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Evidence of asymmetric autocatalysis in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde using chiral pyrimidyl alkanol

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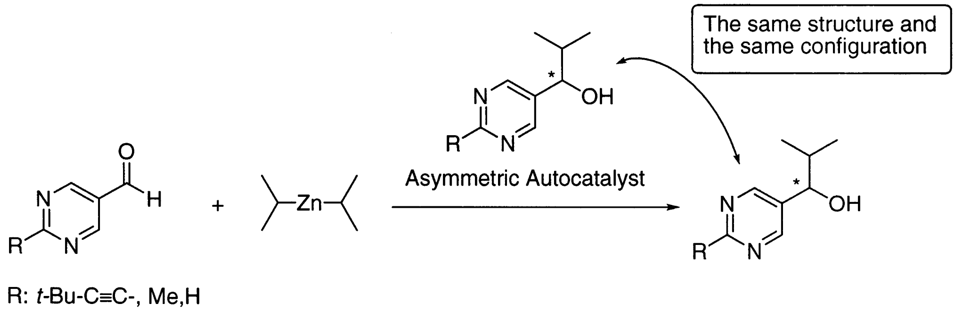
Abstract—Kinetic analysis of the relationship between the reaction time and the yields of the product in the enantioselective addition of diisopropylzinc to pyrimidine-5-carbaldehyde using chiral pyrimidyl alkanol proves that the reaction is autocatalytic.

Asymmetric autocatalysis[1] has attracted much attention as a new method for asymmetric synthesis in which a chiral product acts as a chiral catalyst for its own production.[2] We have been studying the highly enantioselective asymmetric autocatalysis in the enantioselective addition of di-*iso*-propylzinc (*iso*-Pr_2Zn)[3] to pyrimidine-5-carbaldehyde, quinoline-3-carbaldehyde and 5-carbamoylpyridine-3-carbaldehyde to afford chiral 5-pyrimidyl alkanols, 3-quinolyl alkanols, and 5-carbamoyl-3-pyridyl alkanols, respectively.[2] The enantiomeric excess (e.e.) of the autocatalysts increase during the reaction.[1g,2a,4] Among asymmetric autocatalysts, 5-pyrimidyl alkanols are known to be the most highly enantioselective (Scheme 1).[2b,2f]

We report herein the evidence that the enantioselective addition of *iso*-Pr_2Zn to pyrimidine-5-carbaldehyde using a homochiral 5-pyrimidyl alkanol catalyst proceeds through asymmetric autocatalysis.[5] The evidence is based on the kinetic analysis of the relationship between the reaction time and the yields of the product in the enantioselective addition of *iso*-Pr_2Zn to 2-alkynylpyrimidine-5-carbaldehyde using a homochiral 2-alkynyl-5-pyrimidyl alkanol catalyst.

2-Alkynylpyrimidine-5-carbaldehyde was added to a toluene solution of *iso*-Pr_2Zn and 10 or 1 mol% of (*S*)-2-alkynyl-5-pyrimidyl alkanol with >99.5% e.e. at either 0°C or −45°C. Portions of the reaction mixture



Scheme 1.

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were quenched periodically with saturated aqueous sodium chloride. Yields of the products were determined by HPLC analysis using naphthalene as an internal standard. Three sets of measurements were conducted: individual experimental conditions are summarized in Table 1. The results are plotted as closed circles in Fig. 1a–c.

The plots in Fig. 1a–c constitute S-shaped curves; after an initial incubation period in the first stage, the reaction proceeds rapidly in the middle stage and relatively slowly in the final stage. These S-shaped curves are characteristic of autocatalytic reactions (Scheme 2).

One of the reaction mechanisms to be applied for kinetic analysis is related to dimer formation:

$$\mathrm{P+P} \rightleftarrows \mathrm{P{\cdot}P} \qquad K=\frac{[\mathrm{P{\cdot}P}]}{[\mathrm{P}]^2} \tag{1}$$

$$\mathrm{A+B+P{\cdot}P} \xrightarrow{k} \mathrm{P+P{\cdot}P} \tag{2}$$

K is the equilibrium constant of a pre-equilibrium (1) between two monomers and a dimer, whereas k is the

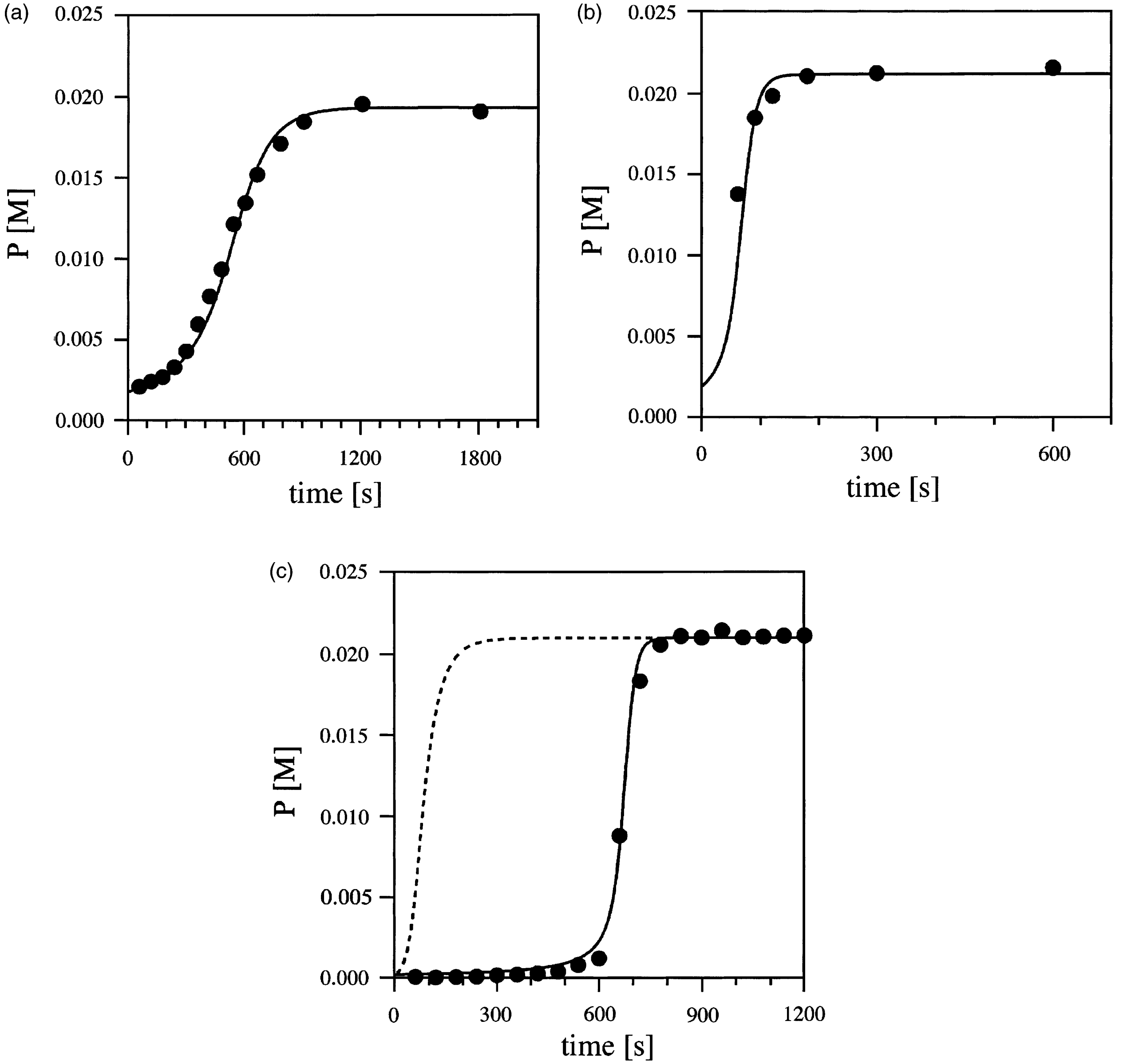


Figure 1. Comparison of simulation (P_{calcd}:solid lines) with experimental points (P_{exp}). Experimental conditions: (a) $T=-45$°C, $A_0=2.08\times10^{-2}$ M, $B_0=3.13\times10^{-2}$ M, $P_0=2.08\times10^{-3}$ M; (b) $T=0$°C, $A_0=2.08\times10^{-2}$ M, $B_0=3.13\times10^{-2}$ M, $P_0=2.08\times10^{-3}$ M; (c) $T=0$°C, $A_0=2.08\times10^{-2}$ M, $B_0=3.13\times10^{-2}$ M, $P_0=2.08\times10^{-4}$ M. A broken curve represents the simulation assuming the first-order autocatalytic reaction. See text for details.

Table 1. Values of kK and f

	T (°C)	A_0 (M)	B_0 (M)	P_0 (M)	f	kK ($M^{-3}\ s^{-1}$)
Set 1	−45	2.08×10^{-2}	3.13×10^{-2}	2.08×10^{-3}	1.20	1.50×10^{3}
Set 2	0	2.08×10^{-2}	3.13×10^{-2}	2.08×10^{-3}	1.08	1.20×10^{4}
Set 3	0	2.08×10^{-2}	3.13×10^{-2}	2.08×10^{-4}	1.00	1.15×10^{4}

rate constant of an autocatalytic reaction (2). Then the reaction rate, v, is expressed as:

$$v=-\frac{d[A]}{dt}=k[A][B][P{\cdot}P]=kK[A][B][P]^2$$
$$=kK[A_0-x][B_0-x][P_0+x]^2=\frac{dx}{dt}, \tag{3}$$

where A_0, B_0 and P_0 are initial molar concentrations of the species A, B, and P, respectively. The direct integration of Eq. (3) under the initial condition of $x=0$ at $t=0$ yields the next equation:

$$kKt=a\ln\frac{A_0}{A_0-x}+b\ln\frac{B_0}{B_0-x}-c\ln\frac{P_0}{P_0+x}+\frac{d}{P_0}-\frac{cx+d}{x+P_0} \tag{4}$$

with

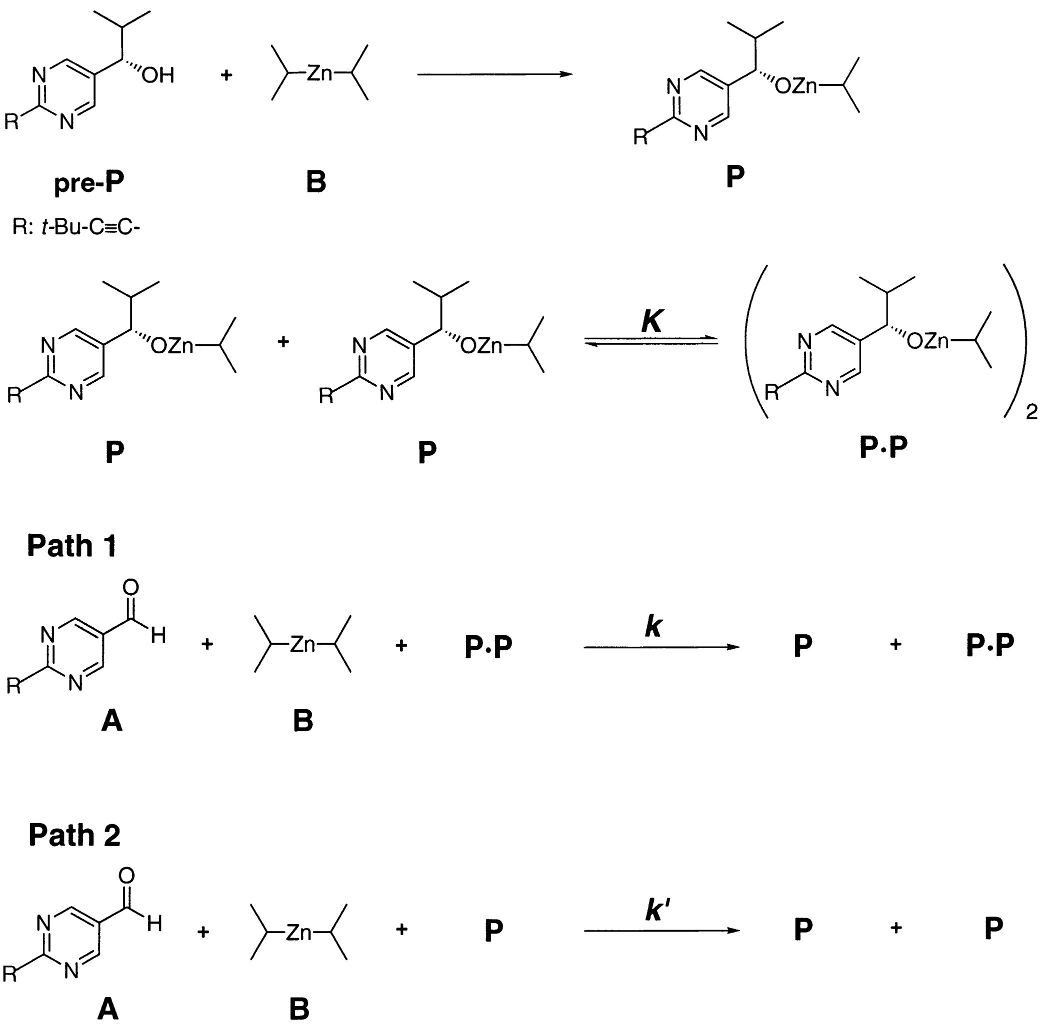
$$a=-\frac{1}{(A_0+P_0)^2(A_0-B_0)}$$

$$b=\frac{1}{(B_0+P_0)^2(A_0-B_0)}$$

$$c=a+b$$

$$d=a(A_0+2P_0)+b(B_0+2P_0)$$

The above formula, involving no approximation in its derivation, provides a strict relation between the reaction time and product concentrations. The value of kK



Scheme 2.

is a variable parameter for simulation. In actual fitting, however, one more parameter, f, is introduced:

$$P_{\text{calcd}}=\frac{P}{f}=\frac{P_0+x}{f} \quad \text{or} \quad x=P_{\text{calcd}}\cdot f-P_0 \tag{5}$$

The value of f is chosen so that the asymptote of the simulated curve (P_{calcd}) overlaps with that of the experimental points (P_{exp}) at sufficiently large t.

The results of simulation for data sets 1–3 are illustrated in Fig. 1a–c, respectively. The solid lines, representing the plots of P_{calcd} versus t, are the best fit to the experimental points. The values of kK and f are also tabulated in Table 1. On the whole, the agreement between calculations and experiments are satisfactory.

Several significant details are as follows:

(i) It would be advantageous to check the propriety of the dimer model (path 1) in comparison with a simpler autocatalytic reaction, $A + B + P \xrightarrow{k'} P + P$. If dimer formation is not taken into consideration, this is a first-order reaction for catalyst. The difference of reaction order is reflected in the reaction rate at lower reactant concentrations (at smaller t). If we attempt to reproduce the steep rise seen in Fig. 1c with the first-order scheme, the incubation period becomes substantially shorter (as indicated by the broken curve). Rapid termination of the reaction after a long incubation period is not reproducible with this simple model. It should be emphasized that, in monomer mechanism, fast dimer formation, reducing the monomer concentration at small t, may lengthen the incubation period (path 2). Such a reaction scheme (the integrated rate law being unavailable) is a subject of future studies.

(ii) The dimer model is not the only candidate to explain observed reaction rates consistently. A mechanism associated with complex formation between reactants and catalyst,

$$A+P \rightleftarrows AP \quad K=\frac{[AP]}{[A][P]}$$

$$B+P \rightleftarrows BP \quad K'=\frac{[BP]}{[B][P]}$$

$$AP+BP \xrightarrow{k'} P+P+P$$

$$v=k'[AP][BP]=k'KK'[A][B][P]^2$$

is another example of a second-order reaction for catalyst, giving rise to a similar rate law as Eq. (3).

(iii) Sets 2 and 3 were performed with different reactant concentrations at the same temperature. The fact that the values of kK obtained under these two conditions agree within experimental error justifies the second-order reaction law.

As described above, we have established that the enantioselective addition of *iso*-Pr_2Zn to pyrimidine-5-carbaldehyde in the presence of chiral pyrimidyl alkanol proceeds autocatalytically. We believe that our present observations are essential to clarify the reaction mechanism of asymmetric autocatalysis with amplification of e.e.[1g,2a,6]

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References

1. Reviews: (a) Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1657–1659; (b) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Chem. Commun.* **2000**, 887–892; (c) Soai, K. *Enantiomer* **1999**, *4*, 591–598; (d) Soai, K.; Shibata, T. *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.)* **1997**, *55*, 994–1005; (e) Soai, K.; Shibata, T. In *Advances in Biochirality*; Palyi, G.; Zucchi, C.; Caglioti, L., Eds. Asymmetric autocatalysis and biomolecular chirality; Elsevier Science: Oxford, 1999; pp. 125–136; (f) Soai, K.; Shibata, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed. Asymmetric amplification and autocatalysis; Wiley-VCH: New York, 2000; Chapter 9, pp. 699–725; (g) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 382–390; (h) Soai, K.; Sato, I.; Shibata, T. *Chem. Rec.* **2001**, *1*, 321–332.
2. (a) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature (London)* **1995**, *378*, 767–768; (b) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471–472; (c) Shibata, T.; Choji, K.; Morioka, H.; Hayase, T.; Soai, K. *Chem. Commun.* **1996**, 751–752; (d) Shibata, T.; Morioka, H.; Tanji, S.; Hayase, T.; Kodaka, Y.; Soai, K. *Tetrahedron Lett.* **1996**, *37*, 8783–8786; (e) Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K. *J. Am. Chem. Soc.* **1998**, *120*, 12157–12158; (f) Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 659–661; (g) Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Sato, I. *J. Am. Chem. Soc.* **1999**, *121*, 11235–11236; (h) Sato, I.; Kadowaki, K.; Soai, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 1510–1512; (i) Sato, I.; Omiya, D.; Saito, T.; Soai, K. *J. Am. Chem. Soc.* **2000**, *122*, 11739–11740; (j) Sato, I.; Yamashima, R.; Kadowaki, K.; Yamamoto, J.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 1096–1098.
3. (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (b) Yu, H. B.; Pu, L. *Chem. Rev.* **2001**, *101*, 757–824.
4. Reviews: (a) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532–3556; (b) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418–3438.
5. Presented at the 72nd National Meeting of The Chemical Society of Japan: Shibata, T.; Tabira, H.; Sakaguchi, S.; Soai, K. Abstract 2G126, March 1997, Tokyo.
6. For a proposed ML_2 model of asymmetric autocatalysis with amplification of e.e., see: (a) Bailey, P. D. *J. Chem.*

Soc., *Chem*. *Commun*. **1995**, 1797–1798. For monomer and ML_n models of asymmetric amplification in *non-autocatalytic* reactions, see: (b) Noyori, R.; Kitamura, M. *Angew*. *Chem*., *Int*. *Ed*. *Engl*. **1991**, *30*, 49–69; (c) Noyori, R.; Suga, S.; Oka, H.; Kitamura, M. *Chem*. *Rec*. **2001**, *1*, 85–100; (d) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J*. *Am*. *Chem*. *Soc*. **1986**, *108*, 2353–2357; (e) Guillaneux, D.; Zhao, S.-H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J*. *Am*. *Chem*. *Soc*. **1994**, *116*, 9430–9439; (f) Girard, C.; Kagan, H. B. *Angew*. *Chem*., *Int*. *Ed*. **1998**, *37*, 2922–2959; (g) Blackmond, D. G. *Acc*. *Chem*. *Res*. **2000**, *33*, 402–411.