ACS central science

Research Article

Cite This: ACS Cent. Sci. 2018, 4, 776−780

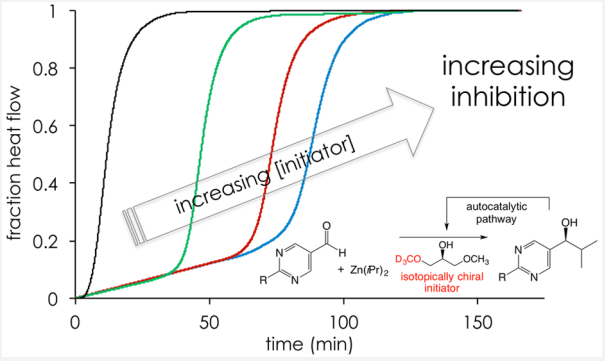
Rationalization of Asymmetric Amplification via Autocatalysis Triggered by Isotopically Chiral Molecules

Neil A. Hawbaker and Donna G. Blackmond*

Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States

Supporting Information

ABSTRACT: Asymmetric amplification induced in the Soai autocatalytic reaction by chiral initiators that are enantiomeric only by virtue of an isotope, e.g., $-CH_3$ vs CD_3-, is examined by spectroscopic, kinetic, and DFT modeling studies to help understand requirements for the emergence of biological homochirality. We find that the initiator *inhibits* the autocatalytic pathway at the outset of the reaction but ultimately provides the imbalance required for asymmetric amplification. This work provides clues in the ongoing search for prebiotically plausible versions of asymmetric autocatalysis.



The origin of homochirality in the chemical building blocks on which life is based is a question that has long intrigued scientists and laymen alike.[1] One of the most compelling proposals is that of asymmetric amplification via autocatalytic reactions, perhaps because such a process represents self-replication at its most basic molecular level and prefigures the self-replication of RNA. Theoretical models for autocatalysis in the emergence of homochirality were first presented in the mid 20th century,[2] but experimental proof-of-concept of asymmetric amplification by such a reaction process eluded researchers until Soai's report of the autocatalytic alkylation of pyrimidyl aldehydes in 1995.[3] The reaction product feeds back to catalyze its own formation, and beginning with a catalytic amount of product of low enantiomeric excess, product enantioenrichment increases with reaction turnover (Scheme 1).

Since the original report, Soai has gone on to demonstrate that the reaction may be initiated and directed with fidelity by a wide array of physical and chemical chiral sources in addition to its own reaction product, including circularly polarized light,[4] chiral crystals,[5] and most strikingly, isotopically chiral molecules.[6−12] In this latter case, molecules that are enantiomeric only by virtue of an isotope (^{13}C, ^{2}H, ^{18}O, and ^{15}N, see Table 1) are shown to direct enantioselectivity in the Soai autocatalytic reaction with remarkable fidelity.

Scheme 1. Chiral Amplification in the Soai Autocatalytic Reaction

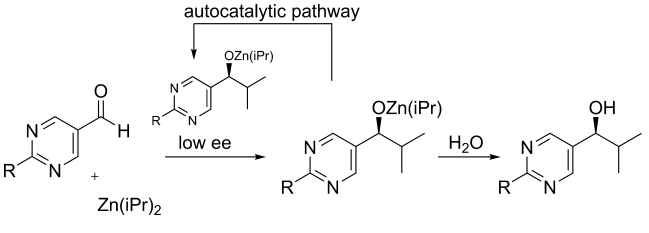
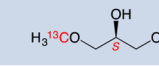
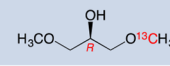
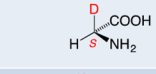
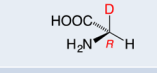
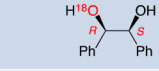
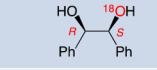
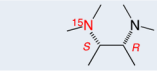
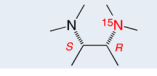


Table 1. Isotopic Enantiomers Employed as Enantioselective Initiators in the Soai Autocatalytic Reaction

isotope	triggers *S*-pathway	triggers *R*-pathway	ref.
$^{12}C/^{13}C$			6
H/D			7
$^{16}O/^{18}O$			8
$^{14}N/^{15}N$			9

The Soai reaction remains the sole documented experimental example of asymmetric amplification via autocatalysis. While the chemistry of this singular reaction has little prebiotic significance in its own right, understanding how such an exceedingly small difference between the two enantiomers of isotopically chiral initiators can dictate the stereochemical outcome of the Soai reaction may provide clues to the general requirements for asymmetric amplification via autocatalysis. Together with our knowledge of the Soai reaction mechanism accumulated from extensive experimental study over the past

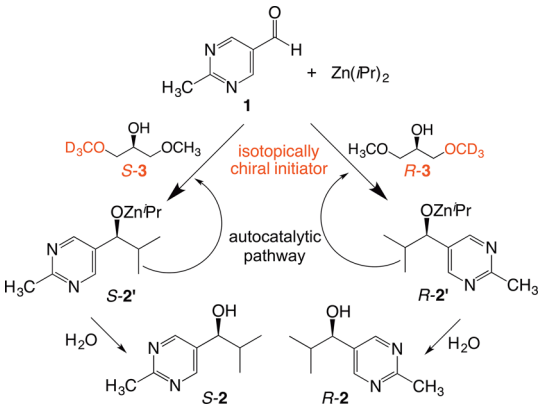
Received: May 9, 2018
Published: June 6, 2018

DOI: 10.1021/acscentsci.8b00297
ACS Cent. Sci. 2018, 4, 776−780

two decades,[13−20] such investigations may in turn help evaluate the feasibility of asymmetric autocatalysis as a mechanism for the emergence of biological homochirality beyond the specific case of the Soai reaction.

We report here the first mechanistic investigation probing the role of isotopically chiral initiators in selectively directing the Soai autocatalytic reaction, using initiator **3**, which is chiral by means of methoxy $-OCH_3$ and $-OCD_3$ groups, as shown in Scheme 2. In the absence of added reaction product, **3** directs

Scheme 2. Soai Autocatalytic Reaction Initiated by Isotopically Chiral Alcohol 3



the outcome of the Soai reaction with fidelity as shown in Scheme 2. Kinetic, spectroscopic, and DFT computational studies are employed to identify key species and deconvolute their role in the complex reaction network. We show that diastereomeric 2:1 product:initiator complexes are formed that *inhibit* the autocatalytic reaction regime at the outset, producing a minute difference in product enantiomeric excess that ultimately enables asymmetric amplification via autocatalysis.

Initiator **3** offers the unique opportunity to employ both ^{1}H and ^{2}H NMR spectroscopy to probe simultaneously the methoxy $-OCH_3$ and $-OCD_3$ groups of the molecule interacting with Soai reaction components. We investigated interactions between these molecules by titrating initiator **3** with increasing amounts of product **2**. Under reaction conditions in the presence of $(i\text{Pr})_2\text{Zn}$, both product **2** and initiator **3** alcohols are present as Zn-alkoxides, denoted as **2′** and **3′**, respectively, and their interactions are shown in Figure 1. ^{1}H spectra (top panel) and ^{2}H spectra (bottom panel) of initiator *S*-**3′** are shown in the presence of 2 equiv of reaction product *S*-**2′** (in blue) and *R*-**2′** (in magenta). The initiator *S*-**3′** methoxy groups appear between 3.1 and 3.3 ppm in both ^{1}H and ^{2}H NMR spectra. In the presence of product **2′**, these peaks shift significantly, and the spectra simplify to a single peak at the point where 2 equiv of product are added.[21] Shifts of different magnitude for *S*-**3′** in the presence of *S*-**2′** compared to *R*-**2′**, along with collapse to a single peak at 2 equiv of product, imply formation of distinct diastereomeric product−initiator species that reach saturation at a 2:1 ratio between product and initiator.

Interestingly, Figure 1 reveals that the magnitude of the chemical shift for **3′** is greater for the *mismatched* (*S*-**3′** + *R*-**2′**) species in the ^{1}H NMR spectrum (which monitors the initiator $-OCH_3$ group), but greater for the *matched* (*S*-**3′** + *S*-**2′**) species in the ^{2}H NMR spectrum (which monitors the initiator $-OCD_3$ group). These differences between matched vs

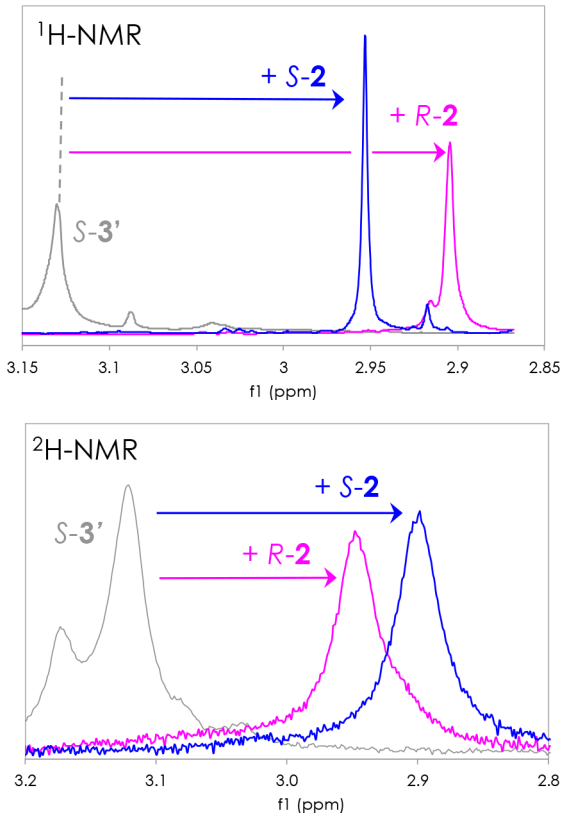


Figure 1. Titration of initiator *S*-**3′** with 2 equiv of product *R*-**2** (90% ee, magenta) or *S*-**2** (90% ee, blue) in the presence of 10 equiv of $(i\text{Pr})_2\text{Zn}$ at 0 °C monitored by ^{1}H NMR (top) and ^{2}H NMR spectroscopy (bottom).[21]

mismatched[22] interactions in the $-OCD_3$ and $-OCH_3$ regions are consistently observed with either hand of initiator **3** and either hand of product **2**.[21]

^{1}H DOSY measurements provide further support for formation of a 2:1 product:initiator complex. DOSY spectra of the species formed at 25 °C from $[(i\text{Pr})_2\text{Zn}]$ = 92 mM, [*S*-**3**] = 8.7 mM, and [*S*-**2**] = 21 mM in d^8-toluene gave a diffusion coefficient $D = 7.20 \times 10^{-10}$ m^2 s^{-1}. Applying a calibration curve developed in our previous work[19] for estimating molecular weights of Soai reaction intermediates to our current DOSY measurement for the complex formed at a 2:1 product:initiator ratio yields a prediction that falls within 12% of the molecular weight of a 2:1 product initiator complex.[21]

Plausible structures for putative 2:1 product:initiator matched and mismatched complexes from *S*-**3** may be proposed based on these considerations and on prior studies of Soai reaction structures as well as known dialkylzinc chemistry. We hypothesized that such complexes would contain the stable Zn−O−Zn−O square core that has been observed for many alkylzinc structures, including the square product dimer first proposed by Brown and co-workers as the resting state in this system,[15,17,18] drawing on the Noyori−Kitamura model for Zn alkylations.[23] DFT calculations identified the matched (*S*-**3′**/*S*-**2′**/*S*-**2′**) and mismatched (*S*-**3′**/*R*-**2′**/*R*-**2′**) complexes shown in Figure 2 as lowest energy structures. Since the tetrahedral Zn adds an additional chiral center, 32 diastereomeric structures are possible. These other potential structures and their relative energies are shown in the Supporting Information.[21]

Figure 2 shows that a "double square" fused Zn−O core incorporates one Zn alkoxide from each of the two product

DOI: 10.1021/acscentsci.8b00297
ACS Cent. Sci. 2018, 4, 776−780

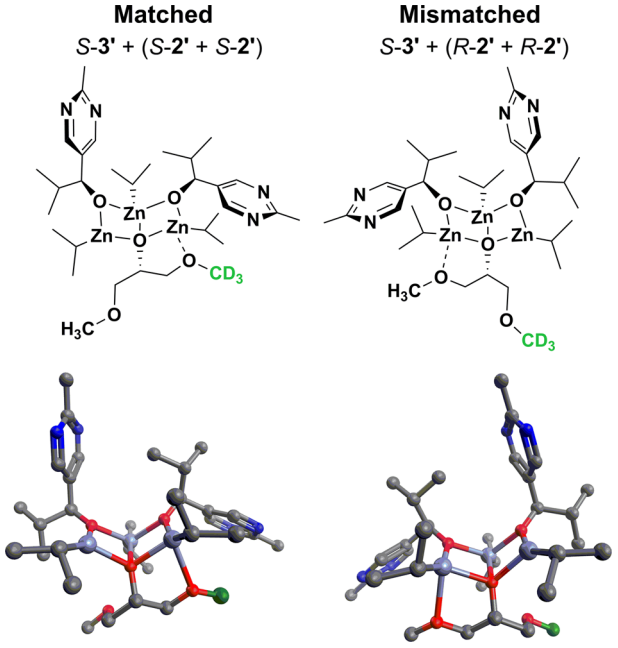


Figure 2. Lowest energy structures for 2:1 product:initiator complexes determined by DFT calculations.[21] Left: matched (*S*-**3**′/*S*-**2**′/*S*-**2**′) complex. Right: mismatched (*S*-**3**′/*R*-**2**′/*R*-**2**′) complex. Protons are removed for clarity. Ball-and-stick models shown with the CD_3 group designated by the green ball. Matched and mismatched designations are defined in ref 22.

molecules and one from the initiator, with the center oxygen arising from the initiator. The two squares are situated nearly perpendicular to one another. The matched and mismatched structures are not measurably different in energy.[21] However, the position of the $-OCD_3$ group in the matched complex compared to that in the mismatched complex may now be considered in light of our observation of the different chemical shift for each species in the ^1H vs ^2H NMR spectrum (Figure 1). The relative magnitude of the shift may correlate with the degree of flexibility of the $-OCH_3$ or $-OCD_3$ group in the structure. If a larger shift indicates less flexibility, or closer interaction between initiator and product, then our NMR results predict that the $-OCD_3$ group may be interacting more closely for the matched species while the $-OCH_3$ group is interacting more closely for the mismatched species. This is indeed suggested by the structures in Figure 2.

The NMR clues about the nature of the interaction between the initiator **3** and the reaction product **2** led us to explore the role of the initiator under reaction conditions, where the initiator is introduced at the outset in lieu of added reaction product, as in Soai's studies of isotopically chiral initiators.[6−9] Temporal progress of the reaction of Scheme 2 was monitored by reaction calorimetry in the presence of increasing amounts of initiator *S*-**3**.[21] Figure 3 reveals that, in the presence of **3**, the reaction exhibits a significant induction period of zero-order kinetics and low reactivity prior to onset of the characteristic autocatalytic profile. In the absence of the initiator, autocatalysis commences within a few minutes; however, the length of the induction period increases with increasing inhibitor concentration, demonstrating that autocatalysis is in fact *inhibited* by the presence of chiral initiator **3**. Figure 3 (bottom) shows that the maximum rate decreases and shifts to higher conversions as initiator concentration increases. The longer background reaction period exhibited at higher initiator concentration

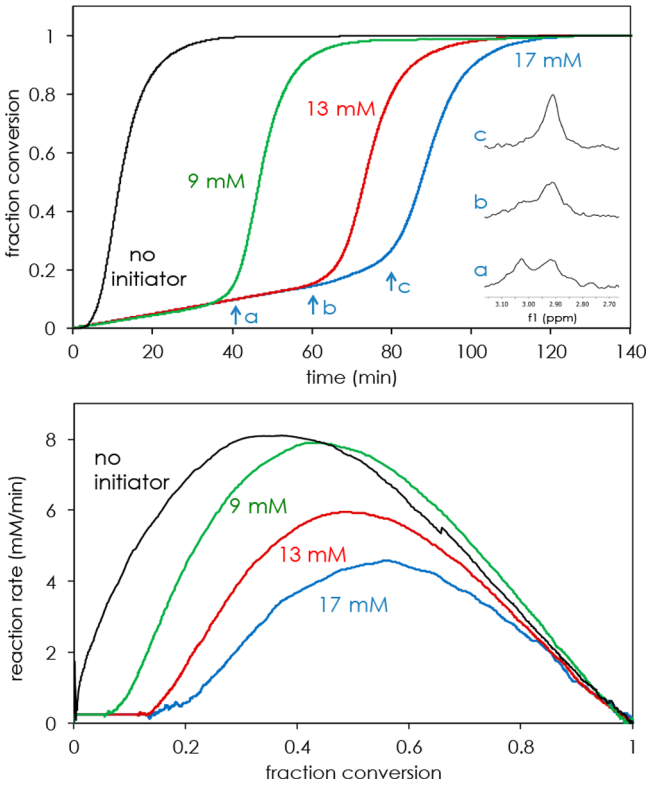


Figure 3. Kinetic profiles of the reaction of Scheme 1 from reaction calorimetry. 110 mM **1**, 275 mM $(i\text{Pr})_2Zn$ in toluene at −12 °C with concentrations of initiator *S*-**3** as shown. Top: fraction conversion vs time. Bottom: reaction rate vs fraction conversion. Inset in top plot shows ^2H spectra of the initiator **3**′ $-OCD_3$ group at reaction time points noted for 17 mM.[21]

results in greater depletion of the aldehyde concentration driving force prior to the onset of autocatalysis.

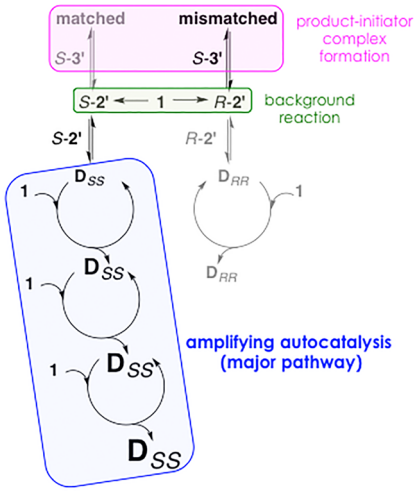
In the absence of initiator, the reaction produces racemic product **2**. Racemic product was also obtained at the end of the reactions using either *S*-3 or *R*-3, but as has been demonstrated by Soai,[6−12] sequential amplifying cycles subjecting the reaction mixtures to additional reactants consistently produce high (>95% ee) enantioselectivity (toward *S*-**2** using *S*-**3** and *R*-**2** using *R*-**3**) for reactions at all levels of initiator.[21] Figure 3 also shows ^2H NMR spectra taken at three time points during a reaction employing high initiator concentration. Comparison with the ^2H NMR spectrum in Figure 1 reveals that the spectrum observed as the autocatalytic regime begins to dominate (point c) resembles that of the initiator−product interaction at 2 equiv of product **2**.

The observed delay in the onset of the autocatalytic profile as a function of increasing initiator concentration along with our NMR observations of a 2:1 product:initiator interaction leads us to propose a plausible rationale for both how the initiator inhibits the autocatalytic pathway and how it imparts selectivity in the reaction. Our earlier study of the Soai reaction,[13] where we developed a modified Kagan ML_2 model[24,25] for autocatalytic asymmetric amplification, demonstrated that, in the case of substrate **1**, product **2** formed in the reaction is driven strongly toward stochastic dimer formation. The fact that only the homochiral species $\mathbf{D}_{RR}$ and $\mathbf{D}_{SS}$ are active as autocatalysts provides the inhibition mechanism that is key to autocatalytic amplification of enantiomeric excess. Scheme 3 pictorially summarizes the proposed role of the initiator for

DOI: 10.1021/acscentsci.8b00297
ACS Cent. Sci. 2018, 4, 776−780

reactions carried out in the absence of added product **2**, overlaid onto a simplified Soai reaction network.

Scheme 3. Soai Reaction Network with Uncatalyzed Pathway (Green), Initiator−Product Pathway (Magenta), and Autocatalytic Pathway (Blue)



The fact that higher initiator concentrations cause the autocatalytic regime to be slower to take off, and that autocatalytic behavior appears to be triggered at a 2:1 product:initiator ratio, supports the proposal that molecules of product **2**′ slowly formed in the background uncatalyzed reaction (green pathway in Scheme 3) react preferentially with the initiator (magenta pathway in Scheme 3) instead of immediately forming self-dimers. After the reaction product has fully saturated the available initiator in forming highly stable matched and mismatched complexes, subsequently formed product **2**′ is free to self-react to give the active homochiral dimers $\mathbf{D}_{RR}$ and $\mathbf{D}_{SS}$, which instigate the autocatalytic regime. Scheme 3 rationalizes selectivity in the autocatalytic pathway by suggesting that a minutely stronger mismatched interaction pulls a slightly greater amount of *R*-**2**′ out of the active catalyst network and thus induces a slight enantiomeric excess toward product *S*-**2**′, allowing the *S*-**2**′ autocatalytic cycle to dominate.

Soai and co-workers have carried out extensive synthetic studies demonstrating the remarkable fidelity with which ^{13}C, ^{18}O, ^{15}N, and ^{2}H isotopically chiral alcohols or amino acids are able to direct enantioselectivity in the Soai autocatalytic reaction.[6−12] While they did not report mechanistic studies, they proposed that the initiator directly induces an enantiomeric excess in the product of the reaction of the pyrimidyl aldehyde with $(i\mathrm{Pr})_2\mathrm{Zn}$, with this slightly enantioenriched product ultimately allowing amplifying autocatalysis. However, this hypothesis cannot account for the inhibiting role of the initiator observed in Figure 3 or its strong interaction with product shown in Figure 1. Our mechanistic studies suggest that the role of the isotopically chiral initiator may not be in acting directly as a chiral catalyst or chiral auxiliary in the Soai reaction itself;[26] instead, by selectively and strongly binding to chiral product **2**′, the initiator modulates the concentration and enantiomeric excess of **2**′ available at the point where the autocatalytic reaction begins to dominate the network. The net result is akin to seeding the reaction with an immeasurable amount of slightly enantioenriched product **2** at that point in time. In support of this proposal, the parameters for the kinetic model developed from a fit to the reaction progress data at different initiator concentrations based on the mechanism in Scheme 3 also successfully predict both rate and temporal enantiomeric excess for reactions carried out with added product **2** as catalyst.[21]

The fidelity with which the isotopically chiral initiator is able to direct the Soai reaction product is based on two requirements: (1) a minute difference between the stability of the matched and mismatched product−initiator species; and (2) a greater affinity of the product for the initiator than for its self-interaction.

The Soai reaction remains a singular, striking example of amplification of enantiomeric excess in an autocatalytic reaction and a manifestly efficient means of approaching homochirality. The fact that the system can be directed with fidelity by chiral sources with the slight differences exhibited by isotopically chiral molecules such as **3** is a testament to the sensitivity of this reaction at the point where it enters the autocatalytic regime. In general, our work suggests that, for all the myriad different physical and chemical means through which chiral induction has been demonstrated in this reaction,[27] autocatalytic amplification of enantiomeric excess is unleashed in all cases by selective product interrogation that creates a tiny enantiomeric imbalance in the Soai reaction product itself. The identity of the directing force may thus be seen as incidental; the autocatalytic power of the active Soai product species itself accounts for both the efficiency and the remarkable chiral amplification characteristic of this reaction.

Autocatalysis with asymmetric amplification is a far-from-equilibrium reaction system that is defined by two events:[28] (i) a symmetry breaking transition that is highly sensitive to small asymmetric influences; and (ii) a reaction that exhibits a higher-order burst of autocatalytic activity. The first criterion is necessary to obtain selectivity; the second criterion is required for two reasons: first to maintain this selectivity above stochastic noise, and second to propagate the selective pathway at the expense of that of its enantiomer. Our work reveals that the Soai reaction meets these requisites when any given chiral directing force becomes large enough to overcome the stochastic noise level of the racemic background reaction just at the point where the reaction enters its autocatalytic regime. This elegant solution to the question of homochirality will help fuel the ongoing search to discover an autocatalytic reaction that exhibits these features and exemplifies prebiotically plausible chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.8b00297.

Details of the experimental protocols, analytical procedures, kinetic and spectroscopic studies, kinetic modeling, and DFT calculations (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Blackmond@scripps.edu.

ORCID

Donna G. Blackmond: 0000-0001-9829-8375

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acscentsci.8b00297
ACS Cent. Sci. 2018, 4, 776−780

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge funding from the Simons Foundation Simons Collaboration on the Origins of Life (SCOL 287625). Preliminary experiments by Dr. Timo Gehring and discussions with Dr. John M. Brown are acknowledged. We thank Dr. R. Erik Plata for advice on DFT calculations. We are grateful for the expertise of Dr. Laura Pasternack of the Scripps NMR facilities.

■ REFERENCES

(1) Blackmond, D. G. The origin of biological homochirality. *Cold Spring Harbor Perspect. Biol.* **2010**, *2*, a002147.
(2) Frank, F. C. On spontaneous asymmetric synthesis. *Biochim. Biophys. Acta* **1953**, *11*, 459−463.
(3) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule. *Nature* **1995**, *378*, 767−768.
(4) Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K. Amplification of a slight enantiomeric imbalance in molecules based on asymmetric autocatalysis: the first correlation between high enantiomeric enrichment in a chiral molecule and circularly polarized light. *J. Am. Chem. Soc.* **1998**, *120*, 12157−12158.
(5) Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Sato, I. d- and l-Quartz-promoted highly enantioselective synthesis of a chiral organic compound. *J. Am. Chem. Soc.* **1999**, *121*, 11235−11236.
(6) Kawasaki, T.; Matsumura, Y.; Tsutsumi, T.; Suzuki, K.; Ito, M.; Soai, K. Asymmetric autocatalysis triggered by carbon isotope (13C/12C). *Science* **2009**, *324*, 492−495.
(7) Kawasaki, T.; Shimizu, M.; Nishiyama, D.; Ito, M.; Ozawa, H.; Soai, K. Asymmetric autocatalysis induced by meteoritic amino acids with hydrogen isotope chirality. *Chem. Commun.* **2009**, 4396−4398.
(8) Kawasaki, T.; Okano, Y.; Suzuki, E.; Takano, S.; Oji, S.; Soai, K. Asymmetric autocatalysis triggered by chiral isotopomer arising from oxygen isotope substitution. *Angew. Chem., Int. Ed.* **2011**, *50*, 8131−8133.
(9) Matsumoto, A.; Ozaki, H.; Harada, S.; Tada, K.; Ayugase, T.; Ozawa, H.; Kawasaki, T.; Soai, K. Asymmetric induction by a nitrogen $^{14}N/^{15}N$ isotopomer in conjunction with asymmetric autocatalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 15246−15249.
(10) Sato, I.; Omiya, D.; Saito, T.; Soai, K. Highly enantioselective synthesis induced by chiral primary alcohols due to deuterium substitution. *J. Am. Chem. Soc.* **2000**, *122*, 11739−11740.
(11) Kawasaki, T.; Ozawa, H.; Ito, M.; Soai, K. Enantioselective synthesis induced by compounds with chirality arising from partially deuterated methyl groups in conjunction with asymmetric autocatalysis. *Chem. Lett.* **2011**, *40*, 320−321.
(12) Matsumoto, A.; Oji, S.; Takano, S.; Tada, K.; Kawasaki, T.; Soai, K. Asymmetric autocatalysis triggered by oxygen isotopically chiral glycerin. *Org. Biomol. Chem.* **2013**, *11*, 2928−2931.
(13) Blackmond, D. G.; McMillan, C. R.; Ramdeehul, S.; Schorm, A.; Brown, J. M. Origins of asymmetric amplification in autocatalytic alkylzinc additions. *J. Am. Chem. Soc.* **2001**, *123*, 10103−10104.
(14) Buono, F. G.; Blackmond, D. G. Kinetic evidence for a tetrameric transition state in the asymmetric alkylation of pyrimidyl aldehydes. *J. Am. Chem. Soc.* **2003**, *125*, 8978−8979.
(15) Gridnev, I. D.; Serafimov, J. M.; Quiney, H.; Brown, J. M. Reflections on spontaneous asymmetric synthesis by amplifying autocatalysis. *Org. Biomol. Chem.* **2003**, *1*, 3811−3819.
(16) Blackmond, D. G. Asymmetric autocatalysis and its implications for the origin of homochirality. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5732−5736.
(17) Gridnev, I. D.; Brown, J. M. Solution structure and reagent binding of the zinc alkoxide catalyst in the Soai asymmetric autocatalytic reaction. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5727−5731.
(18) Klankermayer, J.; Gridnev, I. D.; Brown, J. M. Role of the isopropyl group in asymmetric autocatalytic zinc alkylations. *Chem. Commun.* **2007**, 3151−3153.
(19) Quaranta, M.; Gehring, T.; Odell, B.; Brown, J. M.; Blackmond, D. G. Unusual inverse temperature dependence on reaction rate in the asymmetric autocatalytic alkylation of pyrimidyl aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 15104−15107.
(20) Gehring, T.; Quaranta, M.; Odell, B.; Blackmond, D. G.; Brown, J. M. Observation of a transient intermediate in Soai's asymmetric autocatalysis: insights from 1H NMR turnover in real time. *Angew. Chem., Int. Ed.* **2012**, *51*, 9539−9542.
(21) See the Supporting Information for details.
(22) Nomenclature for product:initiator complexes is defined as "matched" for the same stereochemistry (product and initiator both *R* or both *S*) and mismatched for opposite stereochemistry (product *R*, initiator *S* or product *S*, initiator *R*).
(23) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. Quantitative analysis of the chiral amplification in the mino-alcohol-promoted asymmetric alkylation of aldehydes with dialkylzincs. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809.
(24) Girard, C.; Kagan, H. B. Nonlinear Effects in Asymmetric Synthesis and Stereoselective Reactions: Ten Years of Investigation. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959.
(25) Blackmond, D. G. Kinetic aspects of nonlinear effects in asymmetric catalysis. *Acc. Chem. Res.* **2000**, *33*, 402−411.
(26) We observed similar inhibitory kinetic behavior for chiral molecules previously shown to act as catalysts in other dialkylzinc alkylations of aldehydes. Soai, K.; Watanabe, M.; Koyano, M. Synthesis of hydroxyl ketones by chemoselective alkylation of keto aldehydes with diakylzincs catalyzed by amino alcohol, diamine, or dilithium salt of piperazine. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2124−2125 See the Supporting Information for details.
(27) Soai, K.; Kawasaki, T.; Matsumoto, A. Asymmetric autocatalysis of pyrimidyl alkanol and related compounds. Self-replication, amplification of chirality, and implication for the origin of enantioenriched chirality. *Tetrahedron* **2018**, *74*, 1973−1990.
(28) Kondepudi, D. K.; Asakura, K. Chiral autocatalysis, spontaneous symmetry breaking, and stochastic behavior. *Acc. Chem. Res.* **2001**, *34*, 946−954.

DOI: 10.1021/acscentsci.8b00297
ACS Cent. Sci. 2018, 4, 776−780