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Relationship between the time, yield, and enantiomeric excess of asymmetric autocatalysis of chiral 2-alkynyl-5-pyrimidyl alkanol with amplification of enantiomeric excess

Itaru Sato,[a] Daisuke Omiya,[a] Hiroyoshi Igarashi,[a] Keiichi Kato,[b] Yoshihiro Ogi,[c]
Koichi Tsukiyama[c,]* and Kenso Soai[a,]*

[a]*Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*
[b]*Department of Mathematics, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*
[c]*Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*

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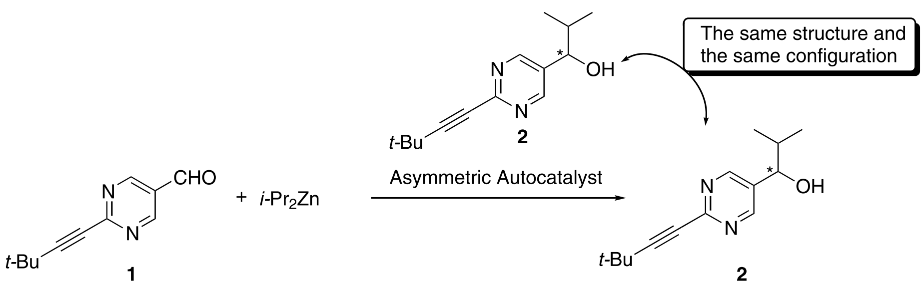
Abstract—Experimental and kinetic analysis of asymmetric autocatalysis with amplification of ee in the enantioselective addition of diisopropylzinc to 2-alkynylpyrimidine-5-carbaldehyde using chiral 2-alkynyl-5-pyrimidyl alkanol with low ee's are described.

Asymmetric autocatalysis[1] is an attractive new entry for asymmetric synthesis in which a chiral product acts as a chiral catalyst for its own production.[2] Several enantioselective asymmetric autocatalyses have been reported.[3] Among them, 2-alkynyl-5-pyrimidyl alkanol is the most highly enantioselective (>99.5% ee) in the enantioselective addition of diisopropylzinc (i-Pr_2Zn) to the corresponding 2-alkynylpyrimidine-5-carbaldehyde.[3f] In our previous report,[4] we applied a second-order kinetic model to the asymmetric autocatalysis of *enantiomerically pure* pyrimidyl alkanol. The model reproduces well the experimental results of asymmetric autocatalysis of enantiomerically pure pyrimidyl alkanol.

Meanwhile, we reported asymmetric autocatalysis with significant amplification of ee.[1f,3a] Now the interest is to understand the asymmetric autocatalysis with amplification of ee.[5] We report here the experimental data and a kinetic analysis on the asymmetric autocatalysis of chiral 2-alkynyl-5-pyrimidyl alkanol with amplification of ee (Scheme 1).



Scheme 1.

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* Corresponding authors. Tel.: +81-3-5228-8261; fax: +81-3-3235-2214; e-mail: tsuki@rs.kagu.tus.ac.jp; soai@rs.kagu.tus.ac.jp

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2-Alkynylpyrimidine-5-carbaldehyde **1** was reacted with i-Pr$_2$Zn using 10 mol% of (S)-**2** with 59.4, 41.2 and 20.4% ee as asymmetric autocatalysts, respectively. Portions of the reaction mixtures were quenched periodically and the yields and ee of the produced alkanol were determined by HPLC using naphthalene as an internal standard. The results are shown in Figs. 1–3 and Table 1. The experimental yield (hollow circle) and ee (filled circle) are represented as a mixture of the initially used alkanol **2** (10 mol%) and the newly formed alkanol **2** (they have the same structure), which gives rise to the apparent yield up to 110 (=100+10)%. As shown in Figs. 1–3, after incubation times, yields increased rapidly in short periods. As well as the increase in the yields, the ee increased from 59.4 to 94% (Fig. 1), from 41.2 to 92% (Fig. 2) and from 20.4 to 87% (Fig. 3), respectively.

For the kinetic analysis, we used the following equations (Scheme 2):

$$P_S+P_S \rightleftarrows P_S{\cdot}P_S \quad K=\frac{[P_S{\cdot}P_S]}{[P_S]^2} \tag{1}$$

$$P_S+P_R \rightleftarrows P_R{\cdot}P_R \quad K=\frac{[P_R{\cdot}P_R]}{[P_R]^2} \tag{2}$$

$$P_S+P_R \rightleftarrows P_S{\cdot}P_R \quad K'=\frac{[P_S{\cdot}P_R]}{[P_S][P_R]} \tag{3}$$

$$\text{RCHO}+i\text{-Pr}_2\text{Zn}+P_S{\cdot}P_S \xrightarrow{k} P_S+P_S{\cdot}P_S \tag{4}$$

$$\text{RCHO}+i\text{-Pr}_2\text{Zn}+P_R{\cdot}P_R \xrightarrow{k} P_R+P_R{\cdot}P_R \tag{5}$$

$$\text{RCHO}+i\text{-Pr}_2\text{Zn}+P_S{\cdot}P_R \xrightarrow{k'} P_S+P_S{\cdot}P_R \tag{6}$$

$$\text{RCHO}+i\text{-Pr}_2\text{Zn}+P_S{\cdot}P_R \xrightarrow{k'} P_R+P_S{\cdot}P_R \tag{7}$$

with

$$0<P_{R0}<P_{S0}<[\text{RCHO}]_0<[i\text{-Pr}_2\text{Zn}]_0.$$

K and K' are the equilibrium constants of a pre-equilibrium between two monomers and a dimer,[6] whereas k and k' are the rate constants of the autocatalytic reactions. $[\text{RCHO}]_0$, $[i\text{-Pr}_2\text{Zn}]_0$, P_{S0} and P_{R0} represent the initial molar concentrations of the species RCHO, i-Pr$_2$Zn, P_S and P_R, respectively. Under the conditions where the concentration of dimers is vanishingly small compared to that of the monomers, the reaction laws for P_S and P_R are:

$$\begin{aligned}\frac{d[P_S]}{dt} &= k[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_S{\cdot}P_S] \\ &\quad +k'[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_S{\cdot}P_R] \\ &= kK[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_S]^2 \\ &\quad +k'K'[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_S][P_R]\end{aligned} \tag{8}$$

$$\begin{aligned}\frac{d[P_R]}{dt} &= k[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_R{\cdot}P_R] \\ &\quad +k'[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_S{\cdot}P_R] \\ &= kK[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_R]^2 \\ &\quad +k'K'[\text{RCHO}][i\text{-Pr}_2\text{Zn}][P_S][P_R]\end{aligned} \tag{9}$$

Let the reductions of the reactant aldehyde (and also reactant i-Pr$_2$Zn) by the reactions (4), (5), (6), and (7) be Δx, Δy, Δz and Δz, respectively.

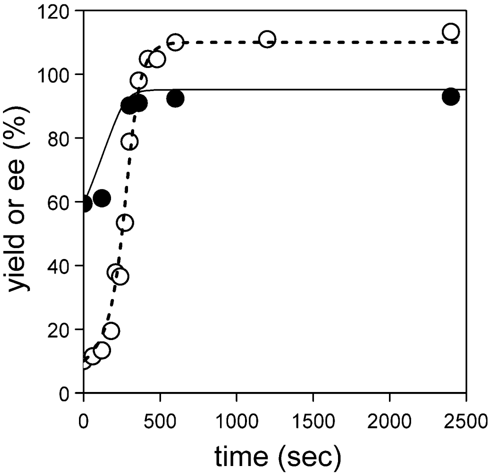


Figure 1. Comparison of simulation [yield (calcd): broken lines, ee (calcd): solid lines] with experimental points [yield (exp.): hollow circle, ee (exp.): filled circle] on asymmetric autocatalysis using (S)-**2** with 59.4% ee$_{\text{in}}$ at −25°C.

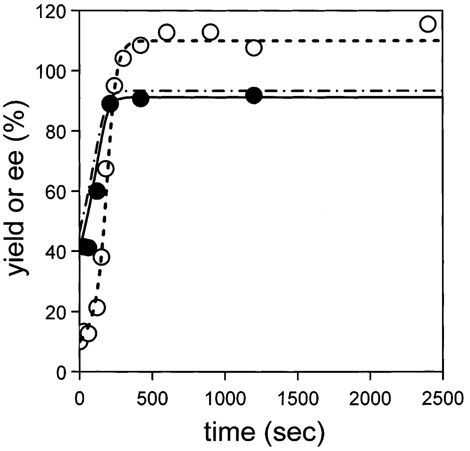


Figure 2. Asymmetric autocatalysis of (S)-**2** with 41.2% ee$_{\text{in}}$ at −25°C. —: calcd I, -·-: calcd II. See text for calcd I and II.

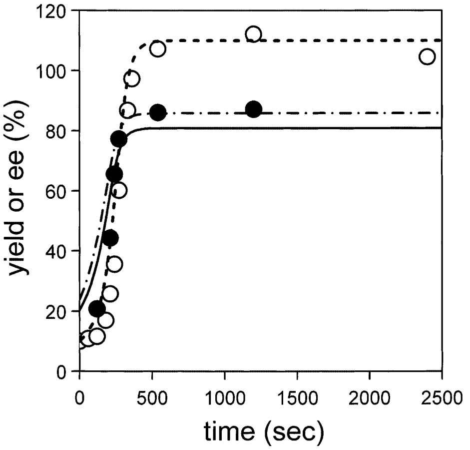


Figure 3. Asymmetric atocatalysis of (S)-**2** with 20.4% ee$_{\text{in}}$ at −25°C. —: calcd I, -·-: calcd II. See text for calcd I and II.

Table 1. Comparison between experimental and calculated enantiomeric excess[a]

Run	ee_{in} (%)[b]	$<kK>$ (M^{-3} s^{-1})[c]	ee_{fin} (exp.) (%)[b]	ee_{fin} (calcd I) (%)[d]	ee_{fin} (calcd II) (%)[e]
1	59.4	2700	94±2	95.2	96.3
2	41.2	3500	92±2	91.2	93.4
3	20.4	3000	87±2	80.9	85.9

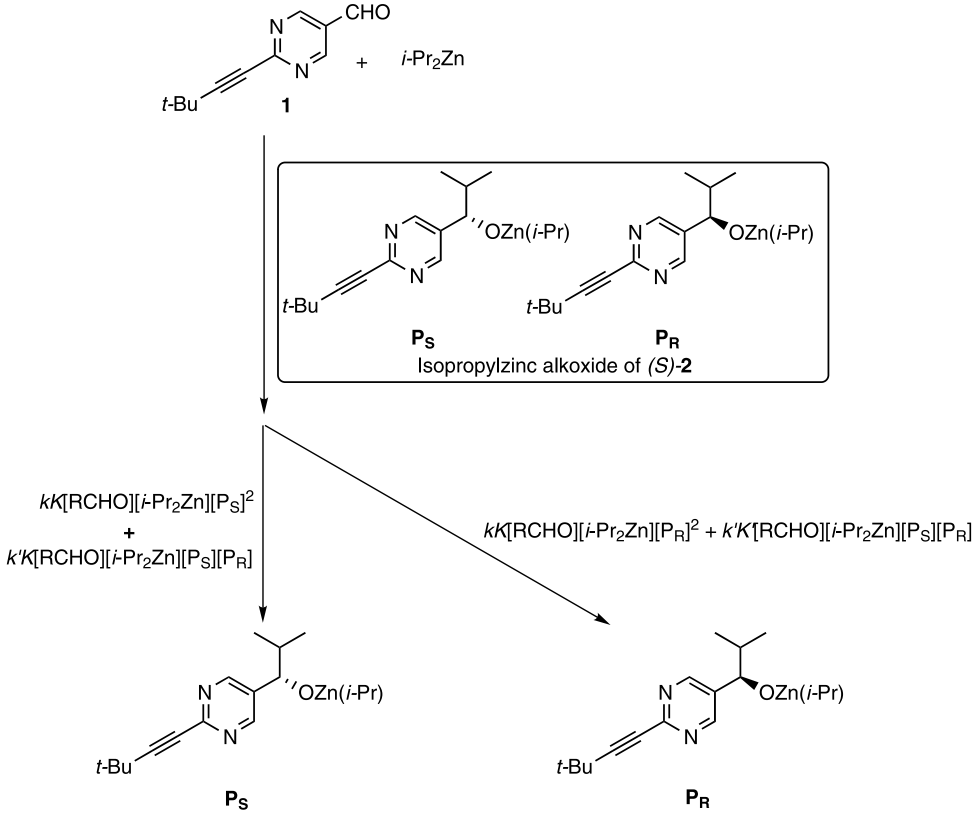
[a] $[\text{RCHO}]_0 = 2.08\times10^{-2}$ M, $[i\text{-Pr}_2\text{Zn}]_0 = 3.33\times10^{-2}$ M, $[P_{\text{S0}}]+[P_{\text{R0}}] = 2.08\times10^{-3}$ M. The reaction was carried out at −25°C (internal temperature of the vessel).

[b] Determined by HPLC analysis using chiral stationary phase.

[c] The error is estimated to be 30%.

[d] Values assuming $\alpha = 1.0$.

[e] Values assuming that the initial P_{R} concentration is consumed to form complexes.



Scheme 2.

$$[\text{RCHO}] = [\text{RCHO}]_0 - \Delta x - \Delta y - 2\Delta z$$

$$[i\text{-Pr}_2\text{Zn}] = [i\text{-Pr}_2\text{Zn}]_0 - \Delta x - \Delta y - 2\Delta z$$

$$[P_{\text{S}}] = P_{\text{S0}} + \Delta x + \Delta z$$

$$[P_{\text{R}}] = P_{\text{R0}} + \Delta y + \Delta z$$

Then, insertion of these stoichiometric relation into Eqs. (8) and (9) lead to the following equations:

$$\frac{dX}{dt} = kK(a-X-Y)(b-X-Y)X^2 + k'K'\ (a-X-Y)(b-X-Y)XY \tag{10}$$

$$\frac{dY}{dt} = kK(a-X-Y)(b-X-Y)Y^2 + k'K'(a-X-Y)(b-X-Y)XY$$

with

$$X = P_{\text{S0}} + \Delta x + \Delta z = [P_{\text{S}}]$$

$$Y = P_{\text{R0}} + \Delta y + \Delta z = [P_{\text{R}}]$$

$$a = [\text{RCHO}]_0 + P_{\text{S0}} + P_{\text{R0}}$$

$$b = [i\text{-Pr}_2\text{Zn}]_0 + P_{\text{S0}} + P_{\text{R0}}$$

Note that X and Y correspond to the concentrations of P_{S} and P_{R} in the reaction system, respectively. The above equations can be converted to:[7]

$$(R+1)^{2\alpha-1}(R-1) = c_0 s^{2\alpha-1} R^{\alpha} \tag{11}$$

with

$$R = \frac{X}{Y} = \frac{[P_{\text{S}}]}{[P_{\text{R}}]},\ \alpha = \frac{kK}{kK+k'K'},\ c_0 = \frac{[P_{\text{S0}}]-[P_{\text{R0}}]}{[P_{\text{S0}}]^{\alpha}[P_{\text{R0}}]^{\alpha}}$$

and

$$s = X + Y = [P_{\text{S}}] + [P_{\text{R}}].^{7}$$

From Eq. (11), we are able to calculate $R(t)=[P_S]/[P_R]$ against $s(t)=[P_S]+[P_R]$ at a given value of α.

In case of $kK \gg k'K'$ (we can show that the maximum ee_{fin} (calcd I) is reached when $\alpha=1$),

$$\frac{dX}{dt}+\frac{dY}{dt}=\frac{d(X+Y)}{dt}=kK(a-X-Y)(b-X-Y)(X^2+Y^2) \qquad (12)$$

Because Eq. (12) cannot be integrated, we introduce an effective rate constant $<kK>$ as:

$$\frac{ds}{dt}=<kK>(a-s)(b-s)s^2. \qquad (13)$$

From Eqs. (12) and (13), $<kK>$ should be smaller than kK: $<kK>$ is equal to kK in the case of $kK=k'K'$. The solution of Eq. (13) is:

$$<kK>t=f\ln\frac{[\mathrm{RCHO}]_0}{a-s}+g\ln\frac{[i\text{-}\mathrm{Pr_2Zn}]_0}{b-s}+h\ln\frac{s}{X_0+Y_0}+ i\left(\frac{1}{X_0+Y_0}-\frac{1}{s}\right) \qquad (14)$$

with

$$f=-\frac{1}{a^2(a-b)},\ g=\frac{1}{b^2(a-b)},\ h=\frac{a+b}{a^2b^2},\ \text{and}\ i=\frac{1}{ab}.$$

At first, we simulate time evolution of the experimental product yield with Eq. (14) by varying $<kK>$ as an adjustable parameter. If the fit between experimental data and the simulated curve is reasonable, $s(t)$ can be calculated at arbitrary time t, which in turn enables us to evaluate $R(t)$ from Eq. (11). Then the time dependent ee is obtained from the next relationship.

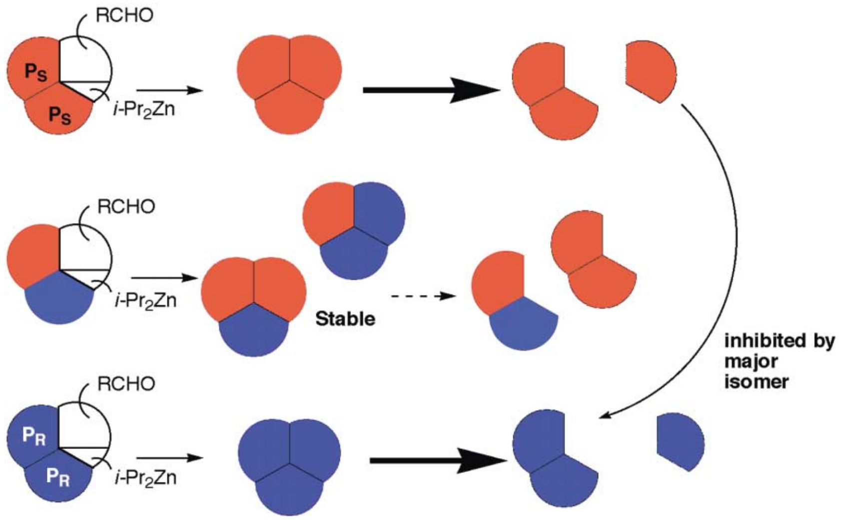
$$\mathrm{ee}(t)=\frac{R(t)-1}{R(t)+1}\times 100$$

In the following discussion, the initial ($t=0$) and final ($t=\infty$) ee are designated by ee_{in} and ee_{fin}, respectively.

Fig. 1 depicts the results of simulation for the reaction system involving asymmetric autocatalyst with moderate (59.4%) ee_{in} at −25°C. The initial concentration of reactants and the total concentration of autocatalyst were as follows (Table 1, run 1): $[\mathbf{1}]_0=[\mathrm{RCHO}]=2.08\times10^{-2}$ M; $[i\text{-}\mathrm{Pr_2Zn}]_0=3.33\times10^{-2}$ M; $[\mathbf{2}]_0=[P_{S0}]+[P_{R0}]=2.08\times10^{-3}$ M. When the value of α is fixed to 1.0, that is, $k'K'$ is practically zero, the fit is satisfactory for not only the time-dependent yield of the product but also the time-dependent ee value of the product. The best fit value for the apparent rate constant $<kK>$ is 2700 $M^{-3}\ s^{-1}$ (Table 1, run 1). The calculated ee_{fin} of alkanol **2** reached 95.2%, which is almost the same as the experimental ee_{fin} of 94%.

The fit for asymmetric autocatalyst with moderate (41.2%) ee_{in} is illustrated in Fig. 2. Again the fit between the experiment and calculation is excellent. The ee_{fin} (calcd I) value of 91.2% reproduces the ee_{fin} (exp.) value of 92% (Table 1, run 2). On the other hand, the fit for the lower (20.4%) ee_{in} is less satisfactory as shown in Fig. 3. It should be noted that the ee_{fin} (calcd I) value of 80.9% is considerably lower than the ee_{fin} (exp.) value of 87% (Table 1, run 3). The value of $<kK>$, falling in the range between 2700 and 3500 for the above three different ee_{in} as listed in Table 1, would be regarded as constant within a large error involved in the determination of the rate constants.

In order to explain the higher ee of the experimental results than those of the simulated ones in the asymmetric autocatalysis with amplification of ee starting with pyrimidyl alkanol with lower ee, we consider a following possibility: Let us assume the concentration



Scheme 3. Schematic representation of product inhibition on asymmetric autocatalysis with amplification of ee. When the hetero-trimeric complex is more stable than homo-trimeric complex: (1) Achiral pathway (middle column) is restrained; (2) catalytically active complex of the minor isomer is inhibited by the major isomer.

of $P_S{\cdot}P_R$ stays constant during the reaction. This reduces $[P_{S0}]$ and $[P_{R0}]$ and increases the ee_{in} apparently. For the case that 20% of the initial P_R concentration is consumed, the ee_{in} increases from 41.2 to 46.6% (run 2) and from 20.4 to 23.9% (run 3), leading to the increases of ee_{fin} (denoted by ee_{fin} (calcd II) in Table 1) from 91.2 to 93.4% (run 2) and from 80.9 to 85.9% (run 3). This effect becomes more and more conspicuous when the ee_{in} is lower: for the higher ee_{in} (run 1), the difference between ee_{fin} (calcd I) and (calcd II) is not quite significant as tabulated in Table 1. Such participation of both autocatalysis and product inhibition has been reported by von Kiedrowski who showed template-directed self-replication of nucleic acid proceeds parabolically.[8] The magnitude of amplification of ee becomes higher when the complex of autocatalyst and product $P_S{\cdot}P_S{\cdot}P_R$ is more stable than the complex of autocatalyst and product $P_S{\cdot}P_S{\cdot}P_S$ (Scheme 3).

As described above, we have demonstrated that the second-order model for asymmetric autocatalyst lead to asymmetric autocatalysis with amplification of ee, which arises from the competitive reactions of enantiomers.

Acknowledgements

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6. It should be emphasized that 'dimer' is the mere representation on theoretical treatment. It means that A, B, and two molar equivalents of P are exists on transition complex. $A{\cdot}P+B{\cdot}P \rightarrow A{\cdot}P{\cdot}B{\cdot}P \rightarrow P+P+P$ is another example of second-order reaction law and the equation gave the same simulation curve. Due to the closely related structures of reactant and product in asymmetric autocatalysis, major existence of product 'dimer' is considered to be one of the possible situations.
7. Readers who are interested in the mathematical derivation are recommended to read a detailed description of the calculation, which is available from one of the authors (K.S.).
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