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Palladium and Copper-Catalyzed Carboxylation of Alkanes with Carbon Monoxide. Remarkable Effect of the Mixed Metal Salts

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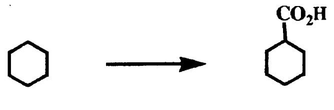
The mixed catalyst Pd(OAc)$_2$–Cu(OAc)$_2$ promotes the carboxylation of cyclohexane and propane with CO in higher yield than either a Pd(II) or Cu(II) catalyst alone. The mixed catalyst has the highest activity when the ratio of Cu(II)/Pd(II) is more than unity. The carboxylations of *p*-xylene with Pd(II)–Cu(II) and Pd(II) afford 2,5-dimethylbenzoic acid, but no carboxylic acid is detected in the reaction with Cu(II), giving rise to *p*-xylene dimer as the major product instead. Clear isotope effect (3.0—3.2) is observed in the reactions of cyclohexane with Pd(II)–Cu(II) and Pd(II), unlike the reaction with Cu(II) (1.0).

Alkane activation and functionalization by transition metal catalysts or metal enzymes have been much explored in the last decade.[1] Previously, we have reported carboxylation reaction of alkanes with CO catalyzed by palladium(II) in the presence of potassium peroxodisulfate and trifluoroacetic acid.[2] This system has good reactivity for secondary C–H bonds, but more effective catalysts are needed for the reaction of alkanes with no methylene unit, such as methane and ethane. When the reaction is carried out in an autoclave with a glass lining, the yield of carboxylic acids decreases comparing with the corresponding reaction without the lining. Thus, we have investigated the effect of metal additives in the catalytic system to overcome these limitations and found that a palladium–copper mixed catalyst had high catalyst activity in the carboxylation of alkanes.[3] This paper gives a detailed account of the carboxylation reaction of cyclohexane and propane catalyzed by the mixed catalyst and some mechanistic information.

Results and Discussion

The effect of metal additives on the reaction of cyclohexane with the palladium(II) acetate–potassium persulfate–trifluoroacetic acid system was investigated (Eq. 1; Table 1). Of the additives tested, the reaction with copper(II) acetate gave cyclohexanecarboxylic acid (**1**) in the highest yield (Run 7). Advantageously, benzoic acid, the by-product, was not formed by the Pd(II)–Cu(II) mixed system, in contrast to the previous reaction.[2]



1 (1)

Control reactions with one or two of the three metal salts [Pd(II), Cu(II), and K$_2$S$_2$O$_8$] were tried to identify their roles in the carboxylation of cyclohexane (Table 2). Palladium (II) and copper(II) acetates gave little or no cyclohexanecarboxylic acid (**1**), respectively, in the absence of the oxidant (Runs 1,2, and 4).[4] Potassium peroxodisulfate alone produced **1** only in 0.3% yield based on cyclohexane (Run 3); the yield was increased slightly by the addition of Pd(II) or Cu(II) (Runs 5 and 6). The highest yield was obtained with the three metals (Run 7).

Carboxylation of propane with CO under similar conditions gave isobutyric and butylic acid (**2**) and (**3**)

Table 1. Effect of Metal Additives on the Carboxylation of Cyclohexane[a)]

Run	Additive	Yield of **1**(%)[b)]
1	None	260 (0.6)
2	Fe	257 (0.6)
3	FeCl$_2$	324 (0.7)
4	FeCl$_3$	237 (0.5)
5	Co(OAc)$_2$	90 (0.2)
6	Ni(OAc)$_2$	82 (0.2)
7	Cu(OAc)$_2$	1981 (4.3)
8	Zn(OAc)$_2$	62 (0.1)

a) Conditions: cyclohexane (5 ml), Pd(OAc)$_2$ (0.1 mmol), additive (0.2 mmol), K$_2$S$_2$O$_8$ (9 mmol), TFA (3.3 ml), CO (20 atm), 80 °C, 20 h. b) GC yield based on Pd(OAc)$_2$ (based on cyclohexane).

Table 2. Effect of Pd(OAc)$_2$, Cu(OAc)$_2$, and K$_2$S$_2$O$_8$ on the Carboxylation of Cyclohexane[a)]

Run	Pd(OAc)$_2$ mmol	Cu(OAc)$_2$ mmol	K$_2$S$_2$O$_8$ mmol	Yield of **1** %[b)]
1	0.1	—	—	0.3 (6.5×10^{-4})
2	—	0.2	—	0
3	—	—	9.0	1.7 (0.3)
4	0.1	0.2	—	0.1 (2.2×10^{-4})
5	0.1	—	9.0	260 (0.6)
6	—	0.2	9.0	148 (0.6)
7	0.1	0.2	9.0	1981 (4.3)

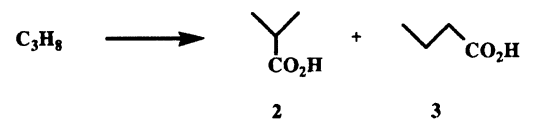
a) Conditions: cyclohexane (5 ml), TFA (3.3 ml), CO (20 atm), 80 °C, 20 h. b) GC yield based on the limiting metal salt (based on cyclohexane).

Table 3. Synthesis of Isobutyric and Butyric Acid (**2** and **3**) from Propane[a]

Run	$Pd(OAc)_2$	$Cu(OAc)_2$	$K_2S_2O_8$	Product and Yield (%)[b]	
	mmol	mmol	mmol	**2**	**3**
1	0.05	0.05	9.0	5500 (6.7)	1600 (2.0)
2	0.05	—	9.0	1400 (1.7)	360 (0.4)
3	—	0.05	9.0	1300 (1.5)	600 (0.7)
4	—	—	9.0	1.5 (0.3)	0.9 (0.2)

a) Conditions: propane (10 atm), CO (20 atm), TFA (5 ml), 80 °C, 20 h. b) GC yield based on the limiting metal salt (based on propane).

(Eq. 2; Table 3). The Pd(II)–Cu(II) mixed catalyst gave superior result to Pd(II) and Cu(II) catalysts (Run 1 vs. 2 and 3). Acids **2** and **3** were formed in the absence of the catalysts at a low yield (Run 4). These results are consistent with those obtained in the carboxylation of cyclohexane.



(2)

The Pd(II)–Cu(II) mixed catalyst promoted carboxylation very effectively, so this system was examined under various conditions for investigation of the mechanism. First, the reactions of cyclohexane and propane were monitored as functions of time (Fig. 1). In the reaction of propane, the total yield of acids **2** and **3** increased rapidly within 20 h and became constant after this time. A similar result was obtained in the reaction of cyclohexane.

Then the effect of Cu(II) was studied in the reactions of propane and cyclohexane for 5 and 20 h with Pd(II) constant (Figs. 2 and 3). When the ratio of Cu(II) to Pd(II) was less than unity, the yields of **1** and (**2**+**3**) were low at both reaction times. Interestingly, their yields increased with the use of equimolar amounts of Cu(II). However, an excess of Cu(II) caused no or little increase in the products.

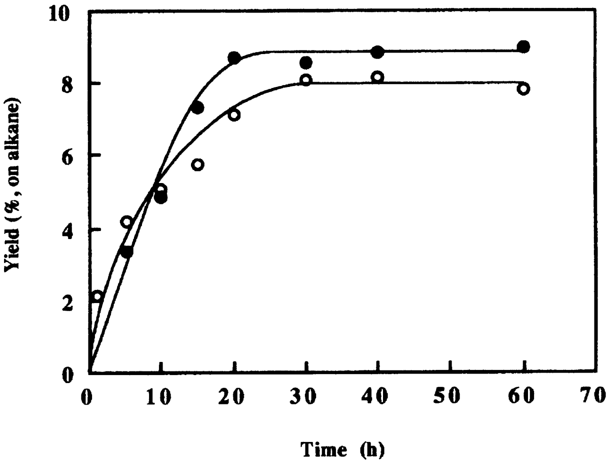


Fig. 1. Yields of carboxylic acids **1** (○) and **2**+**3** (●) versus time: Pd(II)–Cu(II) (0.02 mmol each for **1** and 0.05 mmol each for **2**+**3**).

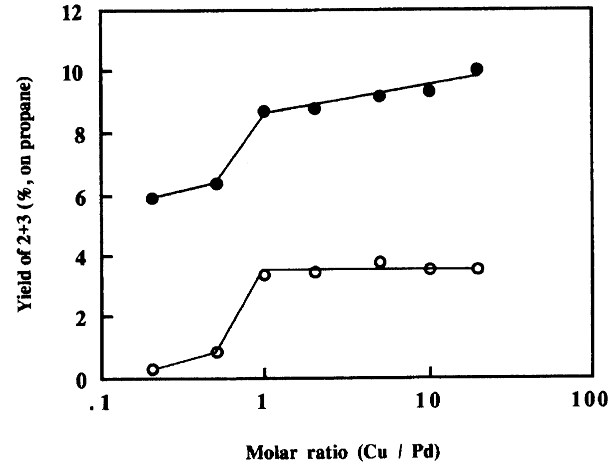


Fig. 2. Plot of the total yield of isobutyric and butyric acid (**2** and **3**) against the molar ratio of $Cu(OAc)_2$ to $Pd(OAc)_2$: (○) 5 h; (●) 20 h, Pd(II) (0.05 mmol).

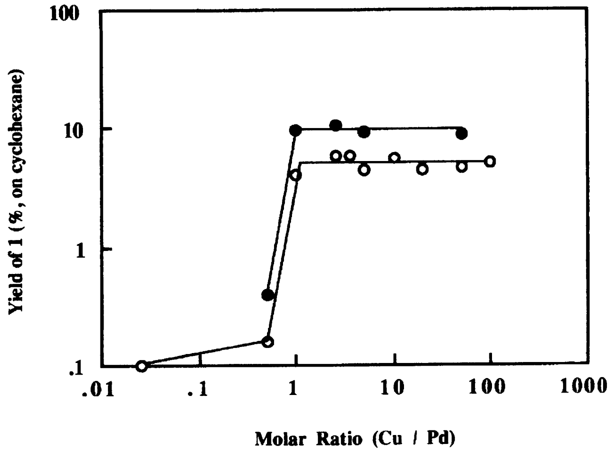


Fig. 3. Plot of the yield of cyclohexanecarboxylic acid (**1**) against the molar ratio of $Cu(OAc)_2$ to $Pd(OAc)_2$: (○) 5 h; (●) 20 h, Pd(II) (0.02 mmol).

On the contrary, the total yield of acids **2** and **3** in the 5-h reaction of propane was plotted against the molar ratio of Pd(II) to Cu(II) with a constant amount of Cu(II) (Fig. 4). The yield increased as the ratio increased and reached a maximum when the ratio was unity. After that, the yield decreased as the ratio in-

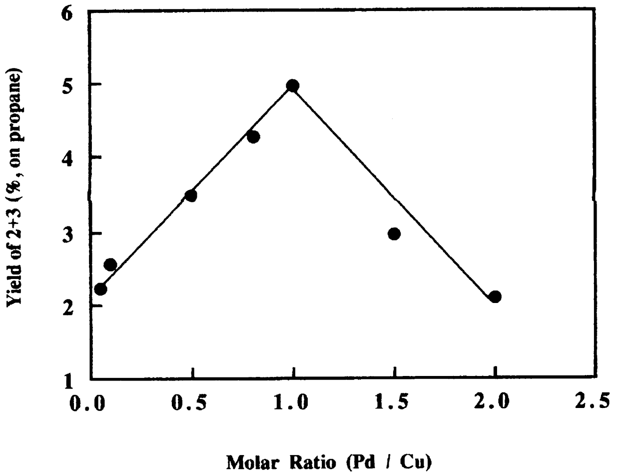


Fig. 4. Plot of the total yield of isobutyric and butyric acid (**2** and **3**) against the molar ratio of $Pd(OAc)_2$ to $Cu(OAc)_2$: Cu(II) (0.5 mmol), 5 h.

creased. Side reactions of products **2** and **3** were not the reason for the decrease, since they were recovered unchanged quantitatively after treatment with Pd(II) or Pd(II)–Cu(II) (1 : 1 and 2 : 1) under similar conditions.

The effect of $K_2S_2O_8$ on the carboxylation of propane for 5 and 20 h was investigated (Fig. 5). In the 5-h reaction, the total yield of **2** and **3** increased as the oxidant increased at low concentrations, but it became nearly constant when a large amount of $K_2S_2O_8$ was used. A similar phenomenon was observed in the 20-h reaction. These results indicate that the reaction proceeds at a constant reaction rate until about 40% of the oxidant has been consumed. That is, the reaction rate does not depend on the concentration of the oxidant, at least within 20 h.

C–H bond activation of cyclohexane and propane was promoted by various combinations of Pd(II), Cu(II), and $K_2S_2O_8$ as shown in Tables 2 and 3 although the yields were vastly changed. Thus, the carboxylation of *p*-xylene was studied in order to distinguish the reaction mechanisms, because exclusive activation of the benzylic C–H by radical reaction and of the aromatic C–H by electrophilic substitution reaction could be expected. The results are summarized in Table 4 (Eq. 3) In the reaction with the Pd(II)–Cu(II) mixed system, 2,5-dimethylbenzoic acid (**4**) was formed in 15730% yield based on Pd(II) together with a trace of by-product tentatively identified as *p*-xylene dimer[5)] (Run 1). However, *p*-tolylacetic acid was not detected by GC or NMR. The ratio of **4** : **5** was 92 : 8, calculated from the intensity of the methyl signals in ^{13}C NMR. A similar result was obtained in the reaction with Pd(II), although at a lower yield (Run 2). On the other hand, carboxylic acids were not formed in the reaction with Cu(II) and $K_2S_2O_8$ alone (Runs 3 and 4). Instead, these reactions afforded mixtures of many products, in which dimer **5** was detected as the major compound. These results indicate that an electrophilic reaction is brought about by the Pd(II)–Cu(II) and Pd(II) catalysts and that only a radical reaction is at work with the Cu(II) and $K_2S_2O_8$ systems. In the latter two reactions (Runs 3 and 4), rapid reaction of the benzylic radical with another molecule of *p*-xylene would hinder the formation of *p*-tolylacetic acid, unlike in the reaction of cyclohexane and propane.

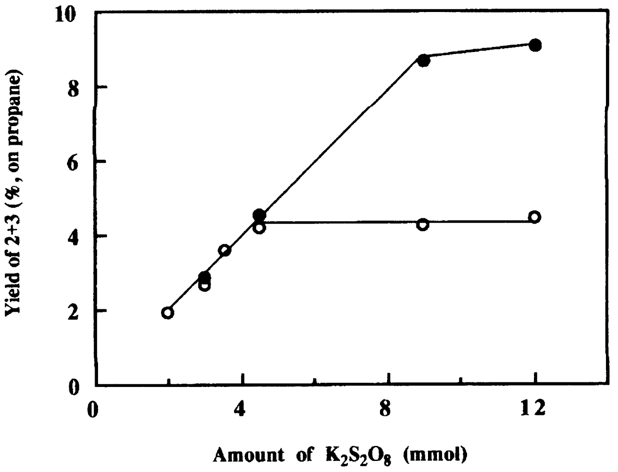
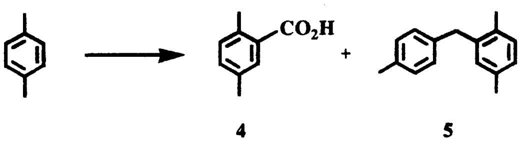


Fig. 5. Plot of the total yield of isobutyric and butyric acid (**2** and **3**) against the amount of $K_2S_2O_8$: (○) 5 h; (●) 20 h, $Pd(OAc)_2$–$Cu(OAc)_2$ (0.05 mmol each).



(3)

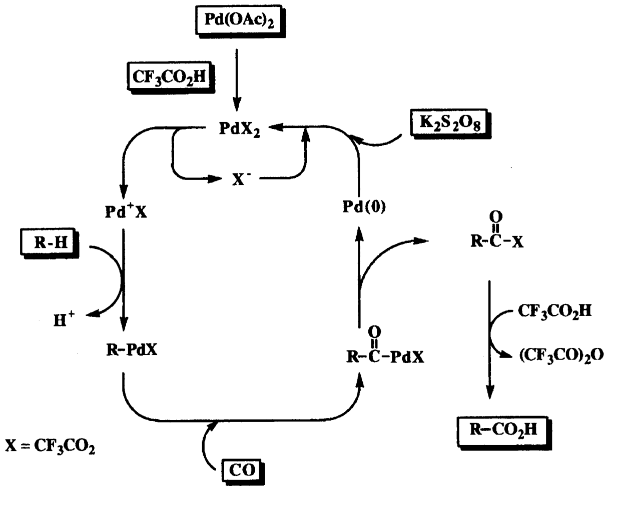
The mechanistic difference between the reaction with Pd(II)–Cu(II) or Pd(II), and that with Cu(II) was also suggested by isotope effects. When a mixture of equimolar amounts of cyclohexane and cyclohexane-d_{12} was treated with the Pd(II)–Cu(II) mixed catalyst under CO, cyclohexanecarboxylic acid (**1**) and the corresponding acid-d_{11} were formed in the ratio of 3.2 : 1.0. A similar ratio (3.0 : 1.0) was obtained in the reaction with Pd(II). The reaction with Cu(II) gave the two acids in equal yields. On the basis of these results, C–H bond cleavage is the rate-determining step in the former two reactions but not in the reaction with Cu(II).

Electrophilic carboxylation by the Pd(II) system might be explained as follows (Scheme 1). Palladium (II) acetate changes to trifluoroacetate in TFA solvent, the electrophilic attack of which on the alkane C–H gives an alkyl-Pd(II) σ complex. Then CO insertion followed by reductive elimination affords a reactive mixed anhydride (RCOX), which is converted to the alkanecarboxylic acid together with the formation of trifluoroacetic anhydride. In fact, an amount of the anhydride equimolar to the carboxylic acids was detected by GC before aqueous work up. Palladium(0) is reoxidized with $K_2S_2O_8$, and thus the catalytic cycle is

Table 4. Reaction of *p*-Xylene[a)]

Run	$Pd(OAc)_2$ mmol	$Cu(OAc)_2$ mmol	$K_2S_2O_8$ mmol	Product and Yield (%)[b)] 4	5	Ratio of 4 : 5[c)]
1	0.02	1.0	9.0	15730 (7.7)	Trace	92 : 8
2	0.1	—	9.0	1726 (4.2)	Trace	93 : 7
3	—	0.1	9.0	0	Major[d)]	0 : 100
4	—	—	9.0	0	Major[d)]	0 : 100

a) Conditions: *p*-xylene (5 ml), TFA (3.3 ml), CO (20 atm), 80 °C, 20 h. b) GC yield based on the limiting metal salt (based on *p*-xylene). c) Determined by ^{13}C NMR. d) Many other products were detected by GC.



Scheme 1.

completed. Accordingly, the net reaction can be represented as Eq. 4. In Scheme 1, rapid reaction of the σ complex with CO seems to be a critical point for successful carboxylation, since the reaction of cyclohexane in the absence of CO gave an untractable mixture in which cyclohexyl trifluoroacetate, a product expected by Sen's system,[6)] was not detected. Interestingly, this mixture exhibited the same peaks in GC as did a mixture obtained in the reaction of cyclohexene under identical conditions, suggesting that β-hydride elimination of the σ-complex and subsequent reactions would take place.[7)]

$$\text{R-H} + \text{CO} + K_2S_2O_8 + 2CF_3CO_2H \rightarrow \text{R-}\overset{\overset{\text{O}}{\|}}{\text{C}}\text{OH} + 2KHSO_4 + (CF_3CO)_2O \qquad (4)$$

With respect to the reaction with Pd(II)–Cu(II), the results in the reaction of *p*-xylene and the isotope effect suggest that the alkane C–H bond is cleaved, probably by palladium in a mechanism similar to Scheme 1, not by copper. In this catalytic system, Pd(II) would be activated by an equimolar amount of Cu(II), and therefore the carboxylation gives an excellent yield. This hypothesis is consistent with excess Cu(II) to Pd(II) not increasing the yield as shown in Figs. 2 and 3. Excess Pd(II) to Cu(II) decreases the yield, as observed in Fig. 4, because the activation of Pd(II) would be insufficient in spite of the increase in the total amount of Pd(II).[8)] However, it is unclear whether Pd(II) is activated by the formation of a 1 : 1 complex with Cu.[9)]

In the reaction with Cu(II), the radical reaction may be predominant. Thus, decomposition of $K_2S_2O_8$ followed by hydrogen abstraction affords an alkyl radical,[10)] which reacts with CO to give the alkanecarboxylic acid via an acyl radical.[11)]

In summary, the Pd(II)–Cu(II) mixed catalyst has higher activity in the carboxylation of alkanes with CO than does a Pd(II) or Cu(II) catalyst. The use of Cu(II) in more than an equimolar amount to Pd(II) is necessary for high yield. Thus, cyclohexane and propane are converted to the corresponding carboxylic acids in good yields without by-products. The reaction with the mixed catalyst is likely to proceed via an electrophilic mechanism similar to that with Pd(II) but different from that with Cu(II).

Experimental

IR spectra were recorded with a Perkin–Elmer 1600-FT apparatus. NMR spectra were obtained on a JEOL JNM-FX90A and a JNM-270. Mass spectra were taken with a Shimadzu GCMS QP-1000. GC analyses were performed on a Shimadzu GC-14A equipped with TCD or FID and 1 m×3.2 mm i. d. and 5 m×3.2 mm i. d. columns of 5% OV-17 or 10% polyethylene glycol 6000 on Chromosorb W. Cyclohexane and *p*-xylene were distilled over LAH. Palladium(II) acetate and copper(II) acetate were dried under reduced pressure prior to use. Propane and carbon monoxide were purchased from Sumitomoseika, and were used as received. Trifluoroacetic acid and potassium peroxodisulfate were purchased from Wako Chemical, and were used without purification.

General Procedure for Carboxylation with $Pd(OAc)_2$–$Cu(OAc)_2$. A 50-ml centrifuge glass tube equipped with a teflon-covered magnetic stirring bar was charged with $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $Cu(OAc)_2$ (3.6 mg, 0.02 mmol), and CF_3CO_2H (3.3 ml). The solution was stirred for 5 min. Then cyclohexane or *p*-xylene (5 ml) and $K_2S_2O_8$ (2.43 g, 9.0 mmol) were added to the solution. A rubber septum with a glass needle was fitted to the tube, which was placed in a 100-ml stainless autoclave. The autoclave was closed and pressurized to 20 atm with CO. The mixture was heated at 80 °C for 20 h with stirring. After cooling and venting of the residual gas, the autoclave was opened and the mixture was filtered. The precipitate was washed with benzene. The filtrate was diluted with 2 M HCl (1 M=1 mol dm^{-3}), extracted with benzene, and washed with brine. The aqueous layer was extracted further with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and concentrated in vacuo.

In the reaction of propane, 5 ml of TFA was used and 10 atm of propane was admitted to the autoclave. The reaction mixture was analyzed directly without aqueous work up.

Identification of Products and Determination of Yield. The products were readily identified by comparison of GC, MS, NMR, and IR spectra with those of the commercially available authentic samples. The yields were determined by GC with hexadecane and valeric acid as internal standards.

Isotope Effect on the Carboxylation of Cyclohexane. A mixture of cyclohexane (780 mg, 9.27 mmol) and cyclohexane-d_{12} (892 mg, 9.27 mmol) was treated with $Pd(OAc)_2$ (4.5 mg, 0.02 mmol)–$Cu(OAc)_2$ (36 mg, 0.2 mmol), $Pd(OAc)_2$ (45 mg, 0.2 mmol) or $Cu(OAc)_2$ (36 mg, 0.2 mmol) under conditions similar to those described above. The ratios of **1** to **1**-d_{11}, determined by mass spectra, were 3.2, 3.0, and 1.0, respectively.

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4) Rapid reduction of Pd(II) to Pd(0) with CO takes place (Runs 1 and 4), but Cu(II) remains unchanged by ESCA analyses (Runs 2 and 4).

5) GC-MS m/z 210 (M^+); ^{13}C NMR ($CDCl_3$) $\delta=19.1$ (CH_3), 20.9 (CH_3), 38.9 (CH_2); one methyl signal may be obscured.

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8) UV spectra of $Pd(OAc)_2$–$Cu(OAc)_2$ in TFA depend on the ratio of Cu/Pd. That is, λ_{max} of Pd(II) is 406 (ratio 0), 375 (0.5), 369 (1.0), and 369 nm (2.0), respectively. The catalyst activity is currently investigated by spectroscopic methods, which will be reported elsewhere.

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