

# Metal complexes-catalyzed hydrolysis and alcoholysis of organic substrates and their application to kinetic resolution

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## Abstract

Metal complexes-catalyzed hydrolysis and alcoholysis of organic substrates such as alkenyl esters, alkenyl ethers, and azlactones (oxazol-5(4*H*)-ones) are described. These reactions were applied for kinetic resolution of chiral compounds and high selectivities were achieved with vinyl ethers of 2-substituted cyclohexanols, 1,1'-bi-2-naphthols, 1,1'-bi-2-phenols, and 4,4-disubstituted azlactones. Oxidative carbon–carbon bond cleavage reactions, which were found in the course of the study of asymmetric hydrolysis were also described. © 2006 Elsevier B.V. All rights reserved.

*Keywords:* Hydrolysis; Alcoholysis; Kinetic resolution; Vinyl ethers; Azlactones

## 1. Introduction

Hydrolysis of organic compounds is one of the most fundamental reaction in organic chemistry, therefore many methods have been developed using homogeneous and heterogeneous catalysts, biocatalysts, basic reagents, and others. Since the first stereoselective hydrolysis reaction was developed employing pancreatic enzymes in early 1900s, biocatalytic hydrolysis has made a significant advancement and applied in the industrial production of optically active compounds [1]. In contrast, little progress has been made in the area of stereoselective hydrolysis using homogeneous metal complex catalysts. In this context discovery of Co(salen)-catalyzed asymmetric hydrolysis of terminal epoxides [2] is a breakthrough, which realized solvent- and pH buffer-free process, possessing extremely high volumetric productivity. Therefore a number of applications have been made both in laboratory scale synthesis and industrial productions [2c]. On the other hand, stereoselective hydro-

lysis of organic molecules other than epoxides still remains undeveloped.

In recent years we have carried out the research on hydration [3], hydrolysis [4], and alcoholysis [5] reactions by means of metal-complex catalysts. We have developed transition metal-catalyzed stereoselective hydrolysis and alcoholysis of alkenyl esters, alkenyl ethers [4,5a], and azlactones [5b]. Efficient kinetic resolutions of these substrates with high selectivities ( $k_{rel}$  up to 41) have been achieved.

## 2. Metal-catalyzed hydrolysis of alkenyl esters and ethers

The goal of this study is stereoselective hydrolysis of alkyl esters such as methyl and ethyl esters. However, these substrates have been recognized as a difficult target due to their low reactivity. Alkenyl esters and ethers including vinyl esters and ethers have somewhat higher activity for hydrolysis with acid catalysis or basic reagent. Nevertheless, small numbers of examples are known for metal-catalyzed hydrolysis of them and no systematic studies have been made. Thus, the catalytic activities of various metal

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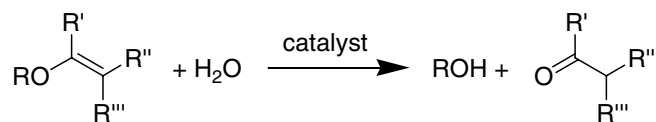
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complexes for the hydrolysis of vinyl benzoate (**1**) and benzyl vinyl ether (**2**) were compared (Table 1) [4]. Reactions were carried out in 1 M solution of substrates at 40 °C with 1–5 mol% catalyst. Alcoholic solvents gave the highest reaction rates in both substrates but small amount of acetal by-products were formed from the ether so that little excess water (5 equiv) in acetonitrile was used to prevent this side reaction (Scheme 1).

Generally, benzyl vinyl ether (**2**) reacted faster than the vinyl benzoate (**1**). Under the condition, hydrochloric acid hydrolyzed **2** but did not hydrolyze **1**, and acetic acid did not catalyze the reaction in both substrates (Table 1, entries 1 and 2). Complexes of Pd<sup>II</sup>, Pt<sup>II</sup>, and Hg<sup>II</sup> were found to be highly effective catalysts for the reaction (entries 4–11). Especially PdCl<sub>2</sub>(MeCN)<sub>2</sub> and HgSO<sub>4</sub>, provided the highest activity, both substrates hydrolyzed in 1 h (entries 4 and 9), while Pd<sup>0</sup> did not catalyze the reaction at all (entry 7). Acetate complexes, Pd(OAc)<sub>2</sub> and Hg(OAc)<sub>2</sub>, showed lower activity than chloride, sulfate, and trifluoroacetate (entries 6 and 11). Other metals, such as Co<sup>II</sup>, Co<sup>III</sup>, Cu<sup>II</sup>, Ru<sup>II</sup>, and Sc<sup>III</sup> also gave moderate catalytic activities (entries 12–17). The cobalt complex **3b** (Co<sup>III</sup>(OAc)(salen)) exhibited higher activity than **3a** (Co<sup>II</sup>(salen)) (Fig. 1).

An optimization study for the highest turnover number with PdCl<sub>2</sub>(MeCN)<sub>2</sub> for the reaction of **1** was made (Scheme 2). The TON value reached 5000 under the condition of 50% (w/w) concentration of substrate. The hydrolysis of **1** in 2-propanol using 0.02 mol% catalyst with 1.4 equiv. of H<sub>2</sub>O was completed within 42 h at 60 °C to give quantitative yield of benzoic acid.

The substrate generality was studied with various alkenyl esters and ethers with PdCl<sub>2</sub>(MeCN)<sub>2</sub> as catalyst. Vinyl esters of aliphatic and aromatic acids gave the products quantitatively under the same condition for **1** in Table 1.



Scheme 1. Hydrolysis of alkenyl esters and ethers catalyzed by metal complexes.

Enol esters, which have substituent on vinyl group, required higher temperature and catalyst loadings to be hydrolyzed. Vinyl and 1-propenyl ether of aliphatic alcohols reacted smoothly to give corresponding alcohols under the same condition for **2** in Table 1. An electron withdrawing substituent (COOMe) on vinyl group made the reaction slower. On the other hand, methyl enol ether of cyclohexanone reacted very fast (Fig. 2).

A hydrolysis reaction using <sup>18</sup>O-labeled water was examined. The ester **1** was hydrolyzed using 1 mol% PdCl<sub>2</sub>(MeCN)<sub>2</sub> and 8 equiv. of H<sub>2</sub><sup>18</sup>O (~95 atm%) at 20 °C in THF. The <sup>16</sup>O/<sup>18</sup>O ratio was 5/95 for acetaldehyde and was >99/1 for benzoic acid. It suggests that a nucleophilic attack of water occurs at α-position of vinyl group to form hydroxymetalated species like Wacker oxidation or alkyne hydration. This makes contrast to usual ester hydrolysis in which the carbonyl carbon undergoes the attack of water (Scheme 3).

### 3. Application to asymmetric reaction: kinetic resolution of vinyl ethers of cyclohexanol derivatives by hydrolysis

In most cases, hydrolysis reaction does not generate a new chiral center, and hence asymmetric hydrolysis reactions catalyzed by biocatalysts usually treat with chiral substrates. Thus, the reactions turn out to be kinetic resolution

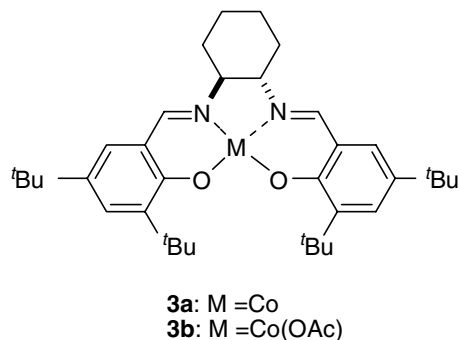
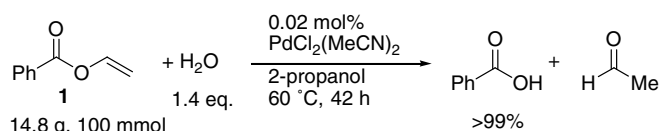
Table 1  
Hydrolysis of vinyl benzoate (**1**) and benzyl vinyl ether (**2**) catalyzed by various metal complexes

Entry	Catalyst	<b>1</b> <sup>a</sup>			<b>2</b> <sup>b</sup>		
		Cat. (mol%)	Time (h)	Yield (%)	Cat. (mol%)	Time (h)	Yield (%)
1	HCl	2	24	0	0.2	1	90
2	CH <sub>3</sub> COOH	–	–	–	100	48	Trace
3	None	–	1	0	–	1	0
4	PdCl <sub>2</sub> (MeCN) <sub>2</sub>	1	1	>99	1	1	>99
5	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub>	1	72	Trace	1	24	98
6	Pd(OAc) <sub>2</sub>	1	2	27	1	23	89
7	Pd(PPh <sub>3</sub> ) <sub>4</sub>	1	24	0	1	24	0
8	PtCl <sub>2</sub> (MeCN) <sub>2</sub>	1	40	>99	1	6	85
9	HgSO <sub>4</sub>	1	1	>99	1	1	90
10	Hg(OCOCF <sub>3</sub> ) <sub>2</sub>	5	19	>99	1	1	94
11	Hg(OAc) <sub>2</sub>	5	18	Trace	1	120	92
12	Co(salen) ( <b>3a</b> )	1	24	0	1	41	73
13	Co(OAc)(salen) ( <b>3b</b> )	1	24	0	1	16	79
14	CuCl <sub>2</sub>	5	16	>99	1	2	93
15	Cu(OTf) <sub>2</sub>	5	24	0	1	18	87
16	[RuCl <sub>2</sub> (C <sub>6</sub> H <sub>6</sub> ) <sub>2</sub> ]	2.5	24 <sup>c</sup>	>99	0.5	120	84
17	Sc(OTf) <sub>3</sub>	5	24	Trace	1	2	87

<sup>a</sup> The reaction was carried out at 40 °C with **1** (1 mmol), 1.5 equiv. H<sub>2</sub>O, and catalyst in 2-propanol (1 mL) under atmospheric air.

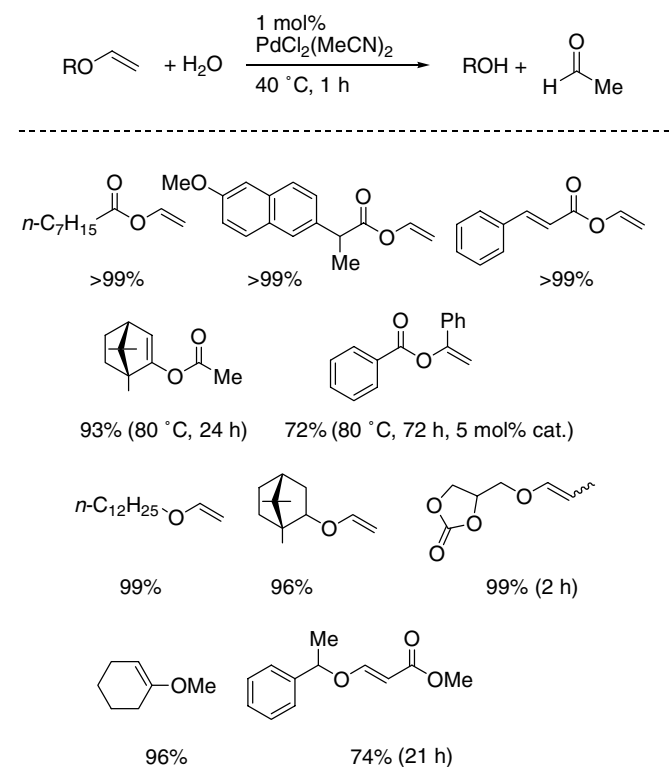
<sup>b</sup> At 40 °C with **2** (1 mmol), 5 equiv. H<sub>2</sub>O in acetonitrile (1 mL) under atmospheric air.

<sup>c</sup> At 80 °C.

Fig. 1. Co(salen) complexes **3**.Scheme 2. Hydrolysis of **1** catalyzed by PdCl<sub>2</sub>(MeCN)<sub>2</sub>.

[2c,6]. In order to develop an asymmetric reaction, we have surveyed combination of several substrates, chiral ligands, and metals.

The cobalt catalysts **3** were found to be effective for hydrolytic kinetic resolution of vinyl ethers of cyclohexanol derivatives [4]. Hydrolysis of *cis*-2-*t*-butylcyclohexyl vinyl ether (**4**) was performed in methanol with 5 mol% Co(OAc)(salen) (**3b**). The reaction proceeded with the moderate selectivity ( $k_{\text{rel}} = 4.9$ ) at 20 °C. Higher  $k_{\text{rel}}$  value

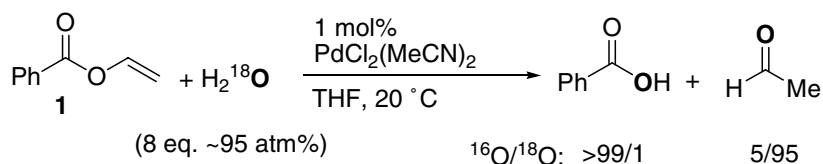
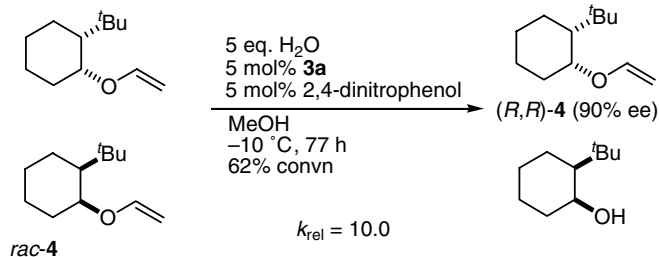
Fig. 2. Hydrolysis of various alkenyl esters and ethers catalyzed by PdCl<sub>2</sub>(MeCN)<sub>2</sub>.

of 7.4 was observed at –10 °C. Then the highest selectivity ( $k_{\text{rel}} = 10.0$ ) was achieved with Co<sup>II</sup>(salen) (**3a**) + 2,4-dinitrophenol at –10 °C: 90% ee of unreacting substrate was obtained at 62% conversion. In this reaction, more active chiral complexes of Pd<sup>II</sup>, Pt<sup>II</sup>, and Hg<sup>II</sup>, such as PdCl<sub>2</sub>((*R*)-binap), gave low selectivities ( $k_{\text{rel}} < 2.0$ ). The present cobalt-catalyzed kinetic resolution was applicable for *dl*-menthyl vinyl ether, but a slightly different condition was found to be suitable. The hydrolysis reaction with catalyst **3b** in 2-propanol gave the highest  $k_{\text{rel}}$  value of 7.8 (Scheme 4).

#### 4. Kinetic resolution of vinyl ethers of axially chiral alcohols

A palladium catalyst system was found to be effective for kinetic resolution of vinyl ethers of axially chiral alcohols such as 1,1'-bi-2-naphthols and 1,1'-bi-2-phenols (**5**) [5a]. The optimized catalyst consists of Pd(OAc)<sub>2</sub> and chiral diamines **7**, which have *trans*-1,2-diaminocyclohexane backbone. An optimization study for *rac*-**5a** revealed that the methanolysis gave higher selectivity than the hydrolysis. The aryl substituent on **7** controls activity and selectivity of the methanolysis reaction. The simplest ligand **7a** gave good  $k_{\text{rel}}$  value (16.5) and moderate reactivity (43% convn at 62 h). At that point 61% ee of (*R*)-**5a** and 81% ee of (*S*)-**6a** were obtained. Ligand **7d** having methyl substituent on the *para*-position of phenyl group exhibited higher  $k_{\text{rel}}$  value (16.0) than **7b** (*meta*-,  $k_{\text{rel}} = 5.8$ ), and **7c** (*ortho*-,  $k_{\text{rel}} = 1.1$ ). Then several kind of substituent at the *para*-position was compared (**7d-h**). A typical bulky group, *t*-butyl group made the reaction sluggish (**7e**: 11% convn at 111 h). Electron withdrawing fluoro group improved the activity (**7f**: 41% convn at 42 h), but slightly lower selectivity ( $k_{\text{rel}} = 13.8$ ) was observed. Phenyl group gave higher  $k_{\text{rel}}$  value (18.3), but this time activity was decreased (**7g**: 35% convn at 61 h). The best performance was achieved with ligand **7h** having 2,3,4,5-tetraphenylphenyl group. The highest  $k_{\text{rel}}$  value (20.3) and activity (58% convn at 61 h) was attained: (*R*)-**5a**, 41.8% yield, 95.8% ee, and (*S*)-**6a**, 58.2% yield, 68.9% ee were isolated. Although the reason of the high performance of 2,3,4,5-tetraphenylphenyl group is unclear, we have reported another example in which the tetraphenylphenyl group showed unique steric effect. In a Pd/pyridines-catalyzed aerobic oxidation of alcohols, catalyst lifetimes were improved considerable extent and the highest turnover number in homogeneous catalysts was achieved with a pyridine having the group at *meta*-position [7] (Fig. 3).

Next various kinds of axially chiral compounds **5b-j** were examined (Fig. 4). The reaction was applicable to all the substrates, giving moderate to high selectivity ( $k_{\text{rel}}$ : 12.1–35.8). In Fig. 4,  $k_{\text{rel}}$  values and the structures of unreacting substrate (**5**: vinyl ethers) or product (**6**: alcohols) were illustrated. The differences in selectivity and reactivity between ligands **7h** and **7a** were again observed. The  $k_{\text{rel}}$  value was decreased from 31.4 to 25.3 when **7a** was used instead of **7h** for the reaction for *rac*-**5e**. Noteworthy is that

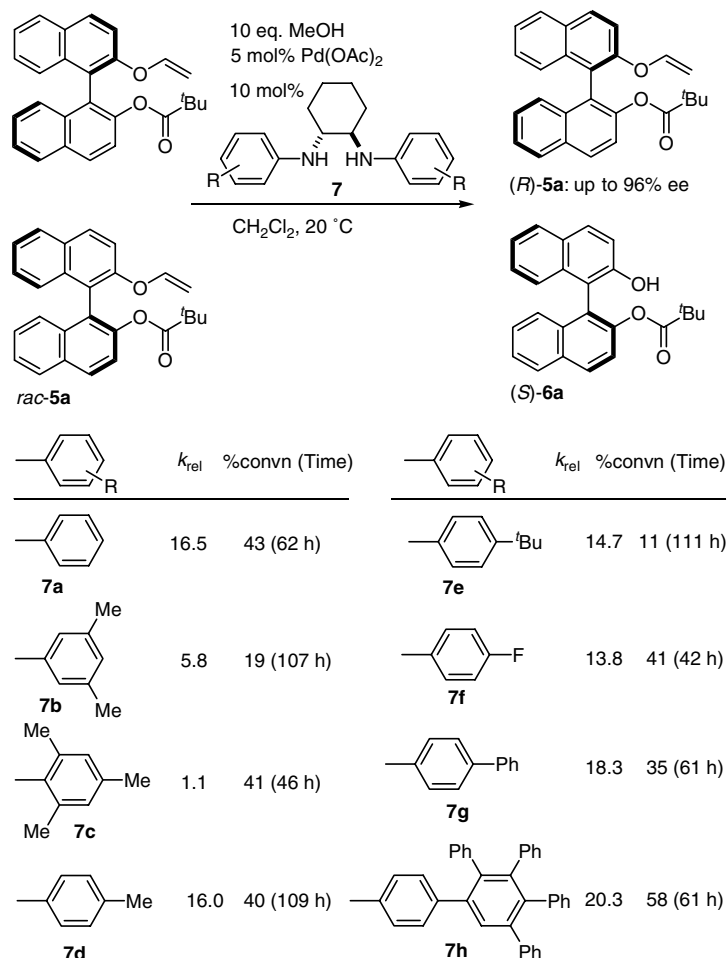
Scheme 3. Hydrolysis of **1** with  $\text{H}_2^{18}\text{O}$  catalyzed  $\text{PdCl}_2(\text{MeCN})_2$ .Scheme 4. Co-catalyzed hydrolytic kinetic resolution of a chiral vinyl ether **4**.

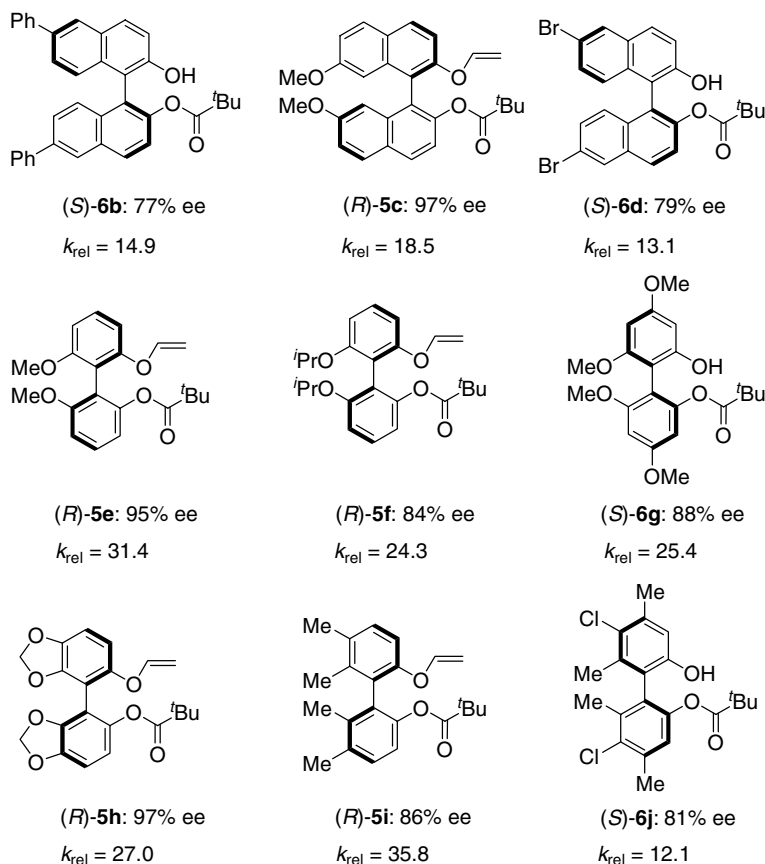
1,1'-bi-2-phenols have been a difficult target in asymmetric synthesis, because enantioselective oxidative coupling to access these class of compounds are only useful in 2-naphthols into 1,1'-bi-2-naphthols but not in phenols into 1,1'-

bi-2-phenols [8]. With regard to alcoholic reagent, although methanol exhibited the best performances in the present alcoholysis reaction in terms of reactivity, the  $k_{\text{rel}}$  value was improved to 41.2 for **5a** by the use of 2-chloroethanol as reagent.

### 5. Kinetic resolution of azlactones by copper-catalyzed alcoholysis

Azlactones (oxazol-5(4*H*)-ones) are heterocyclic compounds which have somewhat higher reactivity for hydrolysis and alcoholysis into amino acid derivatives. Since enantiomerically pure natural and non-natural amino acids have been applied in the synthesis of chiral ligands, catalysts, pharmaceuticals, peptides and many other valuable molecules, their enantioselective synthesis has

Fig. 3. Pd-catalyzed alcoholytic kinetic resolution of *rac*-**5a**.

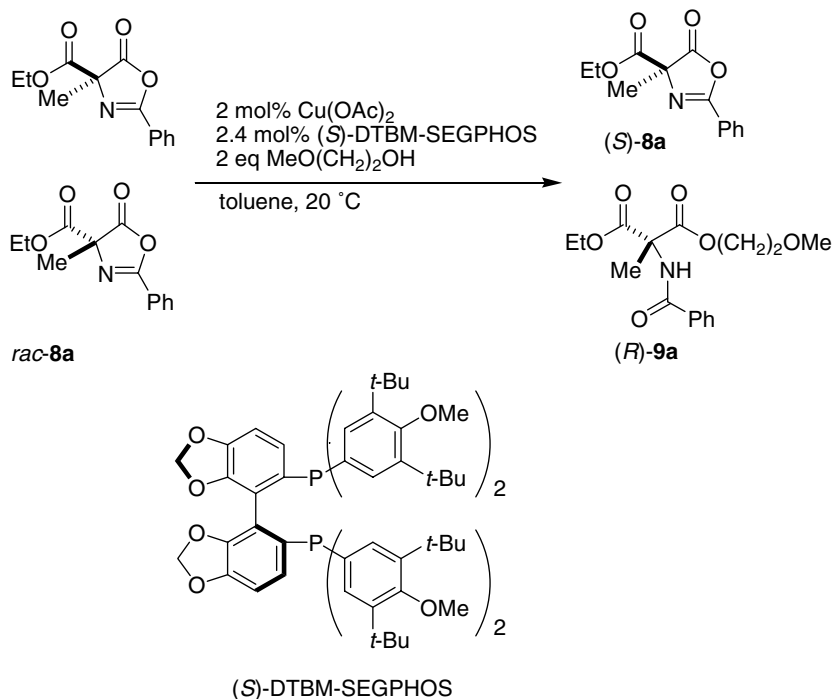
Fig. 4. Pd(OAc)<sub>2</sub>/7h catalyzed alcoholytic kinetic resolution of *rac*-5.

attracted considerable attentions in recent years. Several kinds of asymmetric reactions have been developed including acyl transfer [9c,9h], alkylation [9d,9e,9f], and alcoholysis [9a,9b,9g]. With regard to alcoholysis, although several reports employing organic catalysts have been made but no article has been appeared with metal catalysts. In addition, the reaction of disubstituted azlactones to afford non-natural quaternary amino acid remains undeveloped probably due to its low reactivity. In this context, we have examined the alcoholysis of disubstituted azlactones with homogeneous metal catalysts and found that Cu(OAc)<sub>2</sub>/DTBM-SEGPHOS is an efficient catalytic system for the asymmetric alcoholysis of azlactones **8** (Scheme 5) [5b].

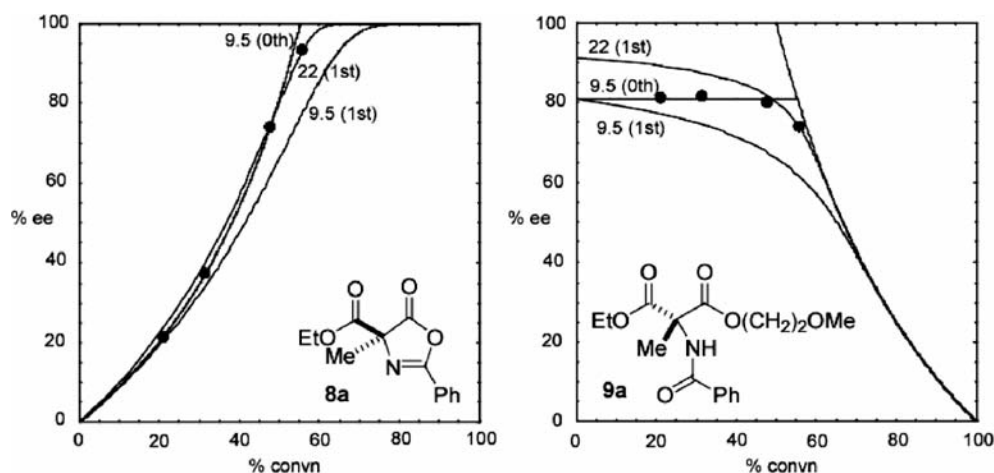
Among the examined alcoholic reagents, 2-methoxyethanol gave the highest selectivity. Table 2 shows the result of asymmetric alcoholysis of **8a** into **9a**. The unreacted (*S*)-**8a** with 93% ee and the product (*R*)-**9a** with 74% ee were obtained at 52 h, 56% conversion (entry 4). The  $k_{rel}$  value was calculated as 6.6 from Eqs. (1) and (2) as a zeroth-order reaction, and 22 from Eqs. (3) and (4) as a first-order reaction [10]. In the early stage of this reaction (entries 1–3), the ee of **8a** increased as 22, 38, then 74% along with the reaction proceeding as 21%, 32%, then 48%, but the ee of **9a** becomes constant around 81%. The  $k_{rel}$  values as first-order reaction change 12, 14, 20, and then 22 for entries 1–4. On the other hand, the  $k_{rel}$  values as zeroth

order becomes constant around 9.5. This result suggests that zeroth order is more appropriate than first order for this reaction. Fig. 5 illustrates the variation of ee of **8a** and **9a** with conversion. The experimental results (dots) coincide well with a simulated line of a zeroth-order reaction ( $k_{rel} = 9.5$ ) both in the case of **8a** and **9a**, but the point at 56% convn slightly deviates from that probably due to the change of the reaction order from zeroth to first (or fractional) order at the final stage. Obviously the simulated line of first-order reaction ( $k_{rel} = 22$ ) does not fit at the early to middle stage of the reaction. Similar experiments were performed with four other substrates and found all reactions follow well with zeroth-order lines. In addition, kinetics experiments with **8a** indicated that the reaction follows zeroth-order dependence on **8a** and first-order dependence on 2-methoxyethanol.

Substrate generality was examined with quaternary azlactones **8b–i**. The reaction was found to be applicable to all the substrates. When the alkyl substituent at 4-position was changed from Me (**8g**) to Et (**8h**), *n*-Pr (**8i**), and *n*-Bu (**8j**), the reactivity and selectivity were decreased. However, electron withdrawing substituent on phenyl group at *para*-position improved both reactivity and selectivity (**8k**). Comparing **8j** with **8k**, *p*-chloro group increased the  $k_{rel}$  from 4.4 to 8.8, and the rate was improved approximately twice. It is noteworthy that 93% ee of unreacted substrates were obtained with **8e** and **8h**, although  $k_{rel}$  was only 5.6

Scheme 5. Cu-catalyzed alcoholytic kinetic resolution of azalactone **8a**Table 2  
Asymmetric alcoholysis of azalactone **8a** with Cu(OAc)<sub>2</sub>/(S)-DTBM-SEGPHOS catalyst<sup>a</sup>

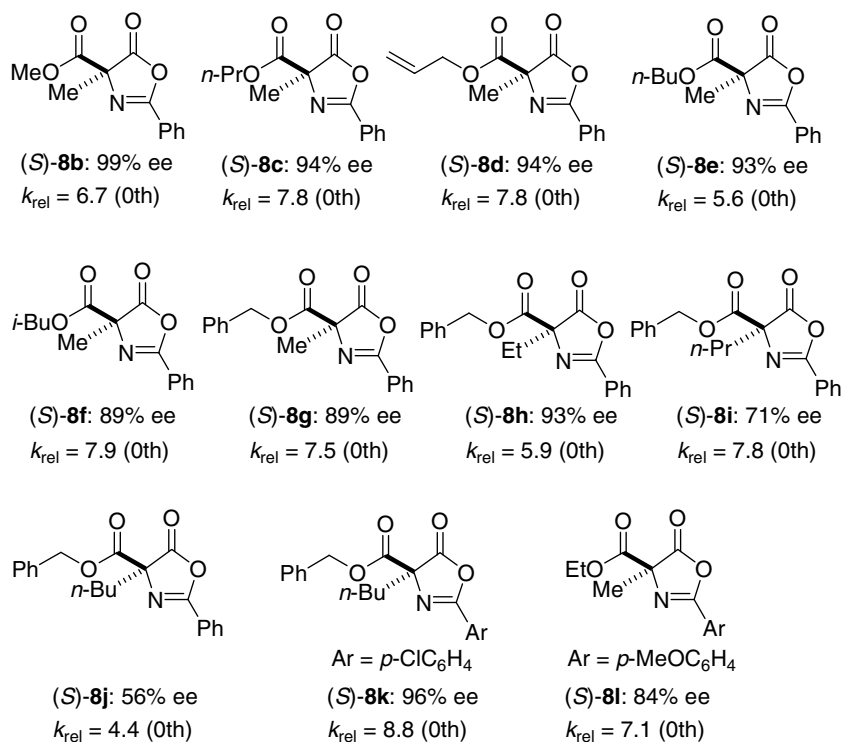
Entry	Time (h)	Conv'n (%)	Ee of <b>8a</b> (%)	Ee of <b>9a</b> (%)	$k_{\text{rel}}$ (0th) <sup>b</sup>	$k_{\text{rel}}$ (1st) <sup>c</sup>
1	8	21	22	81	9.6	12
2	17	32	38	82	9.8	14
3	30	48	74	80	9.1	20
4	52	56	93	74	6.6	22

<sup>a</sup> Conditions: see Scheme 5<sup>b</sup> Calculated by Eqs. (1) and (2) in Ref. [10].<sup>c</sup> Calculated by Eqs. (3) and (4) in Ref. [10].Fig. 5. Kinetic resolution of *rac*-**8a**: experimental values (dots), simulated lines as zeroth-order reaction ( $k_{\text{rel}} = 9.5$ ), and as first-order reaction ( $k_{\text{rel}} = 9.5$  and 22).

and 5.9, which clearly indicates the higher efficiency of zeroth-order kinetic resolution (Fig. 6).

Zeroth-order dependence in substrate is often observed in catalytic reactions, for instance Ru-catalyzed oxidation [11a], Rh-catalyzed hydrogenation [11b], Pd-catalyzed

Heck reaction [11d], alkali metal catalyzed amination of olefins [11e], and needless to say, most cases of enzymatic reactions. When these reactions are applied for a kinetic resolution, it will be easier to achieve higher ee than first-order reactions.

Fig. 6.  $\text{Cu}(\text{OAc})_2$ -(S)-DTBM-SEGPHOS catalyzed alcoholytic kinetic resolution of *rac*-**8**.

## 6. Oxidative cleavage of carbon–carbon bond of enol ethers and aldehydes with molecular oxygen

During the course of the study of asymmetric hydrolysis and alcoholysis of enol ethers using  $\text{CuCl}_2$  as a catalyst, an oxidative C=C bond cleavage reaction was found unexpectedly [12a]. The original purpose of the project was to develop asymmetric hydrolysis of prochiral enol ethers (Scheme 6, lower reaction), however, acetophenone derivatives were found as a by-product (upper reaction). After optimization, the exact control of hydrolysis and C=C bond cleavage was possible by surrounding gas as shown in Scheme 6. A remarkable feature of our reaction system is needless of activated oxygen such as ozone or singlet oxygen.

Interestingly, Brønsted acids also catalyzed the oxidation reaction though the activity was moderate. When 5 mol% HCl was used as a catalyst, hydrolysis of **10** into **12** occurred exclusively. However, 0.5 mol% HCl catalyzed the oxidative cleavage into **11** slowly and afforded a mixture of **11** and **12** (52% and 21%). In addition, 5 mol% *p*-toluenesulfonic acid also gave a mixture of **11** and **12** (64% and 11%) under  $\text{O}_2$  atmosphere, but gave **12** as sole product (95%) under argon atmosphere. In the absence of a catalyst, the reaction did not proceed at all.

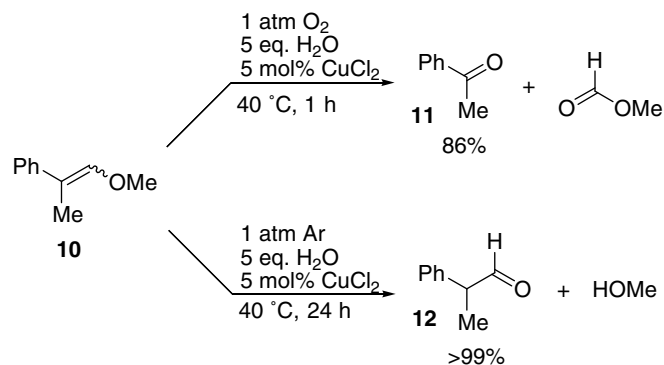
The substrate generality was examined with various aromatic enol ethers (Scheme 7). All the substrates gave acetophenone derivatives in good yields in high selectivity. Electron donating substituents at the *para*-position of the

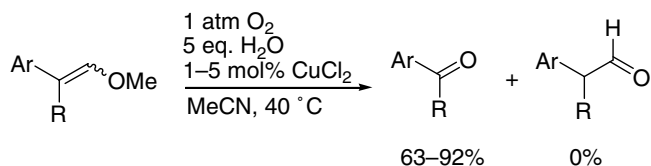
aromatic ring made the reaction faster than electron withdrawing groups.

The oxidative cleavage seems to involve radical cation intermediate generated by Cu(II) via one-electron oxidation, followed by the formation of dioxetane. An alternative route, oxidative cleavage of the aldehyde **12** to the ketone **11** (via enolization) is unlikely because the conversion of **12** to **11** under the condition (40 °C) found to be very slow (5% after 52 h) [12a].

Next our interest turned into this aldehyde C–C bond cleavage reaction. Although oxidative C–C bond cleavage between carbonyl carbon and vicinal carbon of cycloalkane derivatives with stoichiometric metal reagents are known [13], few reports have been made on aldehydes.

A screening study revealed that  $\text{Ce}(\text{SO}_4)_2 \cdot 4\text{H}_2\text{O}$  has higher activity than  $\text{CuCl}_2$  for C–C bond cleavage reaction

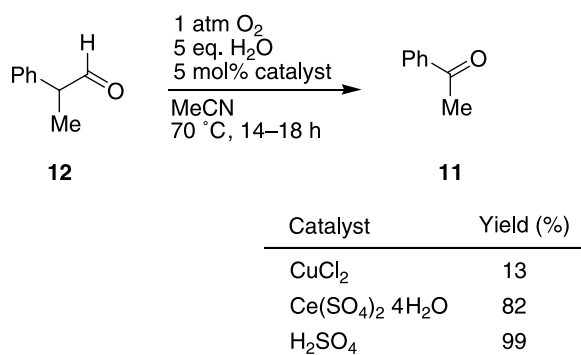
Scheme 6. Cu-catalyzed oxidative C=C bond cleavage of enol ether **10**.



Ar = Ph, *p*-MeC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>

R = Me, Et, *n*-C<sub>11</sub>H<sub>23</sub>, Ph

Scheme 7. Cu-catalyzed oxidative C=C bond cleavage of various enol ethers.



Scheme 8. Oxidative C–C bond cleavage of aldehyde **12**.

(Scheme 8). Acetophenone (**11**) was obtained in 82% at 70 °C [12b]. In addition, it was found that sulfuric acid catalyzed the reaction more effectively. Almost quantitative yield of **11** was formed [12b]. Other Brønsted acids such as *p*-toluenesulfonic acid, hydrochloric acid, Amberlist-15, and Montmorillonite K10 exhibited slightly lower activities. Measurement of gas uptake using sulfuric acid as catalyst (1 mmol scale, 60% convn at 3 h) revealed reasonable consumption of molecular oxygen: ca 15 mL, 0.6 mmol of O<sub>2</sub> was consumed. Since C=C cleavage auto-oxidation of styrene derivatives is common process [14], the present reaction seems to proceed through the enol form. We expect Brønsted acids act as a catalyst for enolization.

## 7. Conclusion

In this review we describe metal complexes catalyzed hydrolysis and alcoholysis reactions and their application to kinetic resolution of chiral substrates. Asymmetric reactions have been achieved using Co, Pd, and Cu complexes as catalyst with moderate to high selectivities. We also demonstrated the utility of zeroth-order kinetic resolution. Since various reactions are known to follow zeroth-order dependence on substrate, it is possible to apply them on purpose to obtain higher efficiency. We also describe oxidative carbon–carbon bond cleavage reactions. Because utilization of unactivated molecular oxygen as reagent received considerable attention in recent years, the finding might provide a new method of olefin activation for the transformation.

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