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Kinetic Resolution Displaying Zeroth Order Dependence on Substrate Consumption: Copper-Catalyzed Asymmetric Alcoholysis of Azlactones

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Abstract: Kinetic resolution of 4-alkyl-2-aryl-5-oxo-4,5-dihydrooxazole-4-carboxylic acid esters (azlactones **1**) were achieved by copper-DTBM-SEGPHOS catalyzed alcoholysis reaction with good selectivity (12 examples). Variation of ee of unreacted substrates **1** and products **2** with conversion was found to follow the theoretical line of zeroth-order kinetic resolution, for which the selectivity profiles and graphical analysis were presented for the first time. The efficiency of resolution in zeroth-order reaction is higher than first-order reaction. For example, the reaction with **1a** afforded (*S*)-**1a** (99% ee) and (*R*)-**2a** (74% ee) at 57% conversion, where the k_{rel} values were calculated to be 6.7 as zeroth-order kinetic resolution and 37 as first-order kinetic resolution.

Introduction

Kinetic resolution of racemic compounds is a powerful tool in asymmetric synthesis (Scheme 1).[1] In particular, in biocatalytic asymmetric synthesis, enzymatic resolution of chiral substrates is a mainstream approach using hydrolysis, esterification, reduction, and other reactions.[1b] With regard to organic and organometallic catalysts, although enantioselective reaction occupies a major part, kinetic resolution also plays an important role[1a,c−f] because asymmetric reactions are mostly applicable to chiral substrates as well as prochiral substrates.

One of the major drawbacks of kinetic resolution is a decrease of ee due to concentration effect (mass action) of slow-reacting enantiomer. The relative rate of enantiomers decreases along with the reaction progress because the relative amount of slow-reacting enantiomer increases.

Recently, this problem has been proficiently avoided by parallel kinetic resolution[2] in which the slow-reacting enantiomer is removed by a parallel reaction to give the product without the loss of initial selectivity. However, since this methodology should generate different products from substrate enantiomers, it requires a stoichiometric amount of pseudo- or quasi-enantiomeric reagent,[2a−c,k] or ingenious contrivance to induce different reactions[2l] or regiodivergent reaction (same reaction at different position)[2d,e,h] on them. In addition, it is not possible to obtain unreacted substrate, asymmetric synthesis being the major purpose of the usual kinetic resolution.

Scheme 1. Kinetic Resolution of a Racemate

$$\mathrm{S}_R \xrightarrow{k_R} \mathrm{P}_R$$

$$\mathrm{S}_S \xrightarrow{k_S} \mathrm{P}_S$$

In this paper we propose kinetic resolution in zeroth-order dependence on substrate consumption as an alternative solution to obtain higher efficiency. In this reaction, as well as in parallel kinetic resolution, the relative rate is maintained constant during the reaction because the reaction rate is not affected by concentration. Moreover, unreacted substrate with high optical purity can be obtained. We present selectivity profiles and graphical analysis of zeroth-order kinetic resolution, and an example of catalytic reaction, which is the first metal-catalyzed asymmetric alcoholysis of azlactones affording useful quaternary amino acid derivatives in high enantiomeric excess.

Kinetic Resolution in Zeroth Order in Substrate

Quantitative analysis and graphical visualization have provided useful information for precise understanding of kinetic resolution.[3−7] Thus, zeroth-order kinetic resolution is graphically presented in Figure 1. For the sake of comparison, first- and second-order reactions are also exhibited. The graphs show the

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(1) (a) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001. (b) Ghanem, A.; Aboul-Enein, H. Y. *Chirality* **2005**, *17*, 1−15. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407−1446. (d) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5−26. (e) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.* **1998**, *2*, 489−526. (f) Kagan, H. B.; Riant, O. *Adv. Asymmetry Synth.* **1997**, *2*, 189−235.

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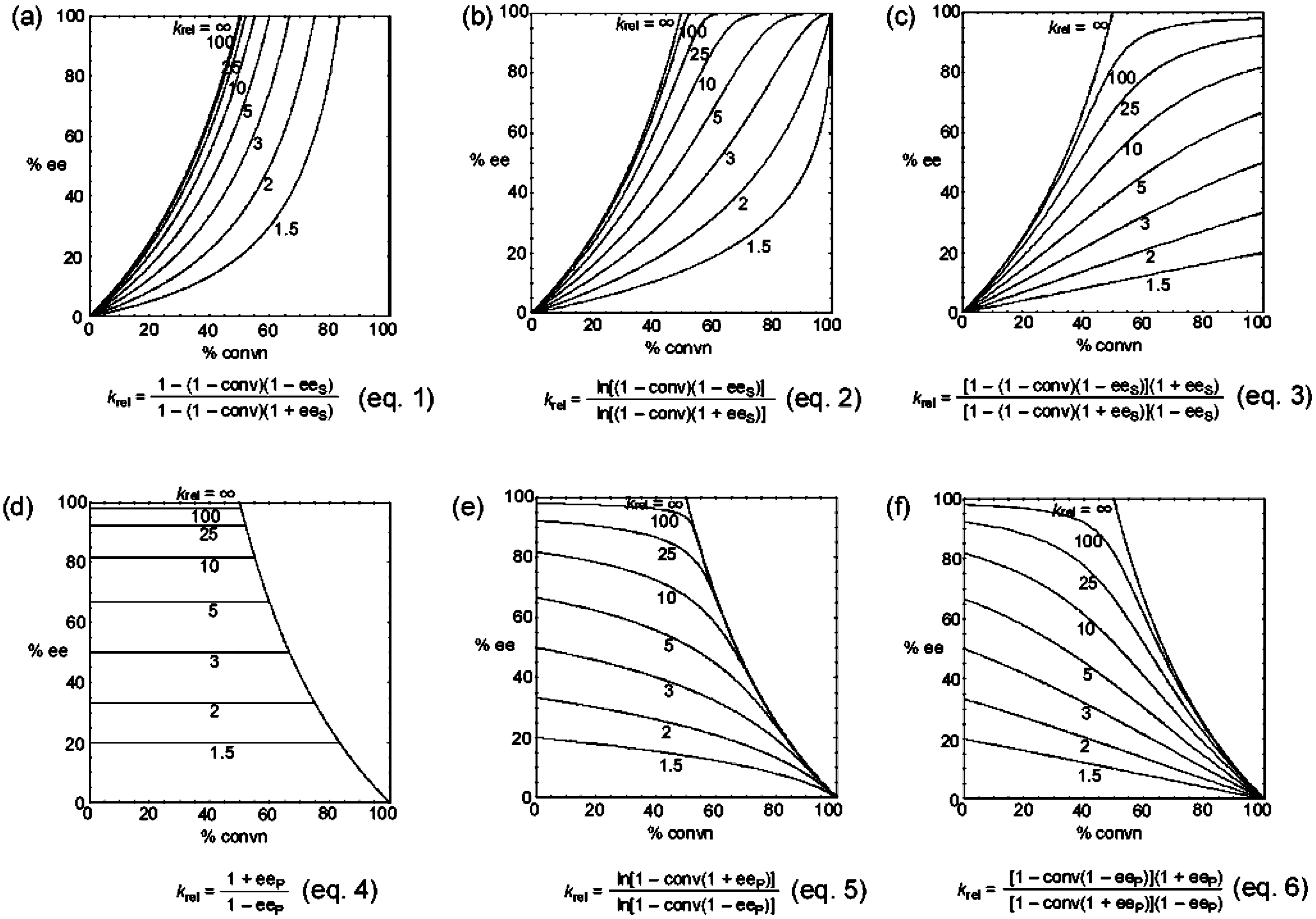

$$k_{rel} = \frac{1 - (1 - conv)(1 - ee_S)}{1 - (1 - conv)(1 + ee_S)} \quad \text{(eq. 1)}$$

$$k_{rel} = \frac{\ln[(1 - conv)(1 - ee_S)]}{\ln[(1 - conv)(1 + ee_S)]} \quad \text{(eq. 2)}$$

$$k_{rel} = \frac{[1 - (1 - conv)(1 - ee_S)](1 + ee_S)}{[1 - (1 - conv)(1 + ee_S)](1 - ee_S)} \quad \text{(eq. 3)}$$

$$k_{rel} = \frac{1 + ee_P}{1 - ee_P} \quad \text{(eq. 4)}$$

$$k_{rel} = \frac{\ln[1 - conv(1 + ee_P)]}{\ln[1 - conv(1 - ee_P)]} \quad \text{(eq. 5)}$$

$$k_{rel} = \frac{[1 - conv(1 - ee_P)](1 + ee_P)}{[1 - conv(1 + ee_P)](1 - ee_P)} \quad \text{(eq. 6)}$$

Figure 1. Variation of ee with conversion of unreacted substrate for (a) zeroth-, (b) first-, and (c) second-order reaction and of product for (d) zeroth-, (e) first-, and (f) second-order reaction.

variation of ee of unreacted substrate and product as a function of conversion. All of the kinetic resolution presented here starts from a racemic mixture. Each graph corresponds as follows: (a) ee variation of substrate in zeroth-order reaction, (b) ee of substrate in first-order, (c) ee of substrate in second-order, (d) ee of product in zeroth-order, (e) ee of product in first-order, and (f) ee of product in second-order, respectively. Corresponding equations (eqs 1−6) for calculation were drawn under the graphs.

All graphs are drawn with the same k_{rel} values ($k_{rel} = \infty$, 100, 25, 10, 5, 3, 2, and 1.5). In graphs (a)−(c), ee of substrate starts at 0% and then gradually increases. When $k_{rel} = \infty$ (infinitely large), ee becomes 100% at 50% conversion (convn); this line does not change depending on the reaction order. On the other hand, lower k_{rel} values gave different lines. When k_{rel} is the same, higher ee can be achieved in lower order reaction (zeroth > first > second) at the same conversion.[8] In graphs (d)−(f), ee of product starts at the value corresponding to initial selectivity, then gradually decreases, and finally reaches 0% at 100% convn. Here, a faster decrease of the ee values can be seen in higher order reactions, while zeroth-order reaction maintains the initial ee value until the fast-reacting enantiomer was completely consumed.[9] On the whole, zeroth-order reaction has higher efficiency of resolution than higher order reaction.

Catalytic reactions often show zeroth-order rate laws in substrate.[12] In some cases change of the catalyst precursor can switch the order from first to zeroth.[12a] However, to present,

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(4) Quantitative analyses of special cases of kinetic resolution have been made: enzymatic reaction,[5] dynamic kinetic resolution,[6] and nonlinear effect in kinetic resolution.[7]

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(8) For example, when $k_{rel} = 10$, in graph (a), ee is 81.8% at 50% convn and then reaches 100% at 55% convn. In graph (b), 67.0% at 50% convn and 90% ee is achieved at 62.1% convn. In graph (c), 51.9% at 50% convn and even at 100% convn, the ee value is 81.8%.

(9) In graph (d), edged corners at the point of complete conversion of fast-reacting enantiomer will be rounded off to a smooth line in the real reactions because that will not follow the zeroth-order kinetics perfectly.[10,11]

(10) Jacobsen noted[1d] that the kinetic order in a substrate can shift from zeroth- to first-order as the substrate concentration decreases in the case of saturation kinetics.

(11) Blackmond demonstrated change of the reaction order from nearly zeroth to more positive order during the reaction progress. Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302−4320.

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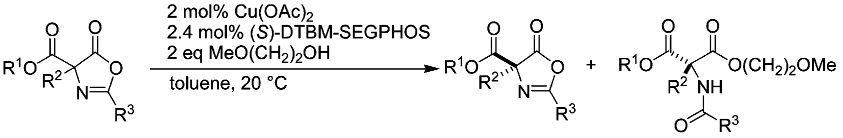
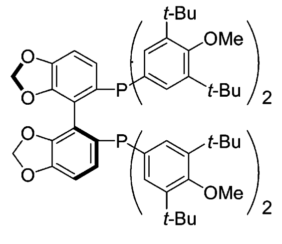
Scheme 2. Asymmetric Alcoholysis of Azlactones **1** with Cu−(*S*)-DTBM-SEGPHOS Catalysts



rac-**1**

2

	R^1	R^2	R^3
a:	Me	Me	Ph
b:	Et	Me	Ph
c:	*n*-Pr	Me	Ph
d:	allyl	Me	Ph
e:	*n*-Bu	Me	Ph
f:	*i*-Bu	Me	Ph
g:	Bn	Me	Ph
h:	Bn	Et	Ph
i:	Bn	*n*-Pr	Ph
j:	Bn	*n*-Bu	Ph
k:	Bn	*n*-Bu	*p*-ClC_6H_4
l:	Et	Me	*p*-$MeOC_6H_4$



(*S*)-DTBM-SEGPHOS

eqs 2 and 5 for first-order reaction have been used almost exclusively.[13,14] Next, we demonstrate an example which follows theoretical lines of zeroth-order kinetic resolution.

Kinetic Resolution of Azlactones 1 via Copper-Catalyzed Alcoholysis

Azlactones (oxazol-5(4*H*)-ones) are *N*,*C*-doubly protected amino acid derivatives and their enantioselective synthesis has attracted considerable attention in recent years.[15] Several kinds of asymmetric reactions have been developed to access this important class of compounds such as acyl transfer,[15c,h] alkylation,[15d−f] and alcoholysis.[15a,b,g] Regarding alcoholysis, dynamic kinetic resolution of monosubstituted azlactones with organic catalysts has been studied but no metal catalyst has been reported. In addition, the reaction of disubstituted azlactones to afford unnatural quaternary amino acid remains undeveloped probably due to its low reactivity. In this context, we have tried the alcoholysis of disubstituted azlactones with homogeneous metal catalysts, which has brought enormous advances in the reaction using alcohols[16] and water[17,18] as a reagent.

A screening study of metals and chiral ligands revealed that $Cu(OAc)_2$/DTBM-SEGPHOS is an efficient catalyst system for the asymmetric alcoholysis of azlactones **1** (Scheme 2). Among the examined alcoholic reagents, 2-methoxyethanol gave the highest selectivity.[19] The results are shown in Table 1. The asymmetric alcoholysis of **1a** into **2a** reached 57% conversion at 67 h (entry 1). The ee of recovered **1a** and the product **2a**

Table 1. Asymmetric Alcoholysis of Azlacones **1** with Cu−(*S*)-DTBM-SEGPHOS Catalysts[a]

entry	substrate	time/h	convn/%[b]	% ee of **1**	% ee of **2**	k_{rel} (0th)[c]
1	**1a**	67	57(55)	99	74	6.7
2	**1b**	8	21(20)	22	81	9.6
3		17	32(30)	38	82	9.8
4		30	48(47)	74	80	9.1
5		52	56(55)	93	74	6.6
6	**1c**	37	17(18)	15	77	7.8
7		61	30(31)	33	77	7.8
8		52	34(34)	40	77	7.7
9		72	55(56)	94	77	7.8
10	**1d**	55	55(56)	89	68	6.7
11[d]	**1e**	76	57(57)	93	70	5.6
12	**1f**	8	15(17)	15	84	11
13		16	32(33)	40	86	13
14		22	39(40)	53	84	11
15		50	53(54)	89	78	7.9
16	**1g**	8	18(19)	19	82	10
17		18	39(39)	52	82	10
18		24	44(44)	65	82	10
19		49	54(53)	89	77	7.5
20[d]	**1h**	100	57(58)	93	71	5.9
21[d]	**1i**	122	48(49)	71	77	7.8
22[d]	**1j**	118	47(47)	56	63	4.4
23[d]	**1k**	74	55(55)	96	80	8.8
24[d]	**1l**	12	14(16)	14	83	11
25[d]		20	25(26)	28	84	12
26[d]		28	47(48)	74	82	10
27[d]		48	53(54)	84	75	7.1

[a] Conditions: see Scheme 2. [b] Conversion was calculated by convn $= ee_s/(ee_s + ee_p)$; experimentally determined value is in parentheses (see Supporting Information). [c] Calculated by eqs 1 and 4 using theoretical conversion value. [d] 5 mol % $Cu(OAc)_2$ and 5 mol % DTBM-SEGPHOS were used.

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(13) Jacobsen pointed out in a review[1d] "the rate laws for synthetically useful kinetic resolutions are almost never determined, but it is generally just assumed that the reactions are first-order in substrate and that eqs 2 and 5 are applicable". More recently, Vedejs noted as well.[1a]

(14) Faller and Tokunaga reported a kinetic resolution did not follow Kagan's first-order equation. The observed k_{rel} values (calculated as first order) increased with the increase of the reaction conversion. We proposed the reaction follows zeroth-order or fractional order that brought about better results than expected as first-order reaction. Faller, J. W.; Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359−7362.

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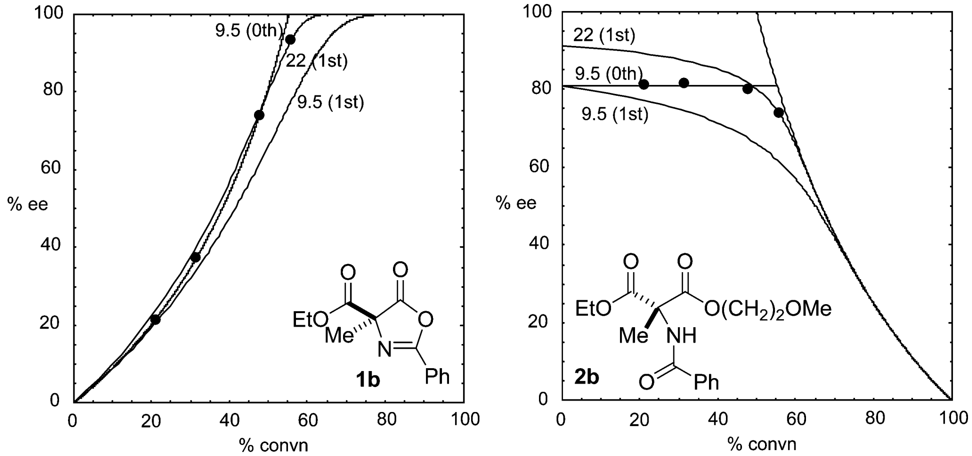

Figure 2. Kinetic resolution of *rac*-**1b**: experimental values (dots); simulated lines as zeroth-order reaction (k_{rel} = 9.5) and as first-order reaction (k_{rel} = 9.5 and 22).

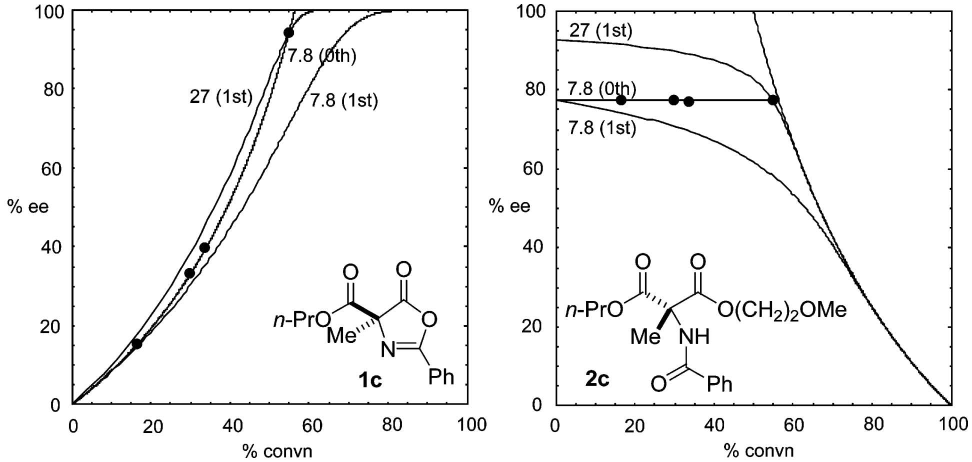

Figure 3. Kinetic resolution of *rac*-**1c**: experimental values (dots); simulated lines as zeroth-order reaction (k_{rel} = 7.8) and as first-order reaction (k_{rel} = 7.8 and 27).

were 99% and 74%, respectively. The k_{rel} value was calculated as 6.7 from eq 1 and eq 4 as zeroth-order reaction.[20] When the k_{rel} value was calculated as first-order kinetic resolution, it becomes 37.[20,21] Similarly, 93% ee of **1b** and 74% ee of **2b** were obtained at 56% conversion and the k_{rel} value was 6.6 as zeroth-order reaction (entry 5). To examine the variation of ee during the reaction, three runs of the same reaction were stopped earlier (entries 2−4). The ee of **1b** increased as 22, 38, and then 74% along with the reaction proceeding as 21, 32, and then 48%, but the ee of **2b** became constant around 81%. The k_{rel} values as zeroth-order became constant around 9.5. On the other hand, when k_{rel} were calculated as first-order reaction, the values change to 12, 14, 20, and then 22 for entries 2−5.[21] This result suggests that zeroth-order is more appropriate than first-order for this reaction. Figure 2 shows the variation of ee of **1b** and **2b** 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 **1b** and **2b**, 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) at the final stage.[9] Obviously the simulated line of first-order reaction (k_{rel} = 22) does not fit in the early to middle stage of the reaction. Similar experiments were performed with **1c**, **1f**, **1g**, and **1l**, and it was found that all reactions follow well with zeroth-order lines (k_{rel} = 7.8, 11.1, 10.2, and 11.0). The experiments for **1c** and **1g** are depicted in Figures 3 and 4. Others (**1f** and **1l**) are in the Supporting Information (Figure S-1 and S-2). The simulated lines of zeroth-order are in good agreement with observed data. In the case of **1c**, the reaction seems to follow zeroth-order line to the final stage of the reaction of fast-reacting enantiomer.

Regarding the synthetic aspects, the reaction was found to be applicable to all tested substrates. When R^2 in the substrate was changed from Me to Et (**1h**), *n*-Pr (**1i**), and *n*-Bu (**1j**), the reactivity and selectivity decreased (entries 20−22). However, electron-withdrawing substituent on R^3 improved both reactivity and selectivity (entry 23). Comparing **1j** with **1k**, those substrates have the same R^1 (Bn) and R^2 (*n*-Bu), the *p*-chloro group increased the k_{rel} from 4.4 to 8.8, and the rate was improved approximately twice (entries 22 and 23). An electron-

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(19) With use of methanol as reagent, 94% ee of **1b** and 24% ee of alcoholyzed product were obtained at 22 h (80% convn).

(20) With use of the value of theoretical conversion from an equation (convn $= ee_s/(ee_s + ee_p)$), the k_{rel} values obtained with eqs 1 and 4 or eqs 2 and 5 become exactly the same, respectively.[21] The differences between theoretical and experimental conversion were within ±2% in all cases. We think the theoretical conversion value well reflects the actual value in this study. Since small difference of conversion value brings about large difference of k_{rel} value, determination of conversion should be performed carefully.[1a,d]

(21) See Supporting Information Table S-1. The k_{rel} values of zeroth- and first-order kinetic resolution were calculated both from theoretical and experimental conversion values using eqs 1, 2, 4, and 5 and are listed as 3 digit numbers.

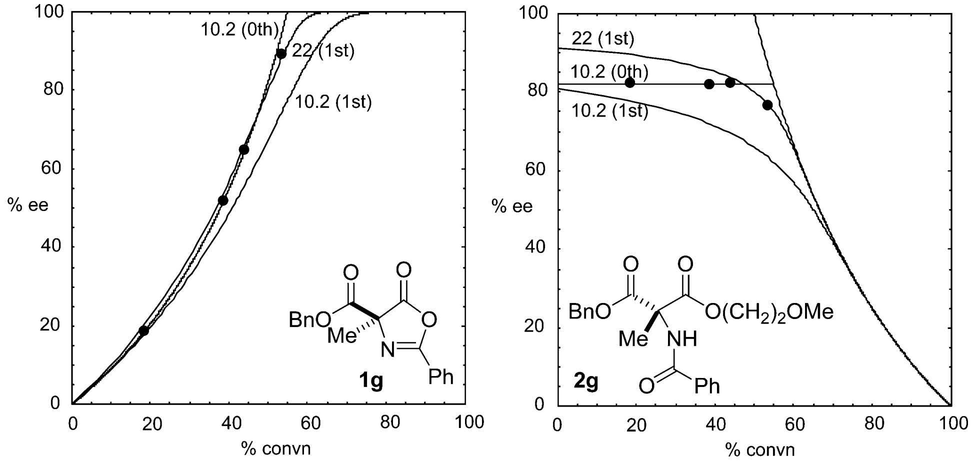

Figure 4. Kinetic resolution of *rac*-**1g**: experimental values (dots); simulated lines as zeroth-order reaction ($k$rel = 10.2) and as first-order reaction ($k$rel = 10.2 and 22).

donating substituent (*p*-MeO) on R^3 (**1l**) decreased the reactivity (entries 24−27). Comparable rate was observed with higher (5 mol %) catalyst loadings (entry 27, cf. entry 5; 2 mol %). It is noteworthy that 93% ee of unreacted substrates was obtained with **1e** and **1h**, although k_{rel} was only 5.6 and 5.9, which clearly indicates the higher efficiency of zeroth-order kinetic resolution.

We assume the rate law of the reaction as eq 7; thus, the first-order plot for alcohol should be fitted.

$$-\frac{d[\mathbf{1}]}{dt} = k[\mathbf{1}]^0[\text{ROH}]^1 \qquad (7)$$

The reaction of **1b** with 0.6 equiv of alcohol for this plot was carried out by a sampling experiment from the same batch. The result showed good fit with first-order plot over 90% conversion based on alcohol (Figure S-3 in Supporting Information), which suggests eq 7 is appropriate for this reaction. The same plots were made for the data in Table 1 and showed reasonable fit, even though the reactions were carried out with different batches.[22] Presumably, the chiral recognition of the two enantiomers of the azalactone occurs in the reversible formation of an azlactone-chiral Cu-catalyst complex and the attack of the alcohol on this chiral Lewis acid−substrate complex is the rate-determining step. On the other hand, a preliminary mechanistic study for the reaction with spectroscopic and kinetics experiments suggest the possibility of a somewhat more complicated mechanism than our expectation: the coordination mode may be different between the fast-reacting substrate and the slow-reacting substrate (O−O chelate and O−N chelate). Further investigation for a detailed mechanism is in progress.

Conclusion

The difference of resolution efficiency between zeroth-, first-, and second-order reaction in kinetic resolution was discussed. Higher efficiency of zeroth-order kinetic resolution was graphically visualized and demonstrated by a newly developed copper-catalyzed alcoholysis reaction of azlactones. Typically, a reaction which has only low selectivity factor ($k_{\text{rel}} = 5.6$, Table 1, entry 11) as zeroth-order reaction is equivalent to a highly selective reaction ($k_{\text{rel}} = 18$) as first-order reaction. Catalytic reaction often shows zeroth-order dependence in the substrate, for instance, Ru-catalyzed oxidation,[12a] Rh-catalyzed hydrogenation,[12b] Pd-catalyzed Heck reaction,[12d] alkali-metal-catalyzed amination of olefins,[12e] and needless to say, most cases of enzymatic reactions. When these reactions are applied for kinetic resolution, it will be easier to achieve high ee than first-order reactions.

Experimental Section

Typical Procedure for Kinetic Resolution: Alcoholysis of 1b (Table 1, Entries 3 and 5). In a dried 20 mL Schlenk flask was placed $Cu(OAc)_2$ (1.9 mg, 0.010 mmol), and then the solid was heated at 80 °C under vacuum for 3 min and the flask filled with Ar. To this were added (*S*)-DTBM-SEGPHOS (14.2 mg, 0.012 mmol) and toluene (1.0 mL); then, the mixture was stirred at 45 °C for 1 h. The mixture was cooled to room temperature, and toluene (1.0 mL) solution of **1b** (123.6 mg, 0.500 mmol) and 2-methoxyethanol (80 μL, 1.0 mmol) was added. The mixture was stirred at 20 °C for 17 h (entry 3) or 52 h (entry 5) in an incubator. The product **2b** and the substrate **1b** were isolated by silica gel column chromatography (elution: hexane/Et_2O 10/1, 1/1, and then 1/2). Entry 3: **1b** (86.6 mg, 69.7%, 37.5% ee) and **2b** (49.3 mg, 30.3%, 81.5% ee). Entry 5: **1b** (52.0 mg, 42.1%, 93.2% ee) and **2b** (89.7 mg, 55.3%, 73.7% ee). **1b** (93.2% ee) HPLC (CHIRALCEL OD (DAICEL), hexane/2-propanol = 200/1, 0.50 mL/min, $T_R = 24.1$ min (minor), $T_R = 26.6$ min (major)), $[\alpha]^{29}_D$ −110.9° (*c* 4.53, benzene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, $J = 7.3$ Hz, 3H) 1.77 (s, 3H), 4.20−4.30 (m, 2H), 7.50 (dd, $J = 7.3$, 8.2 Hz, 2H), 7.60 (t, $J = 7.3$ Hz, 1H), 8.03 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 20.4, 63.0, 72.9, 125.3, 128.2 (2C), 128.8 (2C), 133.3, 163.1, 165.9, 175.1. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.18; H, 5.33; N 5.69. **2b** (81.5% ee) HPLC (CHIRALPAK AD-H (DAICEL), hexane/2-propanol = 4/1, 1.0 mL/min, $T_R = 8.9$ min (major), $T_R = 11.5$ min (minor)), $[\alpha]^{26}_D + 9.0°$ (*c* 1.00, benzene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, $J = 7.3$ Hz, 3H), 1.87 (s, 3H), 3.29 (s, 3H), 3.54−3.57 (m, 2H), 4.21−4.30 (m, 2H), 4.35 (t, $J = 4.5$ Hz, 2H), 7.43 (dd, $J = 7.6$, 7.8 Hz, 2H), 7.51 (t, $J = 7.6$ Hz, 1H), 7.55 (brs, 1H), 7.80 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.1, 59.0, 62.9, 63.2, 65.4, 70.1, 127.2 (2C), 128.7 (2C), 132.0, 133.5, 166.0, 168.8, 168.9. Anal. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.30; H, 6.66; N, 4.29.

Acknowledgment. We thank Takasago International Corporation for providing DTBM-SEGPHOS. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (NO. 16033204, Reaction Control of Dynamic

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(22) First-order plot (ln([ROH]/[ROH]$_0$) = −*kt*) for **1b** (Table 1, entries 2−5), **1f** (entries 12−15), and **1g** (entries 16−19) were well fitted below 50% convn (25% convn based on alcohol), **1l** (entries 24−27) was moderately fitted, but **1c** (entries 6−9) was not fitted (see Supporting Information Figure S-4).

Complexes) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and characterization of new compounds, Table S-1, introduction of equations, and Figures S-1−S-4 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA058112J