OP value of +0.025 with MeOH in model **1** (ketone) is larger than that of −0.025 in model **2** (aldehyde), methyl ketone is produced. In the case of *t*-BuOH, $\Sigma\Sigma$OP of −0.087 in model **2** is larger than that of −0.564 in model **1**. Thus, aldehyde becomes the major product. The same trend is again confirmed with EtOH and *i*-PrOH. The reactivity of ROH appears to correlate with the $\Sigma\Sigma$OP value, albeit not exactly.

In summary, the present study shows the following results. (1) The formation of Pd–C bond in the oxypalladation step is facile. (2) The relative ease for making Pd–C and C–OR bond at either C_1 or C_2 is responsible for the regioselectivity. (3) The PIO analysis clarifies the local characteristics of the bond-forming step in the present reaction. We believe that these facts must contribute to the organic chemistry of palladium as parts of fundamental information.

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2 For related references, see: a) T. Hosokawa, S. Aoki, M. Takano, T. Nakahira, Y. Yoshida, and S.-I. Murahashi, *J. Chem. Soc., Chem. Commun.*, **1992**, 1559. b) T. Hosokawa and S.-I. Murahashi, *Acc. Chem. Res.*, **23**, 49 (1990). c) T. Hosokawa and S.-I. Murahashi, “Handbook of Organopalladium Chemistry for Organic Synthesis,” ed by E.-i. Negishi, John Wiley & Son, New York (2002), Vol. II, pp. 2141–2159.

3 T. Wenzel, *J. Chem. Soc., Chem. Commun.*, **1993**, 862.

4 a) H. Fujimoto and T. Yamasaki, *J. Am. Chem. Soc.*, **108**, 578 (1986). b) H. Fujimoto, *Acc. Chem. Res.*, **20**, 448 (1987). c) http://www.rsi.co.jp/kagaku/cs/pio/

5 In the case of MeOH, ~24% of 1-decene was isomerized to 2- and 3-decene (5:1) under the conditions described in the text, and a mixture of 3- and 4-decanone (~1:1) was formed in ~22% yield for 0.5 h. Similar trends were observed with EtOH. However, in the cases of *i*-PrOH and *t*-BuOH, virtually no isomerization of 1-decene occurred in 0.5 h.

6 T. Motoki and A. Shiga, *J. Comput. Chem.*, **25**, 106 (2003).

7 The distance of C–OR bond was changed from 2.40 to 1.80 Å by the interval of 0.20 Å, and calculations for the extended Hückel energies of the interacting system C, which was constructed by fragment A (propene + $PdCl_3^-$) and fragment B ($^-$OMe or $^-$O-*t*-Bu), were performed. As the result, the distance of 2.20 Å was selected as appropriate by judging the value of $\Delta E = E_C - (E_A + E_B)$, where the symbols of E_C, E_A, and E_B represent the extended Hückel energies of C, A, and B noted above. The bond lengths and angles in alkoxy groups (OR) were taken from the usual values, such as C–C = 1.54 Å and H–C–H = 109.5°.

8 a) T. Hosokawa, T. Ohta, S. Kanayama, and S.-I. Murahashi, *J. Org. Chem.*, **52**, 1758 (1987). b) T. Hosokawa, Y. Ataka, and S.-I. Murahashi, *Bull. Chem. Soc. Jpn.*, **63**, 166 (1990). c) T. Hosokawa, T. Yamanaka, M. Itotani, and S.-I. Murahashi, *J. Org. Chem.*, **60**, 6159 (1995).

9 As the reaction proceeds, water or hydroperoxypalladium(II) formed in situ must attack the alkene to induce the ketonization (see Ref. 8b). In fact, the relative formation of decanal in *t*-BuOH decreased with reaction time; e.g., **1**/**2** = 29/71 in 12% yield for 1 h.

10 For the analysis with MeOH, one H atom of methyl group was placed on the plane perpendicular to the plane containing C=C bond, and the C–OMe bond of this conformer was then rotated by 180°. Between these two conformers thus formed, the extended Hückel energies (E_C) of the interacting system (see Ref. 7) were compared, and the more stable conformer was selected. The

ΣOP value listed in Table 1 was taken from that of the more stable conformer. For the analysis with *t*-BuOH, the same treatment as above was performed by replacing H atom with Me group. For the analysis with EtOH and *i*-PrOH, one H atom of Et or *i*-Pr was placed on the same position as that in the case of MeOH. The C–OR bond (R = Et or *i*-Pr) was then rotated by the interval of 60°. When the extended Hückel energies (E_C) of 6 conformers thus formed were compared, it was found that 2 or 3 conformers among them were highly stable and that their stabilities were not much different. Thus, the ΣOP values for EtOH and *i*-PrOH listed were deduced by averaging the ΣOP values of these 2 or 3 conformers.