Kinetic Resolution of Racemic Acetates by Transesterification Catalyzed by Chiral Alkoxocopper(I) Complexes

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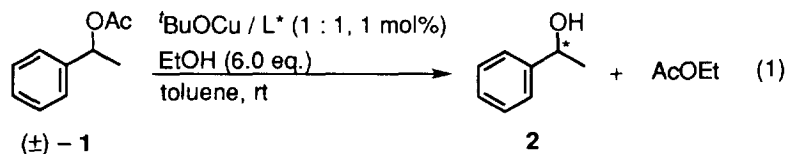
Abstract: Kinetic resolution of racemic acetates, which has been accomplished mainly by means of *Lipases*, was examined by use of a variety of catalyst systems involving chiral alkoxocopper(I) complexes. When a ^{t}BuOCu / (*R*)-BINAP (1 : 1) system was used as a catalyst in ethanol, (±)-1-acetoxy-1-naphthylethane (**4b**) was kinetically resolved to give (*S*)-1-acetoxy-1-naphthylethane in 30% *ee* at 74% conversion.

Although a variety of catalysts for enantioselective reactions have been developed, there have been few reports on efficient asymmetric transformations such as transesterification.[1] On the other hand, very high enantiomer selectivities have been obtained in the transesterification by use of enzymes.[2] Since enzymatic procedure sometimes have disadvantages such as narrow substrate specificity and the necessity to use a large amount of enzymes, we have focused our attention to the development of non-enzymatic catalysts for the asymmetric transesterification utilizing transition metal complexes.

Many catalysts for hydrolysis and alcoholysis of esters have been exploited in achiral systems.[3] Among these it has been known that alkoxocopper(I)—phosphine complexes are one of the most efficient catalysts.[3,4] This time, we wish to report kinetic resolution of racemic acetates by use of chirally modified alkoxocopper(I) complexes as catalysts.
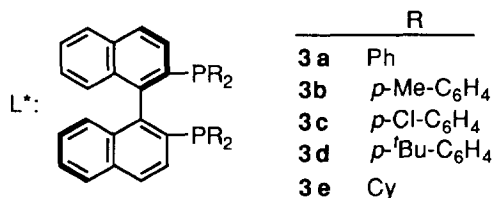
First, the kinetic resolution of (±)-1-acetoxy-1-phenylethane (**1**) by transesterification was investigated in the presence of catalytic amounts of ^{t}BuOCu[5] and various chiral diphosphine ligands. The reaction was carried out in a mixture of toluene and ethanol keeping the solvent / substrate ratio 6.0 (mL / mL) (eq. 1). Some representative results obtained using several diphosphine ligands are summarized in Table 1. From Table 1, the catalytic system using (*R*)-BINAP ((*R*)-**3a**) as a chiral ligand afforded the highest enantiomeric ratio (E) (run 1). The catalytic system with a more electron deficient diphosphine ligand ((*S*)-**3c**) gave a higher catalytic activity (run 3), while use of a more electron donating diphosphine ligand ((*S*)-**3e**) resulted in much lower rate (run 5). These results suggest that Lewis acidity of the copper(I) catalytic center is important for obtaining higher reaction rates.

The transesterification has also been carried out in the presence of various alcohols. The results are listed in Table 2. When ethanol or butyl alcohol was used (runs 2 and 4), larger E values and higher reaction rates were obtained compared to those of the cases with methanol and 2-propanol.

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$$\text{(±) - 1} \xrightarrow[\substack{\text{EtOH (6.0 eq.)} \\ \text{toluene, rt}}]{\text{^{t}BuOCu / L* (1 : 1, 1 mol\%)}} \text{2} + \text{AcOEt} \quad (1)$$

Table 1. Kinetic resolution of (±)-1-acetoxy-1-phenylethane (1) catalyzed by ^{t}BuOCu / diphosphine systems[a]

run	L*	time h	conv.[b] %	ee (%)[c] acetate	ee (%)[c] alcohol	E[d]
1	(R)-3a	2.5	62	21 (S)	9 (R)	1.4
2	(R)-3b	3.5	61	8 (S)	5 (R)	1.1
3	(S)-3c	2.0	87	14 (R)	<1 (S)	1.1
4	(S)-3d	18	62	14 (R)	8 (S)	1.3
5	(S)-3e	136	67	3 (R)	2 (S)	1.1

[a] The reaction was carried out at room temperature in ethanol (6.0 eq. to substate) and toluene (solvent / substrate ratio = 6.0 mL / mL). Substrate / catalyst ratio was 100 (mol / mol). [b] Determined by GLC analysis. [c] Measured by HPLC analysis using a CHIRALCEL OJ column for 1-acetoxy-1-phenylethane (1) and a CHIRALCEL OD column for 1-hydroxy-1-phenylethane (2). [d] E values were calculated from the enantiomeric excesses of the remaining substrate and the product according to ref. 6.

	R
3a	Ph
3b	p-Me-C$_6$H$_4$
3c	p-Cl-C$_6$H$_4$
3d	p-^{t}Bu-C$_6$H$_4$
3e	Cy

Table 2. Kinetic resolution of (±)-1-acetoxy-1-phenylethane by transesterification catalyzed by ^{t}BuOCu / (R)-3a in various alcohols ROH[a]

run	ROH	time h	conv.[b] %	ee (%)[c] acetate	ee (%)[c] alcohol	E[d]
1	MeOH	8.0	62	10 (S)	6 (R)	1.2
2	EtOH	2.5	62	21 (S)	9 (R)	1.4
3	^{i}PrOH	16	57	12 (R)	8 (S)	1.3
4	^{n}BuOH	2.5	74	23 (R)	7 (S)	1.4
5	PhOH	20	0	—	—	—

[a] The reaction was carried out at room temperature in various alcohols (6.0 eq. to substrate) and toluene (solvent / substrate ratio = 6.0 mL / mL). Substrate / catalyst ratio was 100 mol / mol. [b] Determined by GLC analysis. [c] Measured by HPLC analysis using a CHIRALCEL OJ column for 1-acetoxy-1-phenylethane (1) and a CHIRALCEL OD column for 1-hydroxy-1-phenylethane (2). [d] Determined according to ref. 6; see footnote c of Table 1.

Kinetic resolution of racemic acetates **4a—c** were also carried out under similar conditions. As can be seen in Table 3, (±)-1-acetoxy-1-phenylpentane (**4a**) and (±)-1-acetoxy-1-naphthylethane (**4b**) were kinetically resolved with higher E values than that of (±)-**1**.
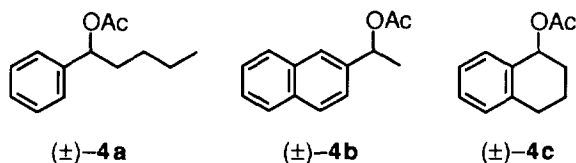

(±)-**4a**   (±)-**4b**   (±)-**4c**

Table 3. Kinetic resolution of **4a—c** by transesterification catalyzed by ^{t}BuOCu / (R)-**3a**^{a}

run	substrate	catalyst mol%	time h	conv.^{b} %	ee (%)^c acetate	ee (%)^c alcohol	E^d
1	**4a**	1.0	3.5	59	19 (S)	11 (R)	1.5
2	**4b**	1.9	2.5	74	30 (S)	8 (R)	1.5
3	**4c**	1.4	6.0	66	11 (R)	4 (S)	1.2

^{a} The reaction was carried out at room temparature in ethanol (6.0 eq. to substrate) and toluene (solvent / substrate ratio = 6.0 mL / mL). ^{b} Determined by GLC analysis. ^{c} Measured by HPLC analysis using a CHRALCEL OJ or OD column. ^{d} See footnote c of Table 1.

Interestingly, complex Cu(OTf)((R)-BINAP) (**5**),[7] which has higher Lewis acidity than alkoxocopper(I) complexes, showed no catalytic activity.
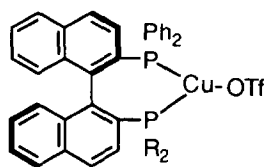
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^{1}H and ^{31}P NMR spectroscopic studies showed that ^{t}BuOCu and (R)-**3a** do not interact each other in the absence of methanol, but when this mixture was exposed to excess CD$_3$OD, the exchange of alkoxyl group occurred to form MeOCu, a part of which further afforded MeOCu—BINAP complex.[8]

For mechanism of the transesterification, three machanisms can be considered *a priori*, (a) Lewis acid mechanism, (b) metal alkoxide mechanism, and (c) four-centered mechanism (Figure 1).[9] All of the above experimental findings suggest that the mechanism (c) is the most plausible as described below.

(1) Higher reaction rates were obtained by use of more electron deficient diphosphine ligands, which suggests that Cu(I) partly acts as a Lewis acid.

(2) Complex **5** does not exhibit catalytic activity, which rules out Lewis acid mechanism (a).

(3) Stronger nucleophilicity of alkoxyl group gave higher reaction rates.

(4) Much lower reation rates were observed in the presence of more electron donating ligands, though stronger nucleophilicity of alkoxyl group can be expected for such complexes. Thus, the present result is not compatible with metal alkoxide mechanism (b).

Figure 1
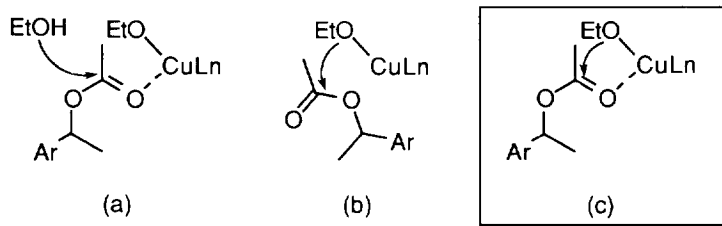
In conclusion, we have found that (±)-1-acetoxy-1-naphthylethane (**4b**) and other racemic acetates **1**, **4a** and **4c** were kinetically resolved in up to 30% *ee* by transesterification in the presence of ^{t}BuOCu / (*R*)-**3a** catalyst system. To the best of our knowledge, this is the first example of asymmetric transesterification of racemic acetates catalyzed by non-enzymatic transition metal complexes. Further work on the development of the more efficient catalysts is in progress.

References and Notes

1.   Enantioselective hydrolysis of amino acid esters were achieved by various metallomicelles or metal–ion complexes. (a) Weijnen, J. J.; Koudijs, A.; Engbersen, J. F. J. *J. Org. Chem.* **1992**, *57*, 7258. (b) Fornasier, R.; Scrimin, P.; Tonellato, U.; Zanta, N. *J. Chem. Soc., Chem. Commun.* **1988**, 716.

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7.   Complex **5** was prepared by the following procedure. In a 20 mL Schlenk tube flushed with argon were placed copper(I) triflate (134 mg, 5.34×10^{-1} mmol), (*R*)-**3a** (320 mg, 5.14×10^{-1} mmol), and dichloromethane (2.0 mL). The resulting bright yellow mixture was stirred at room temperature for 10 min. The solvent was removed under reduced pressure to give **5** as a yellow solid in quantitative yield, ^{31}P NMR (CDCl$_3$, H$_3$PO$_4$ as external standard) δ 1.5 (s).

8.   The species formed from ^{t}BuOCu and (*R*)-**3a** in methanol-*d4* exhibited the following NMR data which supports a formation of methoxocopper—BINAP complex: ^{31}P NMR: δ -14.7 (s) and -7.5 (broad); ^{1}H NMR: δ +1.5 (s, (CH$_3$)$_3$COD).

9.   Chin, J. *Acc. Chem. Res.* **1991**, *24*, 145.