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Hydrolysis of Alkenyl Esters and Ethers Catalyzed by Metal Complexes

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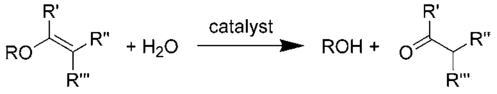
ABSTRACT



R = acyl, alkyl
catalyst = Pd^{II}, Pt^{II}, Hg^{II}, Cu^{II}, Ru^{II}, Co^{III}, Sc^{III}

Various kinds of transition metals catalyzed the hydrolysis of alkenyl esters and ethers under buffer-free, high concentration conditions compared to usual biocatalysts. Hydrolytic kinetic resolution of *cis*-2-*tert*-butylcyclohexyl vinyl ether was achieved by chiral (salen)Co complexes with good selectivity (k_{rel} = 10.0).

Utilization of water as a reagent as well as a solvent is an important topic in synthetic organic chemistry. Because hydration and hydrolysis of organic molecules are among the most common and fundamental reactions, transition metal catalysts have enabled much innovative progress in recent years. For example, we opened up a door to direct transformation of 1-alkynes into aldehydes by Ru^{II}-catalyzed hydration.[1] It has been long known as a textbook example that the hydration follows Markovnikov's rule to give ketones as a sole product. In addition, Co(salen)-catalyzed hydrolysis of 1-epoxides[2] to chiral epoxides and diols realized a solvent- and buffer-free process. This reaction is now applied to industrial processes,[3] with several practical advantages over biocatalysts especially in the product isolation and volumetric productivity.[4]

Asymmetric ester hydrolysis is an unexplored area for transition metal catalysis where biocatalysts play a predominant role both in laboratory and industry because of their high enantioselectivity. Furthermore, many kinds of biomimetic artificial catalysts have been developed for enzyme model studies;[5] however, they are not useful for practical synthesis since activated substrates such as nitrophenyl esters have been mainly employed[5b] under diluted conditions in the presence of buffer salt.

We are interested in vinyl (alkenyl) esters and ethers as substrates for hydrolysis because of their high availability and low preparation cost.[6] Little attention has been given to metal-catalyzed hydrolysis of them, and no systematic studies have been made, whereas acid-catalyzed hydrolysis has been

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(1) (a) Tokunaga, M.; Wakatsuki, Y. *Angew. Chem.* **1998**, *110*, 3024−3027; *Angew. Chem., Int. Ed.* **1998**, *37*, 2867−2869. (b) Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* **2001**, *3*, 735−737. (c) Tokunaga, M.; Suzuki, T.; Koga, N.; Fukushima, T.; Horiuchi, A.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 11917−11924. (d) Wakatsuki, Y.; Hou, Z.; Tokunaga, M. *Chem. Rec.* **2003**, *3*, 144−157.

(2) (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938. (b) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780−10781. (c) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315. (d) Ready, J. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1374−1377. (e) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691−1693.

(3) Stinson, S. C. *Chem. Eng. News* **2000**, *78*, 55−78.

(4) (a) Finney, N. S. *Chem. Biol.* **1998**, *5*, R73− R79. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. (c) Blaser H.-U. *Chem. Commun.* **2003**, 293−296.

(5) (a) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146−152. (b) Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145−152. (c) Zhang, B.; Breslow, R. *J. Am. Chem. Soc.* **1997**, *119*, 1676−1681. (d) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997−2011.

(6) Okimoto, Y.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1590−1591 and references therein.

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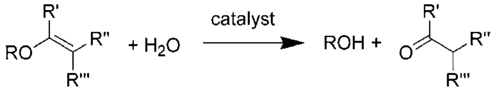
frequently used.[7] In this paper we report a transition metal catalyzed method for the hydrolysis of alkenyl esters and ethers (Scheme 1), as well as a preliminary result of its application to asymmetric reaction.

Scheme 1



We compared catalytic activities of various metal complexes in the hydrolysis of vinyl benzoate **1a** and benzyl vinyl ether **2a** (Table 1). Reactions were carried out in a 1 M solution of substrates with 1.5 equiv of water at 40 °C with 1−5 mol % catalyst under atmospheric air. 2-Propanol was used as solvent for **1a** because alcoholic solvents gave highest reaction rates. However, acetonitrile with excess water (5 equiv) was used as standard condition for **2a**. Although alcoholic solvents also gave higher rates, some of the catalysts listed in Table 1 produce acetal byproducts in alcohol. Complexes of Pd^{II}, Pt^{II}, and Hg^{II} were found to be highly effective catalysts (entries 1−8). Especially, $PdCl_2(MeCN)_2$ provided highest activity; both substrates **1a** and **2a** are hydrolyzed completely in 1 h (entry 1). The highest turnover number, 5000, was achieved with this complex: 100 mmol of **1a** (50 wt % in 2-propanol) was hydrolyzed with 0.02 mmol catalyst and 1.4 equiv of water in 18 h at 60 °C to give quantitative yield of benzoic acid. $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ showed lower activities, and a Pd^0 complex did not catalyze the reaction at all (entries 2−4). $HgSO_4$ exhibited comparable activity with $PdCl_2(MeCN)_2$ (entry 6). Other metal complexes, such as **3a**, **3b**, $CuCl_2$, $Cu(OTf)_2$, $[RuCl_2(C_6H_6)]_2$, and $Sc(OTf)_3$, gave moderate activities (entries 9−14). Noteworthy is that **3a**, **3b**, $Cu(OTf)_2$, and $Sc(OTf)_3$ only catalyzed the hydrolysis of the ether **2a**, the ester **1a** remaining intact with them (entries 9, 10, 12, and 14). Under argon atmosphere, **3a** showed much lower activity (8% yield at 40 h, cf. entry 9 with **2a**) than under air, while **3b** remained active even under Ar (72% yield at 18 h, cf. entry 10 with **2a**). Accordingly, the active species seems to be Co^{III} even when **3a** was employed as a catalyst precursor,[2] which appeared to be gradually oxidized to Co^{III} under air. The ether **2a** was easily hydrolyzed with HCl, while the ester **1a** did not change (entry 15). Acetic acid did not catalyze the reaction at all under the condition (entry 16).

Table 1. Hydrolysis of Vinyl Benzoate **1a** and Benzyl Vinyl Ether **2a** Catalyzed by Various Metal Complexes

		1a[a]			**2a**[b]		
entry	catalyst	catalyst (mol %)	*t* (h)	yield (%)[c]	catalyst (mol %)	*t* (h)	yield (%)[d]
1	$PdCl_2(MeCN)_2$	1	1	>99	1	1	>99
2	$PdCl_2(PPh_3)_2$	1	72	tr	1	24	98
3	$Pd(OAc)_2$	1	2	27	1	23	89
4	$Pd(PPh_3)_4$	1	24	0	1	24	0
5	$PtCl_2(MeCN)_2$	1	40	>99	1	6	85
6	$HgSO_4$	1	1	>99	1	1	90
7	$Hg(OCOCF_3)_2$	5	19	>99	1	1	94
8	$Hg(OAc)_2$	5	18	tr	1	120	92
9	Co(salen) **3a**	1	24	0	1	41	73
10	Co(OAc)(salen) **3b**	1	24	0	1	16	79
11	$CuCl_2$	5	16	>99	1	2	93
12	$Cu(OTf)_2$	5	24	0	1	18	87
13	$[RuCl_2(C_6H_6)]_2$	2.5	24[e]	>99	0.5	120	84
14	$Sc(OTf)_3$	5	24	tr	1	2	87
15	HCl	2	24	0	0.2	1	90
16	CH_3COOH				100	48	tr
17	none		1	0		1	0

[a] The reaction was carried out at 40 °C with **1a** (1 mmol), 1.5 equiv of H_2O, and catalyst in 2-PrOH (1 mL) under atmospheric air. [b] At 40 °C with **2a** (1 mmol), 5 equiv of H_2O in acetonitrile (1 mL) under atmospheric air. [c] Yield of benzoic acid was determined by ^1H NMR where mesitylene was used as internal standard. [d] GC yield of benzyl alcohol. [e] At 80 °C.

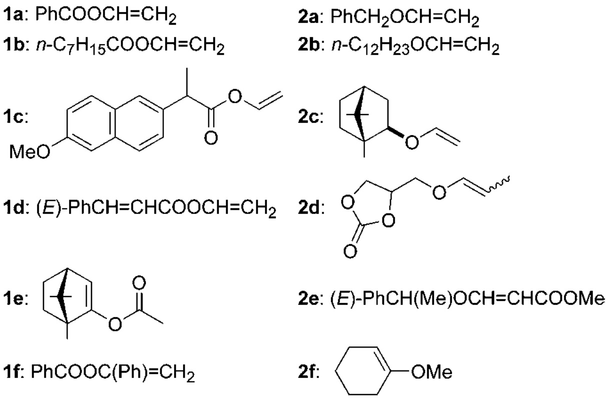


Figure 1. Alkenyl esters **1** and ethers **2** for Table 2.

To explore the substrate generality, we examined various kinds of alkenyl esters **1b**−**f** and ethers **2b**−**f** (Figure 1) using $PdCl_2(MeCN)_2$ as catalyst (Table 2). Vinyl esters of aliphatic acids and conjugated acids gave the products quantitatively (entries 1−3). Enol esters bearing a substituent on vinyl group required higher temperature and catalyst loadings to be hydrolyzed (entries 4 and 5). Vinyl and 1-propenyl ethers of aliphatic alcohol reacted smoothly to give products (entries 6−8). An electron-withdrawing substituent ($COCH_3$) on vinyl group made the reaction slower (entry 9). On the other hand, the methyl enol ether of cyclohexanone reacted very fast (entry 10).

A simple mechanistic study of the present Pd^{II}-catalyzed hydrolysis of vinyl ester has been made with ^{18}O-labeled water. The ester **1a** was hydrolyzed with 1 mol % $PdCl_2(CH_3CN)_2$ and 8 equiv of $H_2{}^{18}O$ (∼95 atm %) at 20 °C in THF. The FD-MS spectrum indicates a $^{16}O/^{18}O$ ratio of 5/95 for acetaldehyde and >99/1 for benzoic acid. It suggests that a nucleophilic attack of water occurs at the α-position of vinyl group to form hydroxymetalated species. A possible catalytic

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[7] Hg, Tl, and Brønsted acid catalyzed hydrolysis of vinyl esters and ethers: (a) Kresge, A. J. *Acc. Chem. Res.* **1987**, *20*, 364−370. (b) Euranto, E. K. *Pure Appl. Chem.* **1977**, *49*, 1009−1020. (c) Gigg, R.; Warren, C. D. *J. Chem. Soc.* C **1968**, 1903−1911. Hydrolysis of 1-propenyl ethers with 20 mol % $Pd^{II}-Cu^I/O_2$: (d) Mereyala, H. B.; Lingannagaru, S. R. *Tetrahedron* **1997**, *53*, 17501−17512.

Table 2. Hydrolysis of Various Alkenyl Esters and Ethers with Pd Catalyst[a]

entry	substrate	solvent	T (°C)	t (h)	yield (%)[b]
1	**1b**	2-PrOH	40	1	>99[d] (97)
2	**1c**	2-PrOH	40	1	>99[d] (97)
3	**1d**	2-PrOH	40	1	>99[d] (92)
4	**1e**	2-PrOH	80	24	93[e] (87)
5[c]	**1f**	THF	80	72	72[e] (66)
6	**2b**	THF	40	1	99[f] (98)
7	**2c**	MeCN	40	1	96[f] (92)
8	**2d**	MeCN	40	2	99[d] (99)
9	**2e**	MeCN	40	21	74[f] (73)
10	**2f**	MeCN	40	1	96[e] (86)

[a] The reaction was carried out with substrate (1 mmol), H_2O (1.5 equiv in entries 1−5, 5 equiv in entries 6−10), and $PdCl_2(MeCN)_2$ (1 mol %) in 1 mL of solvent under atmospheric air. [b] Isolated yields of 3 mmol scale reactions in parentheses. [c] 5 mol % catalyst was used. [d] Yield of carboxylic acid or alcohol was determined by ^1H NMR where mesitylene was used as internal standard. [e] GC yield of ketone. [f] GC yield of alcohol.

cycle for the Pd^{II}-catalyzed hydrolysis of vinyl esters is shown in Figure 2.

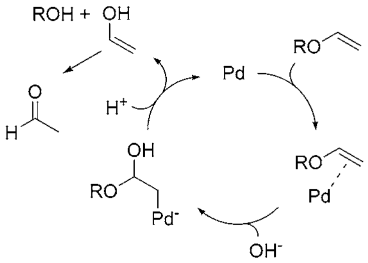


Figure 2. A possible catalytic cycle of hydrolysis of vinyl esters with Pd^{II} complexes.

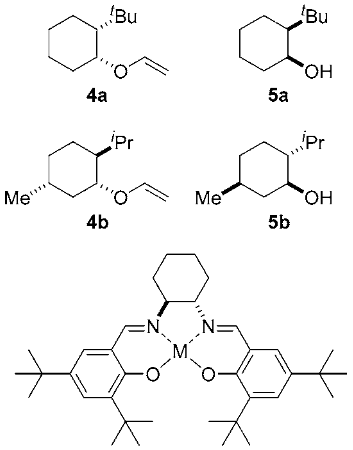
Finally, we tried to apply the reaction to the kinetic resolution of chiral substrates. A number of entries that arise from the combination of several chiral ligands, metals, and substrates were examined for asymmetric reaction. So far, the Co complexes **3** were found to be effective for kinetic resolution of some chiral vinyl ethers, while more active complexes of Pd^{II}, Pt^{II}, and Hg^{II}, such as $PdCl_2$((*R*)-binap),[8] gave low selectivities ($k_{rel} < 2.0$). Hydrolysis of *cis*-2-*tert*-butylcyclohexyl vinyl ether **4a** and DL-menthyl vinyl ether **4b** were performed in the presence of 5 mol % **3** (Table 3). Alcoholic solvent was adequate with regard to reactivity and selectivity in this system. The reaction of **4a** proceeded with moderate selectivity ($k_{rel} = 4.9$) with **3b** at 20 °C in methanol (entry 1), and a higher k_{rel} value of 7.4 was observed at −10 °C (entry 2). The Co^{II} complex **3a** showed slightly higher k_{rel} of 5.8 at 20 °C compared to **3b**, but the reaction was sluggish (entry 3, cf. entry 1). The best result were obtained with a catalyst prepared from **3a** and 2,4-dinitrophenol (entries 4 and 5, k_{rel} 5.4 at 20 °C and 10.0 at −10 °C), where some active Co^{III}-phenoxide species appeared to be generated. On the other hand, a slightly different condition was found to be suitable for **4b**. The hydrolysis reaction with catalyst **3b** in 2-propanol gave the highest k_{rel} value of 7.8 (entry 9). The reactions in methanol (entries 6 and 7) and under the optimum condition for **4a** gave lower k_{rel} values.

Table 3. Hydrolytic Kinetic Resolution of Vinyl Ethers **4** Catalyzed by Co Complexes **3**

$$rac\text{-}\mathbf{4} + H_2O \xrightarrow[\text{alcoholic solvent}]{\text{5 mol\% } (S,S)\text{-}\mathbf{3}} \mathbf{4} + \mathbf{5}$$

entry	substrate	catalyst	T (°C)	t (h)	conv (%)[a]	ee of **4** (%)[b]	k_{rel}[c]
1[d]	**4a**	**3b**	20	11	77 (22)[g]	92[h]	4.9
2[d]	**4a**	**3b**	−10	103	68	91[h]	7.4
3[d]	**4a**	**3a**	20	140	75	94[h]	5.8
4[d]	**4a**	**3a**[f]	20	10	73	90[h]	5.4
5[d]	**4a**	**3a**[f]	−10	77	62	90[h]	10.0
6[d]	**4b**	**3b**	20	1	73	58[i]	2.5
7[d]	**4b**	**3b**	−10	2	88	76[i]	2.3
8[e]	**4b**	**3b**	20	3	68	79[i]	4.9
9[e]	**4b**	**3b**	−10	10	68 (28)[g]	92[i]	7.8

[a] Determined by GC. [b] The value of unreacted substrate determined by GC with chiral column. [c] k_{rel} was calculated as a first-order reaction in substrate using the equation ln[(1 − conv)(1 − ee)]/ln[(1 − conv)(1 + ee)]. [d] Methanol was used as solvent. [e] 2-Propanol was used as solvent. [f] 5 mol % of 2,4-dinitrophenol and **3a** were stirred in toluene under 1 atm air at room temperature for 1 h, and then solvent was removed. The obtained solid was used as catalyst. [g] Isolated yield of unreacted substrate. [h] (*R*,*R*)-isomer. [i] (1*R*,2*S*,5*R*)-isomer.



3a: M = Co
3b: M = Co(OAc)

Figure 3. Substrate **4**, product **5**, and catalyst **3** for Table 3.

Kinetics experiments were performed with benzyl vinyl ether **2a** (0.7 M) and 15 equiv of H_2O using **3b** as catalyst

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[8] Ozawa, F.; Kudo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188−4196.

(0.25−1.5 mol %) in 2-propanol at 40 °C, which revealed a first-order dependence on concentration of **3b**. The result makes a clear contrast to the epoxide hydrolysis by **3b**[2], in which the reaction follows a second-order dependence on **3b** and a bimetallic mechanism has been proposed.

In conclusion, we have established a novel buffer-free hydrolysis method of alkenyl esters and ethers with metal complex catalysts. We have also demonstrated a hydrolytic kinetic resolution of chiral vinyl ethers **4a** and **4b** employing the Co complexes **3**. In general, transition metal catalyzed reactions are easier to perform with a high concentration of substrate than biocatalytic reactions.[4c] Since a wide variety of metals exhibited activity for the reaction, there is great potential for the asymmetric synthesis of alcohols, carboxylic acids, and ketones. The development of more effective and selective process for asymmetric synthesis is in progress.

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C spectral, and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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