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Kinetic relationship in parallel autocatalytic amplifications of pyridyl alkanol and chiral trigger pyrimidyl alkanol

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Abstract

Experimental and kinetic analysis of a chemical system combines autocatalytic amplification of 2-alkynyl-5-pyrimidyl alkanol **2** and 6-alkynyl-3-pyridyl akanol **4** in which **2** acts as a chiral trigger and **4** being the subsequent autocatalyst. Starting from a very low initial *ee*, both alkanols are produced with high enantiopurity in one single cycle. This provides insight into a dual nonlinear amplification of chirality observed with amplifying trigger **2** and accelerated amplification of autocatalyst **4**. These kinetic studies reveal a five-fold magnitude superior amplification rates of **4** associated with trigger's enantiopurity at the outset.

KEYWORDS
amplification, autocatalysis, chirality, kinetic, zinc

1 | INTRODUCTION

Although there are several possible origins of homochirality, propagation and amplification of chirality generated from the initial breaking of symmetry are also key topics for the evolution of homochirality. Soai et al. reported the remarkable asymmetric autocatalysis of (5-pyrimidyl)-alkanol **2**, capable of amplification to extremely high values of enantioenrichment by a sequence of consecutive reactions.[1] Besides the great advantages that this model shows by comparison with asymmetric synthesis that still relies on catalyst generated from the chiral pool, to date, the Soai reaction remains a unique example of amplification of the chiral information in an autocatalytic process.[2] Also, with its capability in amplifying small imbalances in chirality, the Soai reaction represents a perfect tool for the detection of small variations of asymmetry.[3] Symmetry breaking may also rise from statistical fluctuation in the initial enantiomeric ratio and lead to spontaneous asymmetric synthesis.[4] Recently, the Soai autocatalytic reaction was tested to probe the energy imbalance that gives rise to directed symmetry breaking.[5]

Furthermore, the uniqueness of this reaction requires a rigid γ-iminoaldehyde moiety, thus delaying practical uses of this process.[6] Note that 5-carbamoyl-3-pyridyl alkanol exhibits asymmetric autocatalysis with amplification of chirality.[7] We have been studying autocatalysis with other pyridyl-substrates reminiscent of Soai autocatalyst such as alkanols of type **4**.[8] Their performance is mainly attributed to structural features shared with pioneering Soai autocatalyst **2** (Scheme 1). In addition, during this study, we observed remarkable asymmetric amplification properties when **2** and **4** perform in conjunction in a single autocatalytic system. This protocol depicted autocatalyst **2** as a chiral trigger, which was allowed to amplify in *substoichiometric* amount, with

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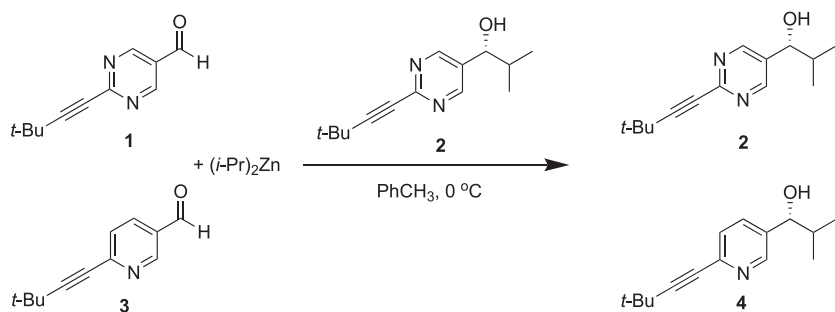
increasing enantiopurity that propagates to autocatalyst **4**. All in one single cycle, amplification of **4** was astonishingly superior to that of **2** during the parallel process with a dual nonlinear effect (NLE), which raises certain mechanistic questions regarding the dynamic chemical network or synergetic course of this reaction.

Recently, we made the demonstration of the absolute asymmetric amplification of autocatalyst **4** under heterogenous phase by addition of *iPr₂Zn vapor on solid aldehyde 3*.[9,10] However, this symmetry breaking is not yet observed in solution.

Because autocatalysis may contribute to understanding the origins of homochirality, several groups have investigated the chemical mechanism of the Soai reaction.[11] This pyrimidyl alkanol has various dimerization patterns and the $(Zn-O)_2$ square dimer structure, which is often observed in other zinc alkoxides.[12] Single-crystal X-ray diffraction analysis revealed that the tetramer structure has two square dimers bridged by one macrocycle structure. Further, crystallization studies revealed that higher oligomeric species also crystallized, by changing the amount of i-Pr₂Zn, and that the existence of a coordinative solvent will change the conformation of tetramers.[13] Results obtained in kinetic studies proposed the involvement of homo- and heterochiral dimers of the Soai Zn autocatalyst.[14]

Experimental studies by kinetic measurements and NMR spectroscopy provided support for the contribution of higher oligomer species.[15] Besides, computational analysis provided a rational for other possible species such as trimers and tetramers, which must dissociate to recover the dimeric catalyst and propagate chirality.[16] Tetramers in ground state were recently shown to have inverse temperature dependence on reaction rate and induction period to release the active catalyst. DFT calculations confirmed that homochiral tetramers are exclusively formed in specific conformations.[17] An integrative model describes the Soai reaction as Frank-like reaction network operating in a closed system, by mutual inhibition of each catalyst enantiomer, to give rise to absolute asymmetric synthesis under kinetic control.[18] Such a system requires an efficient irreversible enantioselective autocatalysis and a fast heterodimerization, which are key for the observed nonlinear amplification of *ee*.[19]

In this work, we report on kinetic investigations of the combined autocatalytic amplification of **2** and **4** in a single chemical system. This provides insight into a dual nonlinear amplification of chirality observed with amplifying trigger **2** and immediately propagated with higher rate to autocatalyst **4**. The magnitude of this rate is shown to be associated to trigger's enantiopurity at the outset.

2 | MATERIALS AND METHODS

2.1 | General procedures

All reactions were performed under inert condition using dry glassware in a nitrogen or argon atmosphere. All the commercially available reagents were used as received, unless stated otherwise. The ¹H NMR spectra were recorded at 400 MHz with a Bruker AV1 400 instrument, at 300 MHz with a Bruker DPX 300 instrument and at 200 MHz with a Bruker DPX 200. ¹³C NMR spectra were recorded with the above-mentioned instruments. HRMS-EI mass spectra were recorded on a VG Prospec instrument. Chiral HPLC analyses were run on an Agilent 1260 Infinity using chiral stationary columns from Daicel. Solvents were purified and degassed by standard procedures.

2.2 | Experimental data

2.2.1 | Preparation of Soai aldehyde (1) and Soai alcohol (2)

Aldehyde **1** and alcohol (*R*)-1-(2-tert-Butylethynyl-5-pyrimidyl)2-methylpropanol **2** at >99% *ee* were prepared according to the literature procedures.[3f]

2.2.2 | Preparation of racemic Soai alcohol (2)

Racemic Soai alcohol **2** is prepared through a Grignard reaction on the aldehyde **1**: In an oven-dried flask under inert atmosphere, a solution of Isopropylmagnesium

chloride 2M in THF (0.53 ml, 1.06 mmol) is added dropwise to a solution of aldehyde **1** (0.71 mmol) in 7 mL of dry THF. The reaction is monitored by thin layer chromatography (TLC). When the reaction gets to completion, it is quenched with 1 mL of NH_4Cl solution. The mixture is extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure. The crude was further purified by flash chromatography on silica gel to give the pure alcohol.

6-(3,3-Dimethylbut-1-yn-1-yl)nicotinaldehyde (3)

The aldehyde was prepared from 6-bromonicotinaldehyde through a Sonogashira crosscoupling reaction using Pd $(PPh_3)_4$ as catalyst. 6-Bromonicotinaldehyde (0.500 g, 2.69 mmol), Tetrakis (tryphenylphosphine) Pd(0) (0.068 g, 0.05 mmol), and CuI (0.025 g, 0.13 mmol) are weighted and dissolved in 4.5 mL of THF. Diisopropylamine (1.53 mL, 10.75 mmol) is then added to the mixture. The solution is degassed through 3 cycles of freeze–thaw under vacuum. The alkyne (2.96 mmol) is then added, at 0°C and under nitrogen atmosphere, to the mixture. The solution is stirred overnight. The mixture is filtered on celite, and the solvent is removed under vacuum to obtain the crude product. Purification was performed by manual flash chromatography on silica gel eluting with Hexane/EtOAc (6:4) increasing gradually the gradient to EtOAc only, to give a pale brown solid. Yield: 96%. ^{1}H NMR (400 MHz, Chloroform-d) δ10.08 (s, 1H), 9.00 (d, J = 1.4 Hz, 1H), 8.11 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 1.37 (s, 9H). ^{13}C NMR (101 MHz, CDCl3) δ189.85, 152.11, 148.89, 135.72, 132.15, 129.57, 128.56, 127.22, 114.99, 30.49, 28.21. HRMS (ESI+) for $C_{12}H_{13}NO$ (M) found 187.0994, calculated 187.0997.

1-(6-(3,3-Dimethylbut-1-yn-1-yl)pyridin-3-yl)-2-methylpropan-1-ol (4)

Purification was done by flash chromatography on silica gel eluting with Hexane/EtOAc (6:4) increasing gradually the gradient to EtAc only, to give a white solid. ^{1}H NMR (400 MHz, Chloroform-d) δ 8.42 (s, 1H),7.60 (dd, J = 8.0, 2.1 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 4.44 (d, J = 6.4 Hz, 1H), 2.17 (s, 1H), 1.94 (m, 1H), 1.34 (s, 9H), 0.96 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ148.30, 142.96, 137.64, 134.45, 126.61, 99.10, 78.81, 77.35, 35.43, 30.87, 28.06, 18.76, 17.91. HRMS (ESI+) for $C_{15}H_{21}NO$ found 231.1622, calculated 231.1623.

2.2.3 | Standard procedure for the one-pot asymmetric autocatalysis of 2 and 4

In an oven-dried flask, Soai alcohol **2** (0.002 mmol, 11% *ee*), Soai aldehyde **1** (0.02 mmol), and aldehyde **3** (0.200 mmol) are dissolved in 2 mL of dry toluene under nitrogen atmosphere. A solution of diisopropylzinc 1M in toluene (0.51 mL, 0.51 mmol) is added slowly over 3 h to the mixture. The reaction is monitored by TLC. The reaction is quenched by the addition of HCl 1M in dioxane (0.210 mmol) and neutralized with saturated aqueous $NaHCO_3$. The mixture is extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure.

The reaction advancement is followed taking samples (0.1 mL) of the reaction mixture, quenching them with a drop of saturated solution of NH_4Cl followed by a quick extraction with EtOAc.

2.2.4 | Procedure for the one-pot competition study

In an oven-dried flask, Soai alcohol **2** (0.002 mmol, >99% *ee*), Soai aldehyde **1** (0.200 mmol), and aldehyde **3** (0.200 mmol) are dissolved in 4 mL of dry toluene under nitrogen atmosphere. A solution of diisopropylzinc 1M in toluene (0.51 mL, 0.51 mmol) is added slowly over 3 h to the mixture. The reaction is quenched by the addition of HCl 1M in dioxane (0.210 mmol) and neutralized with saturated aqueous $NaHCO_3$. The mixture is extracted with ethyl acetate, dried over anhydrous Na_2SO_4, and evaporated to dryness under reduced pressure.

The reaction advancement is followed taking samples (0.1 mL) of the reaction mixture, quenching them with a drop of saturated solution of NH_4Cl followed by a quick extraction with EtOAc.

3 | RESULTS AND DISCUSSION

We began our studies by assessing a set of equivalent experiments with decreasing initial *ee* value of the trigger alcohol (*R*)-**2**. In the following discussion, we use *ent*-**2** and *rac*-**2** for enantiopure and racemic Soai alkanol, respectively. Note that the same reaction with (*S*)-**2** yields product (*S*)-**4**. While trigger with racemic **2** is subject to random symmetry breaking, the correlation in absolute configuration is retained for both **2** and **4**. In the present study, we focus on enantiomer (*R*) for consistency.

All reactions were performed in toluene at 273 K using **1** and **3** at 0.01M and 0.1M, respectively. As shown in Figure 1, the asymmetric amplifications peaks at approximately 99% *ee* in all the experiments, where a non-racemic pyrimidyl alcohol is used (Figure 1, Runs 3–6). Initial *ee* values of the chiral initiator seem to have no relevant effect on the final *ee* of both alkanols (*R*)-**4**
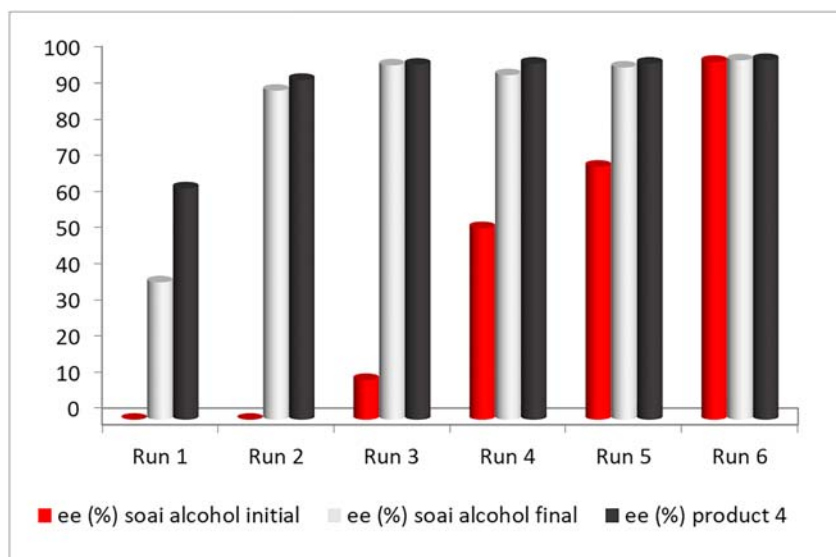
and (*R*)-**2**, which are obtained in values of 97–99% *ee*. Also, Runs 1 and 2 with rac-**2** as trigger suggest breaking of symmetry translated into a nonlinear amplification of **4** with respect to Soai **2**. Thus, alkanol **4** still amplifies greater under the action of trigger **2** in lower *ee* and substoichiometric concentration (*Vide Infra*).

Figure 2 compares the reaction progress for the formation of **4** beside amplification of Soai alkanol **2** used as a trigger at various initial enantiopurity. Parallel amplification reactions were carried out using 10 mol% of **1** and 1 mol% of **2** at various levels of enantiopurity (racemic, 17 and 53% and finally 99% *ee*) and compared with a control reaction for autocatalytic formation of **4** in absence of Soai **2**. Initial analysis suggested high autocatalytic activity after an induction period. The latter is much pronounced for production of **4** in absence

of autocatalyst **2**. Although anticipated, the reaction performs much faster with increasing enantiopurity of chiral initiator than with racemic *rac*-**2**, which presents a kinetic profile comparable with the control reaction without Soai initiator. Such a behavior rises from the absence of the autocatalytic trigger, with the minuscule amount of enantiopurity imbalance. Interestingly, reaction for scalemic **2** was significantly higher and comparable with enantiopure *ent*-**2**.

The graphs shown in Figure 3A report the rate of the reactions plotted against the respective conversion, while Figure 3B reports the rates normalized to the highest value for each case, plotted against the fraction conversion of product **4**. These figures depict the reaction rates individually for the Soai alkanol **2** and pyridyl alkanol **4**. Plotting the reaction rate as a function
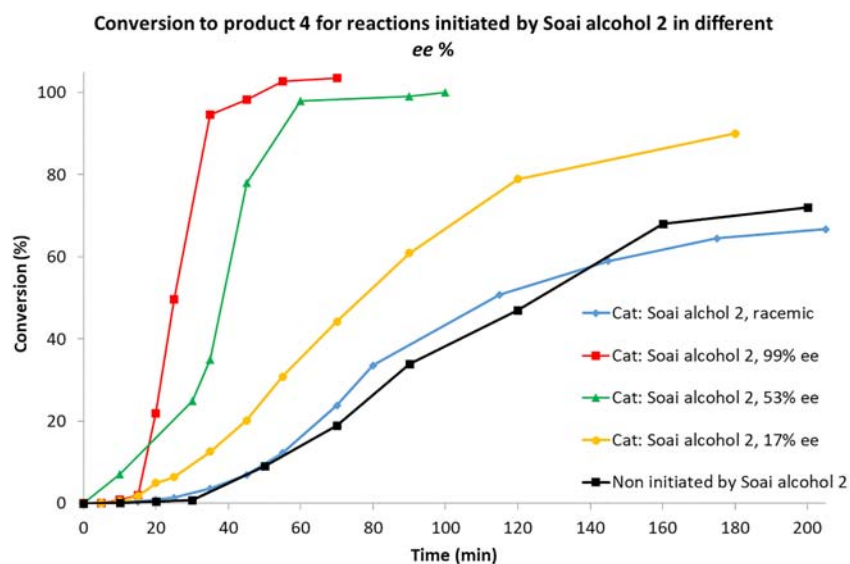

FIGURE 2 Kinetic profiles for conversion of **4** triggered by autocatalytic **2** with varying initial enantiopurity as function of time
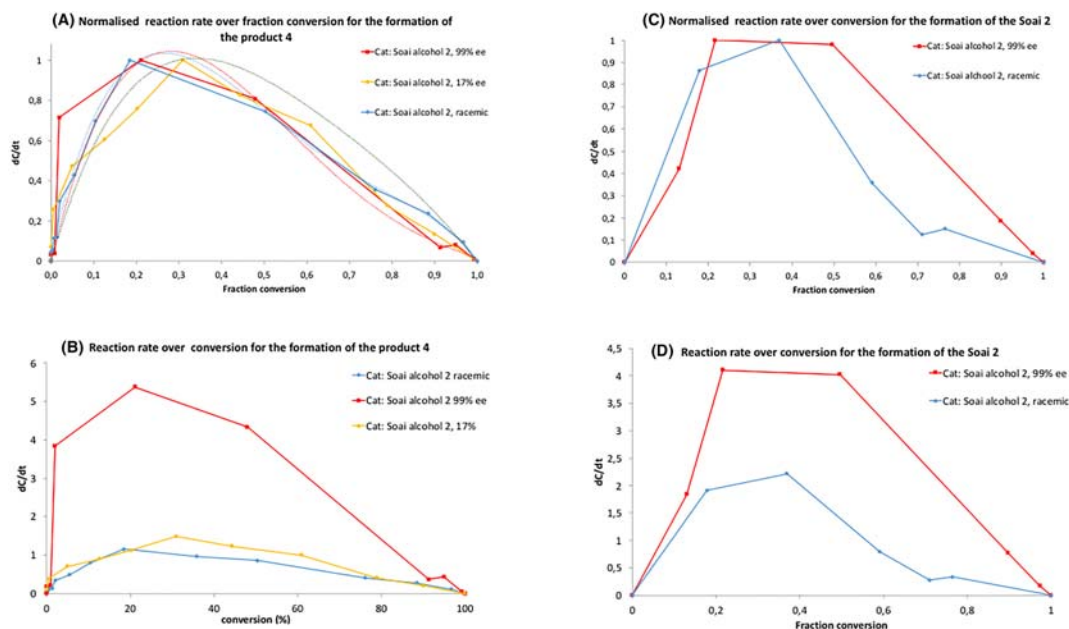
FIGURE 3 Experimental reactin rates for formation of **2** and **4** as a function of fraction conversion: (A) normalized reaction rate pictured as function of conversion to product **4**. The dashed lines in the plot indicate the calculated trend lines that best fit the experimental data. (B) Normalized reaction rate of the reaction pictured as function of conversion to Soai alcohol **2**. (C) Reaction rate of the reaction pictured as function of conversion to product **4**. (D) Reaction rate of the reaction pictured as function of conversion to Soai alcohol **2**

of fraction conversion during reaction progress allows examination of the correlation between the rates of formation of **2** and **4** with enantiopure and *rac*-**2** as trigger catalyst, in separate experiments.[14] Reaction progress was analyzed by sampling with internal standard and chiral HPLC, as can be seen in the Supporting Information.

The normalized graphs show that the measured autocatalysis rates for triggers *rac*-**2** and *ent*-**2** are proportional. In fact, the two traces overlap approximately (Figure 3A). Induction with *ent*-**2** promotes a significantly faster amplification of **4** (Figure 3B), and in

fact, we observe a reaction with five times higher rate as compared with reaction with *rac*-**2** as trigger. Notably, the reactivity with a 17% *ee* seed **2** was almost at the level of the rac-**2**. Similarly, Figure 3c,d depicts the reaction rates and the normalized reaction relative to the simultaneous formation of the Soai alkanol **2** in the same reactions. Thus, amplification of Soai autocatalyst follows a kinetic trend identical to previous description.[14a]

Figure 4 shows the plots of the % conv. of product **4** versus % conv. of Soai **2**. Interestingly, as can be seen, the resulting traces follow two divergent and
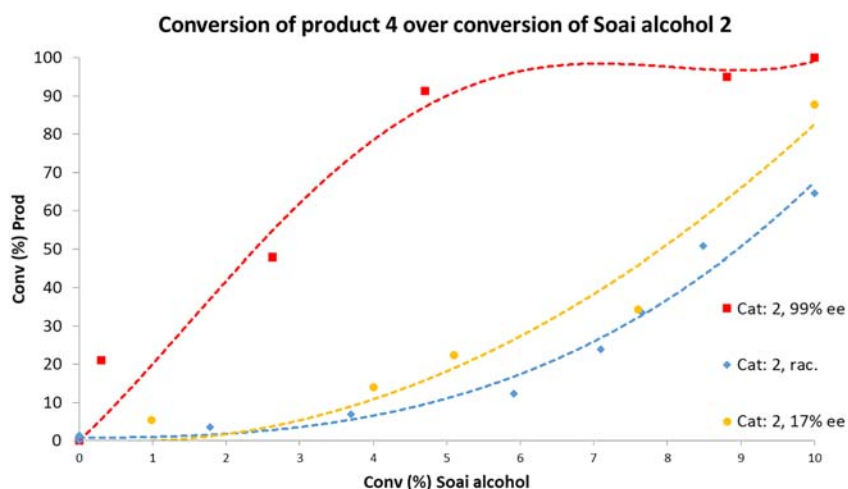

FIGURE 4 Correlation between the formation of product **4** in respect to the formation of Soai alcohol **2**, when the reaction system is initiated by *rac*-**2**, *ent*-**2**, or **2** in 17% *ee*
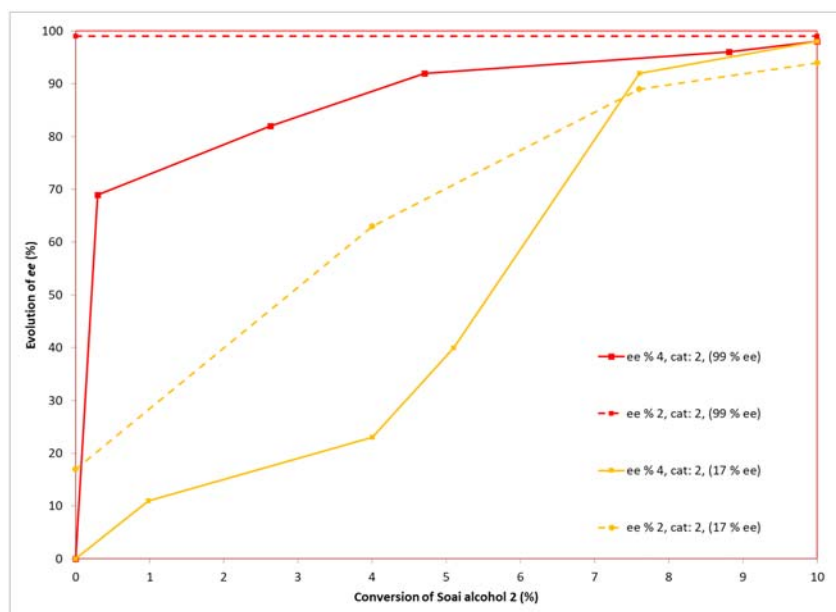
nonlinear shapes. Concentration of alkanol **4** grows significantly with *ent*-**2** as trigger, with no noticeable incubation period. The formation of **4** peaks at 5 mol% autocatalyst **2**, that is, half of its total concentration for the reaction conditions.

In stark contrast, progression of **4** as in relation to *rac*-**2** shows a significant induction period with slow buildup of **4**. A similar trend is observed with low enantiopurity in trigger **2** (17% *ee*). However, when a racemic or low *ee* chiral initiator is used, the formation of a higher amount of the Soai alkanol **2** is required before the conversion rate of **3** to **4** accelerates to reach its maximum. Hence, altogether amplification of trigger **3** promotes a higher rate for formation of **4**, which may account for the significantly greater asymmetric amplification.

Subsequent to autocatalysis of **2**, it is reasonably expected that *ee* of compound **4** would increase gradually. This is easily illustrated in Figure 5 (yellow lines) for amplification of **4** together with a low *ee* trigger **2** at the outset. However, seeding with *ent*-**2** at 99% *ee* reveals a burst from a rather low initial *ee* of **4** followed by rapid amplification to its maximum 99% *ee*. (Figure 5, red lines). The latter can be attributed to amplification of **4** through a background autocatalytic but lower enantioselectivity in initial rates of the reaction.

Figure 5 also shows that enantiopurity of Soai **2** increases steadily, whereas alkanol **4** shows a marked and nonlinear asymmetric amplification to reach 99% *ee*-even surpassing that of **2** (90% *ee*) with *declining* amplification in the second leg of the reaction. It has been shown that enantiopure Soai **2** was not a requirement for high amplification of alkanol **4**. This is also exemplified

on a similar substrate. In fact, alkanol **2** acts as an inductive agent with rising trigger power and contributes to the acceleration of amplification of **4** as a result of
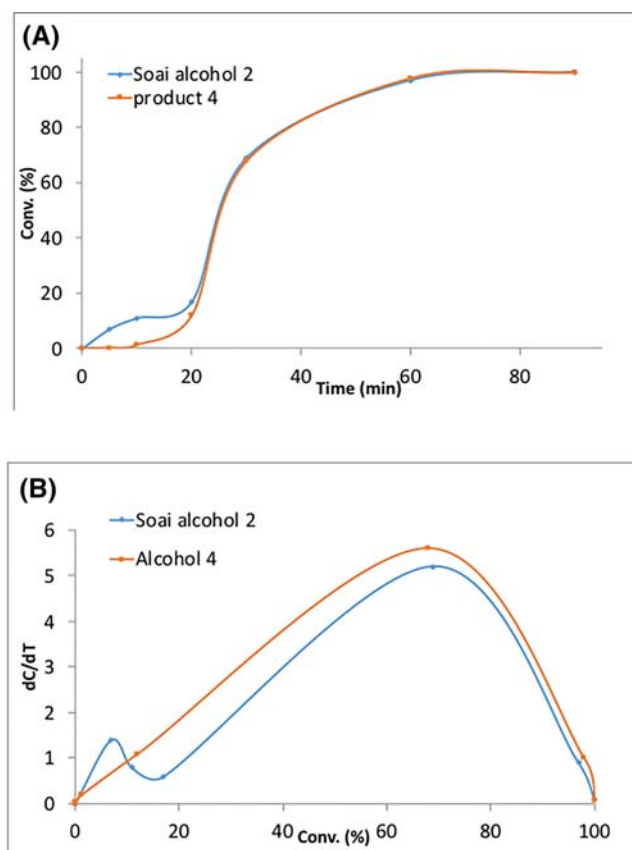

FIGURE 6 (A) Conversion to product (*R*)-**4** and (*R*)-**2** from an equimolar ratio of aldehydes **3** and **1**. Dashed lines show the reaction rates over time for the formation of both products. (B) Normalized reaction rates pictured against fraction conversion

increasing concentration and enantiopurity of **2**. This trigger influence acts in addition to alkanol **4** own autocatalytic performances and probable cross catalysis. However, in view of our results, an alternative explanation with formation of a mixed active species involving newly acquired **4** is not excluded.

In a separate set of experiments, we sought to investigate the sensitivity of the chemical system to a kinetic competition of the reactive species. Thus, an equimolar mixture of aldehydes **1** and **3** was let to react in presence of 1 mol% alkanols **2** (99% *ee*) as initiator and diisopropyl zinc. (*R*)-**2** was employed as chiral initiator with 99% *ee* for this experiment to ensure that the progress of the reaction is not affected by the asymmetric amplification of both **2** and **4**. The kinetic profile in Figure 6a consists of S-shaped curves for the progression of the formation of both alkanols **2** and **4**. Besides, (*R*)-**2** shows a marked forerun at early stage of the reaction, while (*R*)-**4** falls behind after an induction period (Figure 6a). This observation makes sense when considering that formation of **4** alone is slower in absence of autocatalyst **2** (inactivated process) as shown in Figure 2.

The reaction showed a characteristic rise in rate at the early stage of the reaction for the formation of alkanol **2** with a maximum rate at 10% fraction conversion (Figure 6b). Surprisingly, this rate tends first to decrease and increase again while matching the rate of formation of **4**. This behavior is suggestive of the combination of multiple reaction pathways.

4 | CONCLUSION

The present study described a chemical system combining two autocatalytic reactions operating in conjunction with nonlinear amplification of chirality. We provided preliminary kinetic analysis to disclose some mechanistic features that may count for the asymmetric amplification for **2** and **4** in parallel. Our study points out a greater importance of the propagation mechanism. Soai autocatalyst **2**, acting as a trigger, was found to successfully maintain ideal exponential growth that is translated into remote asymmetric amplification at much higher reaction rate for autocatalyst **4**. Autocatalysis of **2** behaves as previously described, even when subjected to presence of a second autocatalytic process. Furthermore, these kinetic studies reveal a five-fold superior amplification rates of **4** with enantiopure trigger **2**. This suggests a powerful reactive species, the structure of which has yet to be established. More detailed investigations are underway.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.