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Structural Contributions to Autocatalysis and Asymmetric Amplification in the Soai Reaction

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three autocatalytic systems representing a continuum of nitrogen Lewis basicity strength suggests how the strength of N-Zn binding events is a predominant contributor toward the rate of autocatalytic progression.

1. INTRODUCTION

1.1. Asymmetric Autocatalysis and the Soai Reaction. The diisopropylzinc alkylation of pyrimidine-carbaldehydes, crowned the Soai reaction (Figure 1a), represents an astonishing and fortuitous confluence of three themes in catalysis: (1) autocatalysis, (2) enantioselective catalysis, and (3) positive non-linear effects. Each product enantiomer catalyzes its own formation (selective autocatalysis) while also inhibiting catalysis by its counterpart (a positive non-linear effect)-resulting in a continuous amplification of the excess enantiomer with reaction progression. Soai's seminal 1995 report describes how the inclusion of scalemic product carbinol 2a at the beginning of the reaction with 1a results in the newly formed product being more enantioenriched than the initial additive (Figure 1b).^{1,2} Near racemic autocatalyst with only 51:49 e.r. provides a higher enantioenriched product with 55:45 e.r. The product from one reaction is used as the catalyst for a subsequent reaction, and in successive reaction cycles, the enantioenrichment of 2a increases to up to 94.5:5.5 e.r. Following this discovery, it was demonstrated that, in general, the reaction of diisopropylzinc with 2-substituted pyrimidinyl aldehydes displays autocatalytic, asymmetric amplification.^{3–} In particular, a bulky alkynyl substituent (Figure 1c) drastically increases the performance of these reactions in terms of enantioenrichment achieved, reaction times, and isolated yields. For example, the asymmetric autocatalytic reaction with 1d affords the product in an enantiopure form in quantitative yield. Following this report, 1d became the workhorse substrate for future studies by the Soai group.

demonstrating amplifying autocatalysis were identified. Comparison of

Curiously, replacement of the *t*-Bu group in 1d by a triisopropylsilyl (TIPS) group (1c) is detrimental to asymmetric amplification.⁴

Although the theoretical framework for amplifying autocatalysis was articulated as far back as 1953 (the term "asymmetric autocatalysis" itself was coined by Wynberg in 1989), the Soai reaction remains the only example of an autocatalytic, non-equilibrium, irreversible chemical transformation capable of robust asymmetric amplification.9,10 With substrate 1d, the reaction provides enantiopure products within three reaction cycles, even when the autocatalyst used has a calculated e.e. as low as 5×10^{-5} %.¹¹ Investigations by Soai¹²⁻¹⁴ and Singleton^{15,16} have demonstrated that the Soai reaction is capable of producing a non-racemic product even in the absence of any added catalyst. This symmetry breaking arises from a statistical imbalance in the formation of the enantiomeric products in the early evolution of the reaction, which is subsequently propagated and amplified by asymmetric autocatalysis.9 The Soai reaction is thus a successful example of absolute asymmetric synthesis.¹⁷ A large variety of chiral additives ranging from amino acids¹⁸ to enantiomorphic

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a. Overall scheme for the amplifying autocatalytic Soai reaction



b. Seminal report (Soai, 1995)



Note: analogous reaction with pyridine-3-carbaldehyde (3a) shows poor asymmetric autocatalysis, with asymmetric erosion (Soai, 1990)

c. Improved Substrates: 2-alkynyl pyrimidine carbaldehydes



Figure 1. (a) The Soai reaction, with the general scheme of amplifying autocatalysis and salient features. (b) Seminal report with substrate 1a. (c) Improved performance with alkynyl-substituted substrates, except in the case of 1c.

crystals,¹⁹ helical hydrocarbons,²⁰ and even cryptochiral molecules²¹ can influence the outcome of the reaction by biasing an initial imbalance of one of the enantiomers.²² Remarkably, even circularly polarized light²³ and isotopic chirality^{24–26} have been demonstrated to result in a non-racemic product. One may state that in multiple cycles of the Soai reaction, symmetry breaking and enantioenrichment are inevitable. The Soai reaction hence qualifies as a chemical transformation with a predisposition to evolve toward homochirality. Soai's seminal discoveries have received wide-spread attention in diverse chemical fields and have revived discussions regarding absolute asymmetric synthesis, symmetry breaking, and the origin of biological homochirality.^{27–31} The interested reader is directed to a number of reviews for further

details, accounts, and descriptions of the remarkable Soai system. $^{17,22,32-35}$

1.2. The Soai Reaction as a Mechanistic Challenge. More than two decades since Soai's initial discovery, fundamental questions regarding its mechanism have remained unanswered. The most obvious outstanding issues are the precise identity of the alkoxide autocatalyst, its genesis and propagation, the origin of its non-linear behavior, and a compelling transition state model accounting for generation of the homochiral product from the reactants.

Empirically, it is clear that the structural constraints on reactants are severe, but the basis for this narrow substrate scope remains enigmatic. In the dialkylzinc alkylations of pyridine-3-carbaldehyde (3a), inclusion of the scalemic

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Figure 2. Crystal structures for the square-macrocycle-square (SMS) tetrameric isopropylzinc alkoxide derived from 2d. Adapted with permission from ref 60. Copyright 2015 John Wiley and Sons.

product carbinol provides newly formed product that is not racemic but has a lower enantioenrichment than the additive.³⁶ The reports with pyrimidine-5-carbaldehydes without exception describe the use of only diisopropylzinc as the nucleophile. The incompetence of other dialkylzinc reagents is presumed, although systematic studies are lacking.^{37,38} Soai et al. have described isolated reports wherein amplifying autocatalysis with diisopropylzinc was demonstrated with other substituted quinoline-3-carbaldehydes and 5-carbamoylpyridine-3-carbaldehyde.³⁹⁻⁴² However, pyrimidine-5-carbaldehydes remain the workhorse substrates for the reaction, and among these, 2-alkynyl-substituted aldehydes display superior autocatalysis and selectivities. TIPS-alkynyl substrate 1c presents a remarkable exception to this trend and highlights the puzzling idiosyncrasies typical of the substrate scope of this transformation. The rationalization of these structural constraints poses a test to any mechanistic proposal.

The reaction is extremely sensitive to initial chiral imbalances, including the extraordinary susceptibility to additives with isotopic chirality and other cryptochiral additives. The fundamental chemical interactions between such additives and the reactants that ultimately trigger symmetry breaking remain poorly understood. Similarly, rationalization of the structural and kinetic boundary conditions assuring symmetry breaking in uncatalyzed reactions remains a key issue.^{43,44}

The study of the Soai reaction also presents technical challenges including: (1) the dialkylzinc reagent is highly pyrophoric and moisture sensitive, complicating experiment design and execution; (2) the autocatalytic nature of the reaction demands non-trivial strategies for kinetic analysis; and (3) structural investigations may be impeded by the stability and solubility of the zinc alkoxide intermediates. Thus, overall, the Soai reaction, with its *sui generis* characteristics, presents unique challenges to mechanistic investigation. A holistic understanding of the reaction raises hopes of developing new transformations that may display amplifying asymmetric autocatalysis and potentially contribute to the understanding of the origin of homochirality in nature.

1.3. Current Mechanistic Consensus. The striking properties of the Soai system have motivated numerous studies to elucidate the mechanism of this iconic transformation. ${}^{34,37,38,43,45--61}$ Because catalyst aggregation is a central contributor to non-linear effects, investigations have

predominantly focused on probing the aggregation states of the product zinc alkoxide. Early kinetic studies with the 3-formyl-6-methylpyrimidine-carbaldehyde system included a comparison between enantiopure and racemic autocatalysts and indicated a dimeric alkoxide aggregate as the catalytic species, while subsequent investigations with an enantiopure catalyst suggested two aldehyde substrates in a tetrameric complex.^{45,48,58} The first structural studies in 2004, deduced from ¹H NMR spectroscopy with the **2b**-derived isopropylzinc alkoxide, are consistent with a dimeric model.^{49,50} Note that these experiments cannot conclusively distinguish between dimers and higher order aggregates. Likewise, modeling studies indicated that the extraordinarily high experimentally observed amplification efficiency (especially for the alkynyl-substituted systems) was not possible with dimeric catalysis and necessitated the invocation of higher order aggregates in the catalytic cycle.^{35,47,55} Theoretical suggestions for possible higher order aggregate structures, including the squaremacrocycle-square (SMS) tetramer, were made for the first time by Gridnev and Brown.^{37,62} Subsequent investigations provided further momentum for a tetrameric catalyst model. Reaction progress kinetic analysis (RPKA) experiments⁵⁷ with substrate 1e indicated the reaction rate to be zeroth order in diisopropylzinc, first order in catalyst (product alkoxide), and 1.6 order in aldehyde. An intriguing inverse temperature dependence of the reaction rate was also observed. On the basis of kinetic and spectroscopic clues, the suggestion that the SMS tetrameric alkoxide might be the active catalyst was raised for the first time. A DFT study to model these tetramers was subsequently reported by Gridnev in 2012.⁵

Finally, in 2015, the first crystal structure of the isopropylzinc alkoxide derived from 2d was published by Soai et al.^{60,61,63} Depending on the conditions for crystallization, a tetrameric or oligomeric aggregate is obtained. The homochiral and heterochiral tetramers possess a 12-member macrocycle with a connectivity resembling the SMS tetrameric structure proposed earlier (Figure 2). The assembly can be considered as a concatamer of two Zn–O square dimers, ligated through pyrimidine-Zn coordination. In the homochiral tetramer, the unbound pyrimidine units (referred to as the tetramer "arms") are oriented on the same face of the macrocycle. The racemic, heterochiral tetramer possesses a similar overall connectivity, but the arms are placed on opposite sides of the macrocycle. In both the homochiral (enantiopure) and heterochiral (racemic)



Figure 3. (a) Amplifying autocatalysis with substrate **3b**. (b) The cube-escape model to rationalize the formation of the (auto)catalytically competent SMS tetramer. (c) (From left) DFT calculated structures and relative energies (kcal/mol) for the ground-state heterochiral and homochiral SMS tetramers. The stereodetermining transition-state structure on the right arises after a *floor-to-floor* binding of the substrate aldehyde **3b** to the homochiral tetramer. The location of the concerned zinc centers (yellow) in the heterochiral tetramer precludes such a binding mode. Adapted with permission from ref 64. Copyright 2020 Springer Nature.

tetramers, a pair of three-coordinate, unsaturated (alkoxy)zinc atoms are present as part of the pyrimidinyl arms. The orientation of these unsaturated zinc centers follows the pattern of the arms. Finally, for both the tetramers, the crystal structure also showed that, except for the two macrocycleresiding nitrogen atoms, all the remaining six pyrimidinyl nitrogen atoms are bound by diisopropylzinc molecules (these are not shown in the structure in Figure 2). Soai's crystal structure elucidation is a landmark achievement in providing a definitive understanding of the solid-state SMS tetramer and revealing the differences in the homochiral and heterochiral tetrameric assemblies.



Figure 4. Structural constituents of the three components (catalyst, reagent, and substrate) in the Soai reaction.

Two decades of investigations into the Soai reaction culminated in the identification of alkoxide tetramers as the likely autocatalysts. However, this knowledge had not provided insights into the mode of action of the catalyst nor a compelling transition-state model or an explanation of the structural constraints on the reactants. Recently, we addressed this central issue regarding the modus operandi of the autocatalyst.⁶⁴ These investigations, summarized in Figure 3, revealed the structural logic behind the assembly and working of the SMS tetrameric (auto)catalyst on the basis of the following key findings: (1) The discovery of amplifying autocatalysis in the diisopropylzinc alkylation of the related pyridine substrate 3b proved that only one nitrogen in the aromatic core is necessary for the Soai phenomenon (Figure 3a). (2) Whereas related structures like PyEE, PyEI, and PyIE predominantly form catalytically inactive, Zn-O cubic tetramers, the steric bulk of the product zinc alkoxide PyII, in combination with pyridyl-nitrogen coordination, enables a "cube-escape" pathway to an alternative, catalytically active tetrameric cluster sharing identical connectivity with Soai's crystal structure (the SMS tetramer) (Figure 3b). (3) This cluster engages the substrate aldehyde through a two-point coordination (via the carbonyl oxygen and the aromatic nitrogen) to the unsaturated (alkoxy)zinc centers on the catalyst floor (highlighted in yellow in the ground-state structures in Figure 3c), termed as the "floor-to-floor" model. (4) The resulting activated aldehyde is alkylated by an activated diisopropylzinc molecule, delivered preferentially from only one of the catalyst arms, leading to the homomorphic product alkoxide (TS-4b) in Figure 3c (the competing transition-state structure which leads to the heteromorphic product and is disfavored by 4.2 kcal/mol is not shown), comporting with an enantioselective, autocatalytic

process. (5) Such a *floor-to-floor* binding is structurally impossible for the thermodynamically preferred *heterochiral* **PyII** SMS tetramer (Figure 3c, $G_{rel} = 0$), and the alternative single-point binding pathway results in an energetic penalty for catalysis, hence providing a basis for the signature non-linear effect in the reaction. Overall, the *cube-escape*, *floor-to-floor* catalysis model rationalizes both the genesis of the SMS tetramer as well as its specific, non-linear, autocatalytic activity.

The current work complements and builds on these findings. Experiments providing specific insights into the structural contributions that affect asymmetric autocatalysis in the Soai reaction are described. Further subtle effects of the nitrogen Lewis basicity in controlling autocatalytic progression are uncovered by a comparison of the pyrimidine and pyridine systems.

1.4. Research Plan and Rationale. The asymmetric autocatalytic reaction of 1b involves three components: the zinc alkoxide "catalyst", the dialkylzinc "reagent", and the aldehyde "substrate". Each component may be divided intuitively into identifiable constituents (Figure 4). For example, at least four constituents of the catalyst are (1) the alkylzinc counterion, (2) the carbinol group (isopropyl in this case), (3) the heteroaromatic core, and (4) the 2-alkynyl substituent. The aldehyde possesses fewer constituents, only the pyrimidine ring and the 2-substituent. No such deconstruction of the dialkylzinc component is possible. An overarching objective as the mechanistic investigations were inaugurated was to holistically delineate the role played by these three components, and their structural constituents, in affecting catalysis, stereoselectivity, and non-linearity in the reaction. Rate enhancement, enantioselectivity, and a nonlinear effect are the most relevant properties of the alkoxide catalyst in combination with the dialkylzinc reagent. However,

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Figure 5. Compound numbering for substrates and zinc alkoxide catalysts.



Figure 6. In situ IR spectroscopic monitoring of the Soai reaction (wavenumber at $\sim 1710 \text{ cm}^{-1}$).

which structural constituents of the alkoxide affect these properties was, at the outset, unclear. Likewise, the contributions from the aldehyde structural constituents that make it an ideal substrate for the catalyst were unknown. Extracting meaningful structure–activity relationships from a set of analogous autocatalytic reactions is challenging because a single structural change cannot be performed—both the (auto)catalyst and the substrate structures have to be modified



^a Measured e.r of product carbinol after workup, N.D. Not determined (no product was detected in these cases)

Figure 7. PmII-catalyzed, "mixed catalyst-substrate" diisopropylzinc alkylations monitored by in situ IR spectroscopy.

at the same time. However, autocatalysis can be considered as a special case of catalysis wherein the substrate structure is "matched" to generate a product that is catalytically active. From such a perspective, it is seen that catalysis, enantioselectivity, and non-linearity arise as a result of the catalyst structure and can manifest in other reactions where the catalyst is operational, whereas autocatalysis is an incidental property emerging from a *matched* substrate structure. We hypothesized that individual contributions from the catalyst and the substrate can be studied independently from each other in a set of reactions where the (auto)catalyst and substrate structures are not matched but the substrates are nonetheless competent (in other words, the reaction is *catalytic* but not autocatalytic). Thus, experiments combining various zinc alkoxides and aldehyde substrates were planned and are described in the upcoming sections. Figure 5 depicts the compound numbering scheme in these experiments.

2. RESULTS AND DISCUSSION

2.1. Structure–Activity Relationships in the Soai Reaction. 2.1.1. In Situ IR Monitoring. To establish a reliable

analytical method, the reactant combination of diisopropylzinc and pyrimidine-5-carbaldehyde 1b was chosen as a model system for investigations. In situ IR spectroscopic analysis was considered a convenient technique to monitor the transformation. A distinct advantage of this method over previously used in situ monitoring strategies (calorimetry or NMR spectroscopy) is that the experimental setup allows for simultaneous manual sampling of the reaction mixture to determine product e.r. at any chosen time point. The aldehyde is added as the final component to the reaction mixture (this time is assigned as t = 0, and the resulting carbonyl IR absorbance peak is tracked over time. Figure 6 depicts a typical data set obtained for such experiments. Combining 1b with diisopropylzinc in the absence of catalyst led to a sigmoidal aldehyde decay with an initial induction period followed by rapid aldehyde consumption (entry 1). Inclusion of scalemic product carbinol as a catalyst in the reaction eliminates the induction period and results in a rapid reaction with higher final product e.r. (entry 2). Such behavior is typical for a reaction showing amplifying autocatalysis. In contrast, the same reaction with diethylzinc shows slow consumption in the





^a Measured e.r of the product carbinol after workup at indicated time

Figure 8. PmIE-catalyzed "mixed catalyst-substrate" diethylzinc alkylations monitored by in situ IR spectroscopy.

absence of added autocatalyst (entry 3). Inclusion of scalemic product results in enantiomeric erosion with no rate enhancement over the uncatalyzed reaction (entry 4). *Thus, the reaction of 1b with diethylzinc demonstrates no autocatalysis or chiral amplification.* The surprising failure of the TIPS analog, 1c, to display amplifying autocatalysis in reaction with diisopropylzinc was also examined. Indeed, in a series of *in situ* IR-monitored experiments with inclusion of the scalemic product carbinol as a catalyst, neither asymmetric amplification nor appreciable rate enhancement was observed over the sluggish background alkylation reaction, thus confirming Soai's previous findings.⁶⁵ *In situ* monitoring in combination with manual sampling emerged as a convenient tool to interrogate catalysis and selectivity in the Soai reaction.

2.1.2. "Mixed Catalyst–Substrate" Experiments and the Discovery of Amplifying Autocatalysis with 5-(Trimethyl-silylethynyl)pyridine-3-carbaldehyde. The investigation of the role of the aldehyde substrate constituents began with a study of the reaction of diisopropylzinc and various aldehydes with the isopropylzinc alkoxide of **2b**, henceforth denoted as **PmII** (nomenclature: Pm/Py/Ph = pyrimidine/pyridine/phenyl indicating the aromatic core, I/E = isopropyl/ethyl

indicating the carbinol alkyl group, and I/E = isopropyl/ethylindicating the alkylzinc group, see Figure 5), as the catalyst (Figure 7). The aim of this survey was to determine if the catalyst–reagent combination of **PmII** and diisopropylzinc could successfully affect rate enhancement and positive nonlinear enantioselectivity in the alkylation of aldehydes distinct from its "natural" substrate **1b** and to simultaneously evaluate the effect of substrate structure on such an activity. The runs are "mixed catalyst–substrate" experiments because the alkylation of the substrate produces a species distinct from the initial catalyst. Note that under these conditions, the uncatalyzed addition of diisopropylzinc to the test substrates is slow with low conversion. In Figure 7, the substrates are arranged in decreasing order of their rate of reaction, and this convention continues in the subsequent figures.

For aldehydes **3b**, **3a**, **1c**, and **3c**, diisopropylzinc alkylation with scalemic **PmII** afforded products with e.r. significantly higher than that of the added catalyst (Figure 7). The relative rates of reaction were qualitatively in the order **3b** \gg **3a** > **1c** > **3c**. In contrast, no product was detected with the analogous phenyl substrates **5a** and **5b**. The striking rate observed with **3b** motivated further detailed control experiments which revealed

that, in fact, the reaction of this substrate with diisopropylzinc displayed robust, amplifying, asymmetric autocatalysis! Thus, the high rate is attributable to an autocatalytic progression supported by the newly formed, catalytically competent product alkoxide. Such a possibility was rigorously ruled out for the other substrates. Thus, such mixed-catalyst experiments led to the discovery of the competent pyridine system, **3b**, and the subsequent *cube-escape*, *floor-to-floor* model summarized earlier.

Clearly, the signature characteristic of **PmII**, namely, catalyzed, positive non-linear, enantioselective addition of diisopropylzinc, is also conserved in reactions with some "unnatural" substrates (**3b**, **3a**, **1c**, and **3c**). However, it appears that, for such a substrate to be competent, the minimal structural requirement is a 3-azaaryl group. In hindsight, these constraints are identical to the ones described for the **PyII** tetramer autocatalyst,⁶⁴ a further confirmation of the striking similarity between the activities and mode of action of **PyII** and **PmII**. Note that the Gridnev transition-state model,⁵⁹ which discounts any interactions between the substrate nitrogen atoms and the unsaturated zinc atoms in **PmII**, cannot be reconciled with the incompetence of **5a** and **5b**.

These results indicated that the alkyl transfer property of the Soai autocatalyst **PmII** could be studied in a manner which is disconnected from autocatalysis by providing a suitable surrogate substrate that does not produce an autocatalytically competent product. Comparison of **3c** with **3a** and **1c**, respectively, suggests preliminary contributions of the substrate structure independent of the (auto)catalyst attributes, as (1) increasing the bulk of the alkynyl substituent reduces the catalytic rate, (2) a pyrimidine substrate is more active than a pyridine, and (3) these changes have a minimal effect on enantioselectivity of the catalytic transformation. Note that these conclusions specifically delineate substrate contributions to the overall catalysis by **PmII**.

In continuing the investigation of structural changes, the effect of the zinc alkoxide substituent was examined. The catalytic activity of alkoxide PmIE can be tested by including 2b as an additive (resulting in the rapid formation of PmIE under reaction conditions) in the diethylzinc alkylation of various substrates (Figure 8). This species represents a combination in which the carbinol alkyl group (isopropyl) is distinct from the (alkoxy)zinc alkyl group (ethyl). The resultant mixed-catalyst experiments can hence show only conventional catalysis without a possibility of autocatalysis. The results of these catalyzed reactions proved to be extremely informative. First, the control reactions of aldehydes 1b, 3a, 3b, 1c, and 3c showed no autocatalysis with diethylzinc (for example, in the case of 1b, see Figure 7). With inclusion of PmIE, varying efficiencies of catalytic diethylzinc alkylations were observed (Figure 8). With aldehyde 1b, a significant rate enhancement and a positive non-linear effect are seen (entry 1). The striking difference in the behavior of 1b here, in comparison to results in entry 4, Figure 6 (which shows the lack of autocatalysis in the diethylzinc alkylation of 1b, that is, the catalytic incompetence of PmEE), demonstrates that a subtle change in the alkoxide structure from PmEE to PmIE turns on amplifying asymmetric catalysis even with diethylzinc. It thus appears that unlike PmEE, PmIE can potentially construct, at least to some meaningful degree, a catalytic structure similar to **PmII** (note that partial cube escape seen in the case of PyIE must be also operative in the case of PmIEwith the difference that the activity of the SMS tetramer in the

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latter is apparently high enough to affect catalysis). Rate and selectivity vary considerably with aldehyde structure (entries 2–5), and a positive non-linear effect is observed with all substrates except **3a** (entry 2). Only marginal catalysis was observed with the challenging TIPS-substituted substrates, **1c** and **3c** (entries 4, 5). As was the case in reactions with **PmII**, the phenyl substrates **5a** and **5b** were unreactive.⁶⁵ Although **3b** reacts more slowly than **3a**, the substituted pyrimidine **1b** is more reactive than either of these, suggesting that a balance of two opposing factors determines aldehyde reactivity: (1) the activating pyrimidine ring and (2) the deactivating 2-alkynyl substitution. Likewise, comparison of entries 2, 3, and 5 suggests that the 2-alkynyl substituent improves substrate-controlled selectivity, and among them, an optimum balance of reactivity and selectivity is achieved for aldehyde **3b**.

These conclusions strengthen and extend the trends deduced from Figure 7. In terms of rate and selectivity, comparison of analogous reactions in Figures 7 and 8 suggests that **PmII**-diisopropylzinc as a catalyst-reagent combination is superior to **PmIE**-diethylzinc. The reduction in activity of the latter allows identification of substrate effects, which are otherwise masked in the case of highly efficient catalysis with the former.

Poor catalysis and asymmetric erosion were observed with **PmEE**-catalyzed "mixed catalyst–substrate" diethylzinc alkylations.⁶⁵ This behavior is consistent with the prediction that **PmEE** will predominantly exist as a catalytically inactive cubic tetramer. Finally, the activity of **PmEI** could not be unambiguously established because insolubility of this alkoxide precluded reliable estimation of catalyst concentration in solution.

2.1.3. An Empirical Structure-Activity Correlation. A qualitative assignment of the contribution of structural constituents in the Soai reaction emerges from the results of the mixed catalyst-substrate experiments. Before elaborating on these assignments, it is instructive to restate the inferences gained through the **PyII** floor-to-floor transition-state model described in our previous work:

- (1) The bulky isopropyl groups enable cube escape from the catalytically inactive cubic tetramer.
- (2) Only a single nitrogen atom is necessary in the aromatic core to assemble the autocatalytically active SMS tetramer.
- (3) The SMS tetramer can process substrates belonging to the pyridine-3-carbaldehyde scaffold; the aromatic nitrogen is indispensable for two-point binding.
- (4) The substrate alkynyl substituent increases alkyl transfer enantioselectivity by disfavoring the minor transition state through an unfavorable steric interaction.

Results of the mixed catalyst-substrate experiments with **PmII** and **PmIE**, while being consistent with all the above conclusions, provide additional inferences to this list:

- (5) The substrate alkynyl substituent decreases reactivity (while increasing selectivity).
- (6) The pyrimidine substrates are more reactive, presumably because of their increased electrophilicity in comparison to the pyridine substrates.
- (7) Diethylzinc, *in principle*, can be accepted as a reagent by the SMS tetramer to affect carbonyl alkylation, albeit with lower enantioselectivity as compared to diisopropylzinc.



Figure 9. Transition-state structures for NII-catalyzed alkyl transfer to 3a. Calculated at the M06-2X/def2-TZVPP-SMD (toluene)//B3LYP/6-31G(d) level of theory. Relative energies reported in kcal/mol. Purple, zinc; yellow, silicon; red, oxygen; blue, nitrogen; gray, carbon. Hydrogens are hidden for clarity.

A case for the role of the alkoxide alkynyl substituent can be made from the following observations: 65(1) The reaction of pyridine-3-carbaldehyde (3a) with diisopropylzinc does not show amplifying autocatalysis, and the product alkoxide is poorly soluble. (2) In our hands, the reaction of pyrimidine-5carbaldehyde (1a) with diisopropylzinc shows asymmetric amplification but with a lower potency than the alkynyl analogs, with the product alkoxide being poorly soluble. (3) The alkylation reactions of 3a and 1a are heterogeneous; precipitation of the product alkoxide is observed early in the reaction. In situ monitoring of the diisopropylzinc alkylation of 1a did not give a sigmoidal profile despite being autocatalytic, perhaps because alkoxide precipitation results in a constant solution-state catalyst concentration. The alkynyl substituent acts favorably by increasing the solubility of the product alkoxide as well as by minimizing formation of unproductive network aggregates by providing a steric shield on one side of the molecule. Thus, 3a is autocatalytically incompetent owing to formation of insoluble, unproductive aggregates of the product alkoxide. Such an aggregation is presumably mitigated in the case of 1a because of weaker binding interactions of the pyrimidine nitrogen, allowing the maintenance in solution of a critical concentration of active catalyst necessary to promote asymmetric amplification. It is important to note that precipitation is not the fundamental cause of autocatalytic amplification in the Soai reaction (reactions with the stalwart, highly efficient alkynyl-substituted substrates, for example, 1b and **3b**, are homogeneous). However, precipitation effects may play an additional role in some cases-for example, with 3a, our observations (and comparisons with reaction of a 1a) suggest that poor solubility of the product alkoxide contributes unfavorably.

To gain further insight into the incompetence of **3a** to undergo amplifying autocatalysis with diisopropylzinc, *floor-tofloor* transition states for alkyl transfer to **3a** by the expected SMS tetramer arising from the isopropylzinc alkoxide of **4a** (termed **NII**, equivalent to **PyII** minus the trimethylsilylalkynyl substituent—thus representing the theoretical autocatalytic alkylation of **3a** by diisopropylzinc) were computationally modeled (Figure 9). Transition structure **TS1** leading to the heterochiral (*R*)-4a product is slightly favored (0.2 kcal/mol) in comparison to TS2, which leads to the homochiral (*S*)-4a product. In contrast to the PyII system, these transition structures are almost isoenergetic, implying a poorly enantioselective alkyl transfer by the NII tetramer.

Hence, the diisopropylzinc alkylation of 3a does not show amplifying autocatalysis for at least two reasons: (1) the poor solubility of the product alkoxide and (2) the poor enantioselectivity of the NII SMS tetramer (the solution concentration of which is already depleted due to poor solubility)-catalyzed alkyl transfer pathway. On the basis of these results, the structure-activity inference list is extended further:

(8) From the perspective of the autocatalyst, the alkynyl substituent contributes to efficient, enantioselective activity by (a) improving solubility characteristics, (b) directing the alkoxide away from unproductive aggregates by providing a steric shield on one side of the molecule, and (c) favoring a specific conformation of the SMS tetramer that increases enantioselectivity to meaningful levels.

The incompetence of substrates 1c and 3c (containing the triisopropylsilylalkynyl substituent; both these systems are highly soluble) in the Soai reaction is among the most bewildering idiosyncrasies of the Soai system. However, the mixed catalyst-substrate experiments demonstrated that both of these were competent substrates for PmII (Figure 7), PmIE (Figure 8), and PyII.⁶⁵ Clearly, these aldehydes can undergo positive, non-linear enantioselective alkylation with a viable SMS tetramer. Thus, it can be concluded that the TIPS substituent maintains substrate competence but renders the corresponding SMS tetramer (derived from isopropylzinc alkoxides of 2c and 4c) inactive, hence impeding autocatalysis. Spectroscopic studies indicate that the isopropylzinc alkoxide of 4c exists as a tetramer.⁶⁵ It is believed that this tetramer may exist in a highly hindered SMS conformation, which precludes substrate approach and binding.

Taken together, these conclusions paint a qualitative picture of the contributions of various structural components in the

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Figure 10. Summary of the roles played by various structural constituents in effecting catalysis and selectivity in the Soai system.

Chart 1. Substituted Nicotinaldehydes Tested for Asymmetric Autocatalysis with Diisopropylzinc



Soai reaction toward effecting amplifying asymmetric autocatalysis and are summarized in Figure 10.

2.2. Investigating Asymmetric Autocatalysis with Pyridine-3-carbaldehyde Derivatives. The observation of amplifying, asymmetric autocatalysis with 3b stimulated a survey of diisopropylzinc alkylations of other substituted pyridine-3-carbaldehyde (nicotinaldehyde) derivatives (Chart

1). Compounds with substituents at either the 5- or 6-position, as well as 5,6-disubstituted substrates were tested.

Aldehydes 7, 8, 9, 10, and 14 were obtained from commercial sources whereas 11, 12, 13, and 15 were prepared by Suzuki–Miyaura or Sonogashira coupling reactions of the parent 6-bromonicotinaldehyde.⁶ Aldehydes 16, 17, and 18 were accessed by routes originating from 5- bromonicotin-





aldehyde (14) and involved the common intermediate 5bromo-6- iodonicotinaldehyde (21) (Scheme 1). Deprotonation of the known dioxolane derivative 20 with tetramethylpiperidinylmagnesium chloride-lithium chloride⁶⁶ followed by trapping with iodine afforded the key intermediate 21. Sonogashira coupling of 21 with 1.0 equiv of ethynyltrimethylsilane afforded 22 in high yield which, after dioxolane deprotection provided target aldehyde 16. Likewise, Sonogashira coupling of 21 with excess ethynyltrimethylsilane and subsequent dioxolane deprotection in a single pot allows direct access to 17. The 5-methyl substituent was introduced by a Kumada coupling of 22 and methylmagnesium chloride and was followed by dioxolane deprotection to afford 18 in good yield. Buchwald (t-Bu₃P)₂Pd-G3 precatalyst was uniquely successful in the Kumada coupling whereas other palladiumligand combinations gave poor yields.

A similar strategy to access 19 was unsuccessful because treatment of the protected dioxolane obtained from 23 (3-(1,3-dioxolan-2-yl)-5-fluoropyridine) with a variety of bases followed by trapping with iodine predominantly yielded iodination at the 4-position. Thus, the TIPS ether 24 was utilized for iodination with tetramethylpiperidinylmagnesium chloride, lithium chloride, and iodine. Carbinol 25 obtained in this way was alkynylated under Sonogashira coupling conditions to yield 26. Finally, Swern oxidation of 26 afforded the target aldehyde 19 in high yield. In a series of *in situ* IR-monitored reactions, each aldehyde was tested for asymmetric autocatalysis by inclusion of the corresponding scalemic product carbinol in the diisopropylzinc alkylation reaction. These reactions were compared to background reactions without any added product. In general, most of the substrates in Chart 1 displayed poor autocatalytic rate enhancement compared to the background reaction.⁶⁵ Apart from **3b**, amplifying asymmetric autocatalysis was observed only with **12**, **16**, **18**, and **19**.

Reaction of substrate 12 without added catalyst (entry 1, Figure 11) shows sigmoidal aldehyde consumption. Inclusion of scalemic product carbinol (entry 2), results in drastic rate acceleration with the product carbinol being more enantioenriched (91:9 e.r.) than the added catalyst (71:29 e.r.). These results contradict a report by Amedjkouh et al. wherein this transformation was reported to proceed with enantiomeric erosion.⁶⁷ From our perspective, Amedjkouh et al.'s findings of enantiomeric amplification in the diisopropylzinc alkylation of 12, with 2b as the catalyst are consistent with 12 itself being autocatalytically competent.

Reactions of 5,6-disubstituted nicotinaldehyde substrates 16 and 18 with diisopropylzinc show asymmetric amplification under autocatalytic conditions, however the rate enhancement compared to the background reaction is only modest (Figure 12, entries 1-4). In case of 16, a number of unidentified side products were observed. Qualitatively, the reaction of 18 appears to be more efficient, with cleaner conversion and a



^a Measured e.r. which includes initially added catalyst

Figure 11. Amplifying asymmetric autocatalysis in the reaction of 12 with diisopropylzinc.

higher final product e.r. Similar experiments with substrate 17 led to poor conversion and multiple side products without any asymmetric amplification in the target carbinol.⁶⁵ Conversely, autocatalyzed diisopropylzinc alkylation of 19 proceeded with robust asymmetric amplification and high rate enhancement compared to the background reaction (Figure 12, entries 5, 6), mirroring the behavior seen with substrate 3b. This outcome demonstrates that in the diisopropylzinc alkylations of 6trimethylsilylethynyl-nicotinaldehydes, increasing the bulk of the 5-substituent adversely affects asymmetric autocatalytic behavior. The autocatalytic isopropylzinc alkoxide generated in the reaction with substrate 19 is labeled FPyII (FPy = fluoropyridine, I = isopropyl) and is discussed below.

2.3. A Comparison of PmII, PyII, and FPyII Systems. 2.3.1. Comparison of Initial Rates with Nicotinaldehyde. The autocatalytic systems arising from substrates 1b, 3b, and 19 differ only in the heteroaromatic core. The pyrimidine nitrogen, with lower Lewis basicity than the pyridine,^{68,69} is expected to display weaker binding to the Lewis acidic diisopropylzinc reagent as well as to the O-Zn moiety. Likewise, the FPyII nitrogen should be less Lewis basic than the **PyII** nitrogen (pK_a : pyridine = 5.23, 3-fluoropyridine = 3.0, pyrimidine = 1.30).^{68,70} The comparison of these three systems thus provides an interesting opportunity to study the effects of such electronic changes on the autocatalytic behavior. To compare the inherent activities of the three alkoxide catalysts (PmII, PyII, and FPyII) derived from these substrates, a comparison of initial rates with a common substrate, pyridine-3-carbaldehyde (3a), was undertaken.

Diisopropylzinc alkylation reactions under identical conditions were evaluated in the presence of 10 mol% of the alkoxide catalyst, with *in situ* IR monitoring of aldehyde consumption. Initial rates were calculated and are reported as averages of three replicates (Figure 13). The three catalysts provide the product carbinol in comparable enantioenrichment. However, initial rates of FPyII and PmII, while comparable to each other, are at least 2-fold lower than the rate with PyII. This observation may be rationalized by taking into account the *floor-to-floor* TS model for the alkyl transfer step. The transferring diisopropylzinc in the PmII and FPyII tetramer is deactivated (as compared to PyII) because of the weaker Lewis basicity of the coordinating nitrogen, resulting in a slower elementary alkyl transfer step. Thus, for an identical substrate, the activities of the three catalysts are in the order PyII > PmII ~ FPyII.

2.3.2. Comparison of Autocatalytic Behavior. Autocatalytic reactions of substrates 1b (PmII system), 3b (PyII system), and 19 (FPyII system) were compared with inclusion of 8 mol% of initial autocatalyst. Under these conditions, rate of reaction in the PyII system is faster than the FPyII system (Figure 14) but significantly slower than the PmII system. While the **PmII** system reaction is nearly complete within one minute, less than 10% conversion is seen for the other two at this time point. In these experiments, each autocatalyst interrogates a different substrate, and thus, the alkyl transfer rate is also affected by changes in the electrophilicity of the substrate aldehyde. On the basis of the increased electronwithdrawing effect of a pyrimidine ring and a fluoropyridine group in comparison to an unsubstituted pyridine core, 1b and 19 are expected to be more electrophilic than 3b. This conflicting balance of catalyst Lewis basicity and substrate electrophilicity must determine the overall rate of alkyl transfer



^a Measured e.r. which includes initially added catalyst





Figure 13. Comparison of alkyl transfer rates of PyII, FPyII, and PmII. TS model for the alkyl transfer with PyII highlighting the transferring diisopropylzinc moiety (blue arrow) bound to the activating arm nitrogen (green arrow).

in the three systems. With this perspective, the relative rates of the **PyII** and **FPyII** system appear reasonable. However, the extraordinarily high rate of the **PmII** system compelled further investigations into factors affecting autocatalytic progression. 2.3.3. Inhibition of Autocatalysis by Excess Diisopropylzinc. The **PyII** system resembles many aspects of the autocatalytic **PmII** system.⁶⁴ However, studies probing the effect of excess dialkylzinc reagent led to the discovery of an



Figure 14. Comparison of autocatalytic progression in PyII, FPyII, and PmII systems.

unexpected divergence in the behavior of the two systems. Consistent with earlier reports,⁵⁷ autocatalytic progression of the **PmII** system was found to be insensitive to diisopropylzinc concentration, but similar experiments with the **PyII** system resulted in inhibition of reaction progression with increasing reagent concentration. This phenomenon was also noted for the **FPyII** system. Increasing diisopropylzinc concentration also adversely affected the selectivity of the reaction, presumably by accelerating the uncatalyzed background addition while concomitantly compromising the catalytic pathway.

Figure 15 presents the results of these comparative experiments (all runs are reproducible and represent one among duplicate experiments). The reactions of the three systems were carried out under identical conditions, with varying concentration of diisopropylzinc. The yellow curves represent reactions with the PmII system, which are extremely rapid, are invariant in rate with respect to diisopropylzinc concentration, and provide the product with >99:1 e.r. in all cases. Reaction profiles with the PyII and FPyII system are represented by solid and dashed curves, respectively. The autocatalytic reaction of PyII was inherently faster than that of FPyII at lower concentrations of zinc reagent (compare entries 1 and 5, also see Figure 14). However, with increasing diisopropylzinc concentration, reactions of the former were inhibited more significantly than the latter (entries 1-8). Thus, at diisopropylzinc concentrations upward of 2.4 equiv, the FPyII reactions were faster than those of PyII (compare entries 2 and 6, 3 and 7, 4 and 8). These results demonstrate

that the extent of inhibition by excess diisopropylzinc is greater for **PyII** than for **FPyII** and is entirely absent for **PmII** (i.e., **PyII** > **FPII** > **PmII**).

Qualitatively, the correlation of this trend with decreasing Lewis basicities of the aromatic cores in these systems provides suggestions for the cause of this inhibitory behavior (Figure 16). Spectroscopic investigations prove that the substrate aldehyde is involved in dynamic association with the dialkylzinc reagent by coordination of the ring nitrogen (red equilibrium).⁶⁴ However, such a binding precludes the *floor-to*floor association to the tetrameric catalyst, which is necessary for catalyst activity. Thus, it is hypothesized that inhibition results from competitive binding of the reagent to the substrate ring nitrogen, making the substrate unavailable for association to the O-Zn center in the catalyst. Consistent with observations, the extent of inhibition correlates with the strength of the N-Zn association, which in turn must depend on the Lewis basicity of the azaaryl moieties. This hypothesis was further explored by reaction modeling of kinetic data to an autocatalytic mechanism and model simulations.

2.3.4. Insights from Kinetic Modeling—Steps Affecting Reaction Progression. On the basis of the mechanistic knowledge gained so far, a minimal set of elementary steps can be compiled for the definition of the autocatalytic reaction pathway (the *simplified floor-to-floor* "SF" model, Figure 17). These steps are (1) equilibrium binding of substrate aldehyde (A) and diisopropylzinc (Z) to yield the N–Zn bound adduct (AZ); (2) equilibrium binding of the catalyst (C) to diisopropylzinc (Z) at the pyridyl arm (binding by only one

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Figure 16. Schematic of the autocatalytic process (represented for the PyII system) and hypothesis for the origin of inhibition in the three systems.

SF: a simplified reaction model for autocatalysis

A = aldehyde, Z = Diisopropylzinc,C = SMS tetrameric catalyst, P = product alkoxide monomer ΑZ A + Z substrate - dialkylzinc (N-Zn) association K₁a = k₁/k_{m1} catalyst arm – dialkylzinc (N-Zn) + Z association steps most significant for rate of substrate – SMS tetramer reaction ACZ progression floor-to-floor docking $K_{3}a = k_{3}/k_{m3}$ ACZ alkyl transfer product alkoxide monomer 5 dissociation product alkoxide monomer 2F 6 dimerization product alkoxide dimer 7 С dimerization - newly formed SMS tetramer TMS TMS TMS FPvI Pmll Pyll system system system low value of K1a high value of K1a, intermediate value of K1a, maximal inhibition reduced reagent inhibition faster reaction, minimal reagent inhibition lower value of K₃a due to attenuated Lewis basicity? high value of k_c due to enhanced electrophilicity of the substrate? сно сно *i*-Pr₂Zn Still Competent **Better Electrophile?** TMS TMS

Figure 17. SF model of autocatalysis. Steps affecting rate of reaction progression are highlighted in red. The consequences of these steps in the PyII, FPyII, and PmII systems are indicated.

arm is considered for simplicity) to yield the active species (CZ); (3) equilibrium binding of substrate aldehyde (A) to the catalyst-diisopropylzinc adduct (CZ) to yield the activated complex (ACZ); (4) alkyl transfer from the SMS tetramer active complex (ACZ) to yield the catalyst-bound product alkoxide adduct (PC); (5) equilibrium dissociation of the product monomer alkoxide (P) to regenerate the SMS tetramer (C); (6) dimerization of the monomeric alkoxide (P) product to a dimeric unit (2P); and (7) dimerization of the dimeric unit (2P) to yield the newly constituted SMS tetramer (C). Rate constants for each step are designated. Arguably, this is a simplified picture of the actual catalytic process, and additional steps can be envisaged. For example, the binding of two molecules of diisopropylzinc to the catalyst is ignored; the order of binding of the reagent and aldehyde to

the SMS tetramer may be different than the one suggested here; reagent binding to the product alkoxide may exist; the precise mechanism of tetramer reformation is reasonable but nonetheless speculative; the contribution of an uncatalyzed background alkylation is ignored; etc. However, the scheme incorporates all fundamental binding events necessary and sufficient to achieve compatibility with the "SMS tetramer– *floor to floor* (SF)" autocatalysis model.

This model could qualitatively reproduce the autocatalytic reaction profiles for the **PyII** system, including the inhibitory effect of diisopropylzinc, and with chemically realistic kinetic parameters.⁶⁵ Model simulations reveal that among the seven proposed elementary steps, *the rate of reaction progression is sensitive only to the kinetic parameters of steps 1, 3, and 4* (Figure 17, red) in the following manner:⁶⁵ (1) decreasing the

association constant K_1 results in faster reactions and decreasing extent of diisopropylzinc inhibition, mimicking the transitions from the **PyII** (to **FPyII**) to **PmII** systems; (2) an increase in the value of K_3 results in faster reactions; and (3) an increase in the value of k_c results in faster reactions.

To a first approximation, the relative rates of the PyII, FPyII, and PmII systems and the differences in severity of diisopropylzinc inhibition originate from divergent contributions from the three autocatalytic-progression-determining steps in the SF model (Figure 17). Considering the Lewis basicity of the aromatic nitrogen atoms, the K_1 a values for the three systems are expected to be in the order PmII « FPyII < PyII.⁶⁸⁻⁷⁰ Moreover, the adduct for the pyrimidine system (red box) is, in principle, a competent species because floor-tofloor binding is still feasible with the second pyrimidine nitrogen atom. The binding constant for reagent coordination to this second nitrogen (necessary to render the adduct incompetent) is expected to be very low. Taken together, these factors must contribute to a very low effective value of K_1 in the pyrimidine system, thus accounting for its extraordinary rate and absence of inhibitory behavior (this is reproduced in the model simulations). The qualitative prediction of $K_{3}a$ and k_{c} is non-trivial. In the three systems, the Lewis basicity of the substrate nitrogen atoms and the Lewis acidities of the unsaturated tetramer zinc atoms follow opposite trends, thus confounding a comparative estimate of the association constant for step 3. Similarly, the nucleophilicity of the catalyst-arm-bound diisopropylzinc molecule and the electrophilicity of the bound substrate follow opposite trends in the three systems, which complicates a comparative estimate of the alkyl transfer rate constant. Ultimately, an interplay of contributions from these steps must dictate the overall trend of reaction progression. Kinetic simulations are consistent with this hypothesis; modifying the values of K_1a , K_3a , and k_c to mimic the three systems can indeed reproduce their relative rate profiles.⁶⁵ Taken together, these preliminary modeling studies reveal how the substrate-reagent binding equilibrium, the catalyst-substrate binding equilibrium, and the alkyl transfer rate contribute to (1) rate of autocatalytic progression, (2) the origin of the extraordinarily rapid reactions in the **PmII** system, and (3) the origin of the relative extents of inhibition in the PyII and FPyII systems.

3. CONCLUSIONS AND OUTLOOK

The strategy of *mixed catalyst—substrate* experiments allowed extensive study of structure—activity relationships in the pyrimidine and pyridine systems. The results from these studies enabled a formulation of the roles played by structural constituents in effecting catalysis and selectivity in the Soai reaction. Contributions of the alkynyl substituent toward catalyst solubility, autocatalyst conformation, aggregate formation, and enhancing substrate-directed reactivity and enantioselectivity were elucidated. Similarly, subtle correlations of the alkyl groups and the aromatic core were identified.

An exploration of substituted nicotinaldehyde derivatives led to the determination of novel, competent substrates. Among these, the 5-fluoro-6-(trimethylsilylethynyl)-nicotinaldehyde (FPyII) system provided an opportunity to carry out a careful comparison between three autocatalytic systems in regard to the Lewis basicity of the aromatic nitrogen. Model kinetic simulations revealed how this factor critically influences the interplay of three steps in the autocatalytic pathway that are determinants of reaction progression. The low Lewis basicity of the pyrimidine nitrogen abrogates inhibition effects and results in superlative performance in the Soai reaction. These structural insights are completely consistent with the *floor-to-floor* transition-state model presented earlier.⁶⁴

The mechanistic landscape of the Soai reaction can now be summarized as follows: (1) The diisopropylzinc alkylation of Soai substrates affords isopropylzinc alkoxides that can access the SMS-tetramer by a combination of steric effects and nitrogen coordination (cube-escape model). (2) In general, this tetramer can enantioselectively alkylate a variety of aldehydes that belong to the pyridine-3-carbaldehyde scaffold (which includes pyrimidine-5-carbaldehydes) via a two-point floor-tofloor model—an autocatalytic reaction is simply a special case occurring for a "matched" substrate. (3) Structural effects play a critical role in the assembly of the SMS tetramer, its solubility, active conformation, and substrate accessibility, as well as the reactivity and selectivity imparted by the substrate-the rationalization of these effects largely explains the idiosyncratic substrate scope of this transformation. (4) Reaction progression is dictated by the strength of N-Zn binding events—some of which are inhibitory—the low Lewis basicity of the pyrimidine nitrogen allows this system to overcome such inhibitory effects and attain superior autocatalytic rates. (5) The striking non-linear behavior of the reaction is attributed to the poor catalytic competence of the heterochiral SMS tetramer that cannot engage the substrate in the *floor-to-floor* binding mode.

The precise manner in which the autocatalytic cycle is completed (dissociation of the product alkoxide and its reassembly into the SMS tetramer) remains to be elucidated. Likewise, for a scalemic SMS tetramer, multiple interconverting isomeric forms (due to alternative configurations of the chiral, tetracoordinate alkoxyzinc atoms) are theoretically possible. A rigorous study on the distribution and relative catalytic activities of these isomers has not yet been performed. In our opinion, these outstanding investigations, anticipated to be predominantly computational in enquiry, will provide further mechanistic understanding of the remarkable Soai reaction.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c05994.

Full experimental details and characterization data along with descriptions of ancillary experiments (PDF)

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Notes

The authors declare no competing financial interest.

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