

On the mechanism of the Soai autocatalytic reaction: Novel findings

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Abstract — A comprehensive analysis of the available evidence on the Soai reaction leads to remarkable conclusions, concerning both the rate determining transition state and the nature of the catalyst species. Thus, autocatalysis per se cannot account for the experimental observations. In fact, the irreversible formation of a heterochiral, non-reacting species from the alcohol product, as also the formation of a dimeric species from the aldehyde substrate are indicated: The former enhances the e.e. of the alcohol that is both product and catalyst, while the latter accounts for the observed rate laws. Furthermore, the non-involvement of the dialkyl zinc species in the rate determining step, and its nucleophilic addition to aldehyde with high enantioselectivity are also indicated. Indeed, it appears there is no other way to account for the remarkable experimental findings on one of the most spectacular discoveries in chemistry.

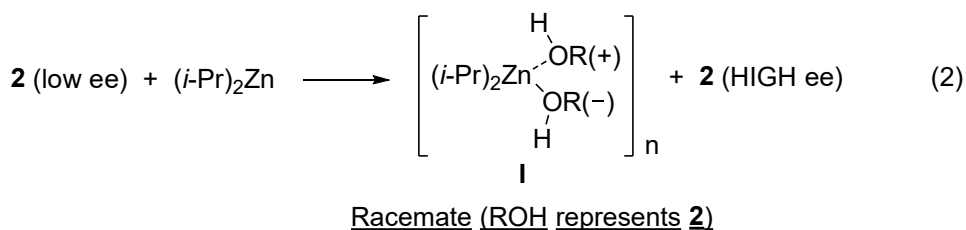
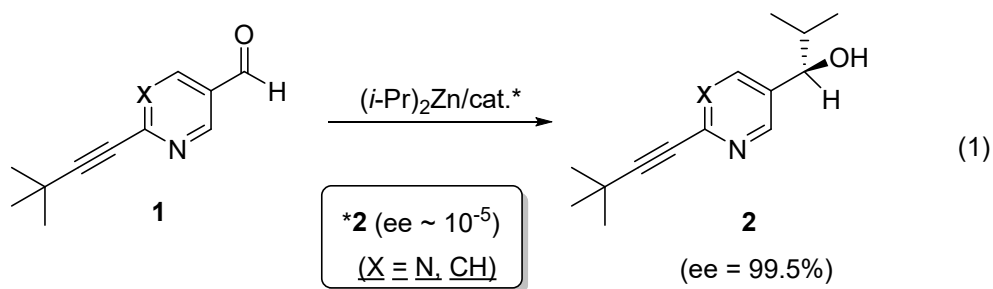
Introduction

Recent decades have witnessed remarkable developments in organic chemistry of immense fundamental and practical importance. These pertain to discoveries that impact—inter alia—not only on the synthesis of life-saving medicinal agents but also on esoteric theories about the origin of life. These developments also pose an intriguing challenge to current concepts and dogmas, particularly concerning organic stereochemistry and asymmetric synthesis.^{1–4}

This efflorescence pertains to the general phenomenon of non-linear effects in asymmetric catalysis, with two somewhat related branches depending on whether autocatalysis is involved or not. Both cases involve reactions that employ a chiral catalyst, with the enantiomeric excess (ee) of the final product (often) vastly exceeding the ee of the starting catalyst. Although this should be a cause for joyous celebration, it does indeed raise intriguing theoretical questions!

These essentially concern the challenge of explaining how a high entropic system (low ee) can produce a lower entropic system (high ee) without—apparently—any input of energy. In fact, as previously argued,⁵ these non-linear effects can be understood by invoking the idea that kinetically-controlled reactions reach a state of quasi-equilibrium, with irreversibility and non-equilibrium playing key roles.

This paper, however, is focused on non-linear effects observed in autocatalytic systems, the Soai reaction in particular (Scheme 1).^{1–4} This was discovered in 1995, and involves the enantioselective addition of diisopropyl zinc to a heteroaromatic aldehyde, the reaction being autocatalyzed by the final addition product (a secondary alcohol). The quintessential aspect of the reaction is that remarkable—even spectacular—enhancements of the ee of the final product are observed, relative to the ee at the beginning of the reaction. (The enantiomerically enriched product is employed as catalyst, the reaction even being self-initiating under some conditions.)



Scheme 1

The observed enhancements of ee were attributed to the autocatalytic nature of the reaction, a curious notion that persists to this day. The problem with this approach is that, in an autocatalytic process such as the Soai reaction, the ee of the catalyzing product would steadily decrease as the reaction progresses. Hence, alternative explanations must be sought for the experimental

observations that are, indeed, not in doubt. In fact, wide-ranging and intensive studies by several groups of investigators have led to an impressive harvest of experimental data, which establish a plausible mechanism with considerable certainty, as discussed below.

Discussion

General background

Scope of the Soai reaction.^{1–4} The Soai reaction has been carried out on a select range of pyridyl and pyrimidyl aldehydes (**1**), typically possessing para alkynyl substituents (Scheme 1, Eq. 1). The overall reaction, generally performed with diisopropyl zinc in toluene solution, is essentially the nucleophilic addition of an isopropyl moiety on the aldehyde to obtain a secondary alcohol (**2**). As this possesses a stereogenic center, it would generally be formed as a racemate. However, the reaction may also be catalyzed by the product alcohol **2** (autocatalysis): When this is enantiomerically enriched, the ee of the product may be enormously enhanced under certain conditions. (Scheme 1, Eq. 1: *t*-Bu may be replaced by 1-adamantyl or trimethylsilyl, these being preferred for the case X = CH, indicating the fairly wide scope of the Soai reaction.)

The reaction has been subjected to both intensive and extensive synthetic and mechanistic studies over the three decades since its discovery. The spectacular enhancements of ee exhibited by the reaction under certain conditions, along with the enormous amounts of experimental observations obtained by several groups of diligent and ingenious workers, have led to many theoretical proposals. These are essentially focused on the observed autocatalytic mechanism, particularly as the cause of the enhancements of ee. A common theme is also the involvement of aggregated species via the coordination of aldehyde and alcohol with the zinc atom of diisopropyl zinc.

Fundamental considerations. However, intriguing questions remain to be addressed! A central problem is the origin of the observed ee enhancements, as this has both fundamental and practical dimensions. Thus, the ee enhancements imply the spontaneous generation of a state possessing relatively higher order, i.e., a lower entropy state with a correspondingly greater Gibbs energy.⁴ Also, the exact molecular mechanism that leads to this apparent thermodynamic conundrum is inherently intriguing.

Rate laws and reaction orders.⁴ Painstaking mechanistic work employing sophisticated techniques has established the overall rate law that is, in fact, intriguing in itself. Thus, a second order

dependence of the reaction on the aldehyde concentration, and the zero order dependence on the diisopropyl zinc concentration, offer interesting challenges to mechanistic imagination and speculation!

Plausible mechanistic possibilities

The origin of the ee enhancements. The above thermodynamic requirements indicate that the idea of the autocatalytic enhancements of ee is, in fact, dubious. Indeed, repeated cycles of a chiral autocatalytic process, such as the Soai reaction, would only lead to depletion of the ee, if the enantioselectivity—rarely quantitative—in each cycle is taken into account. Thus, the idea that autocatalysis leads to enhancements of ee is based on the assumption of total (100%) enantioselectivity in the key step that generates stereogenicity. Since this assumption cannot be generally valid, other explanations are perforce needed for the experimental observations.

Precedented phenomena. Aspects of the Soai reaction, apparently, bear intriguing kinship to certain precedented stereochemical phenomena, and it is to these that we now turn. These generally pertain to the crystallization of a racemate, which may produce either a conglomerate (spontaneous resolution forming enantiomeric crystals) or a racemic compound (forming crystals containing both enantiomers in the same lattice). In these, the crystallization of an enantiomerically enriched sample can lead to an enhanced ee of the uncrystallized part remaining in solution,^{6,7} the racemic compound case being particularly relevant to the Soai reaction (*vide infra*).

These phenomena are driven by the force of crystallization, the formation of the racemic crystals involving a greater fraction of the minor enantiomer relative to the dominant enantiomer. In fact, an analogous solution–phase enrichment process is known, via the formation of racemic dimers in which opposite enantiomers are linked to an achiral spacer unit.^{7,8} Thus, such ee enhancements are well documented with several examples being known for long, and are clearly driven by statistical and thermodynamic (crystallization case) factors. (It is noteworthy that the overall ee remains constant in these processes, so there is no thermodynamic anomaly!)

These precedents are relevant to the Soai reaction as the catalyst ee can be enhanced by the formation of dimeric species involving the diisopropyl zinc reactant, noting the proclivity of the zinc atom to complex with nucleophilic centers (in this case the alcohol oxygen atom). Thus, opposite enantiomers of the alcohol can coordinate with the zinc center forming a racemic complex (**I**, Eq. 2, Scheme 1), thereby enhancing the ee of the non–complexed alcohol. The complex **I** may

be further aggregated as indicated, and is viable in view of the several complexes proposed for the Soai reaction.^{1–4}

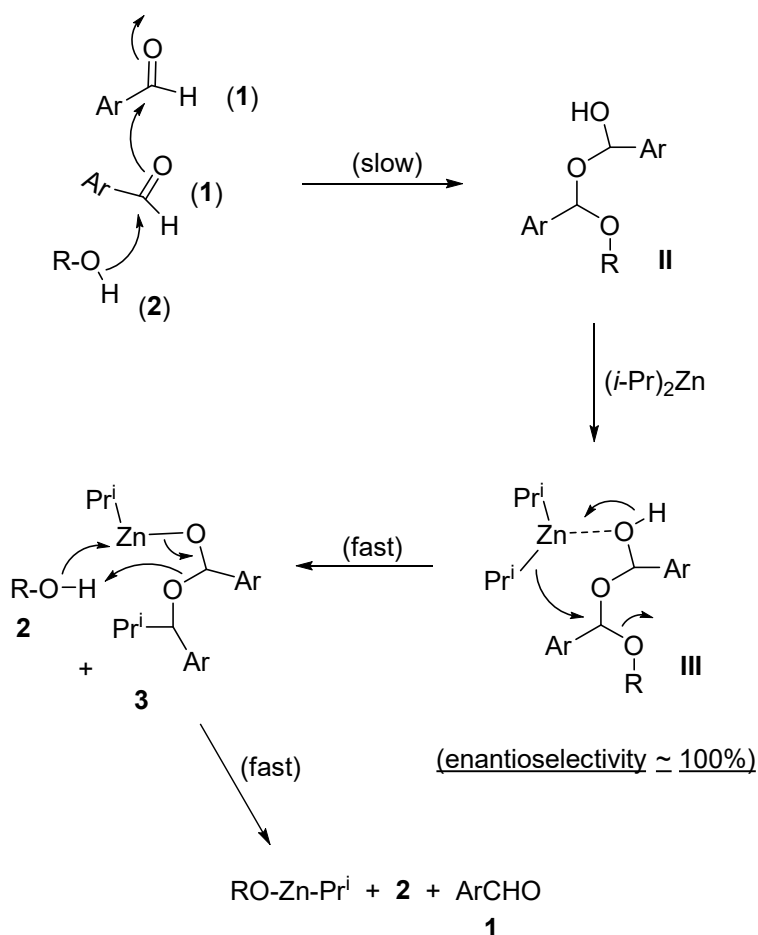
Importantly, however, such complexation needs to be irreversible for it to be kinetically relevant for the overall reaction, as a reversible complexation would nullify the ee enhancement. (The irreversible complexation is analogous to the formation of the racemic compound crystals, mentioned above.) Also, the racemic complex **I** should be non-reactive, i.e., not lie on the main reaction pathway.

A further requirement is that the nucleophilic addition of the diisopropyl moiety should occur with high enantioselectivity, thus avoiding the formation of significant amounts of racemic complex **I**. Thus, a relatively low enantioselectivity in the above addition would produce correspondingly large amounts of the minor enantiomer, the sequestering of which as the racemic complex (**I**) would depress the overall yield. These arguments indicate that the ee of the catalyst at the start of the reaction should be enhanced by the formation of racemic complex **I**, this being largely obviated during the progress of the reaction by the high enantioselectivity of the addition step. Thus, a subtle inverse relationship between the enantioselectivity and overall yield is indicated.

A comprehensive mechanism for the Soai reaction. Although the above arguments provide a rationale for the enhanced ee observed in the Soai reaction, the overall mechanism still remains to be fleshed out. In fact, this is far from straightforward, noting that the reaction is second order in the aldehyde, first order in the alcohol catalyst and zero order in diisopropyl zinc: thus, the rate determining step involves two molecules of the aldehyde and one of the alcohol, but none at all of the diisopropyl zinc! Indeed, this is particularly intriguing as the enantioselectivity occurs in the step involving the diisopropyl zinc! All the same a plausible mechanism can be arrived at by gleanings all of the available observations (Scheme 2), although not without certain reasonable assumptions.

Firstly, the second order dependence on the aldehyde indicates the initial formation of a covalent complex (**II**) involving two molecules of aldehyde (**1I**) and one of the alcohol (**2**), in a slow rate determining step. Complex **II** is formed by the nucleophilic addition of the alcohol to the aldehyde carbonyl group, followed by the addition of the resulting tetrahedral intermediate (not shown) to another aldehyde molecule. The reaction of diisopropyl zinc with **II** then occurs leading, in a series of fast steps, to the final product alcohol (**2**, which acts a catalyst in a subsequent cycle).

The immediate product of the reaction of diisopropyl zinc with complex **II** would be the complex **III**, formed via coordination of the zinc atom with the oxygen atom of a hemiacetal hydroxyl group. The critical transfer of the isopropyl group then occurs, but interestingly to a tetrahedral carbon center in a nucleophilic substitution reaction. This may well be assisted by coordination of the nucleofugic oxygen atom with the zinc atom of another diisopropyl zinc molecule (not shown). As argued above, the formation of **3** should occur with high stereo-control, leading to the predominant enantiomer of **2**.



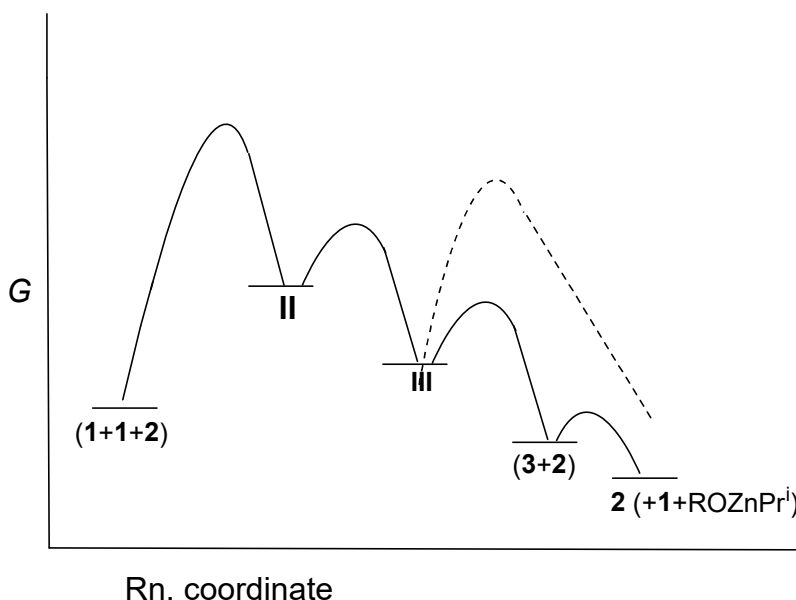
Scheme 2

Indeed, it is likely that hemiacetal **II** exists as a stereoisomeric mixture (not shown), noting the two hetero-benzylic (acetalic) stereogenic centers generated during its formation. Thus, the collapse of the predominant stereoisomer of **III** (with stereochemistry carried over from precursor **II**) leads to covalent zinc complex **3** (precursor of newly formed alcohol **2**) and alcohol **2** (original

catalyst), but with **3** possessing the stereochemical features of the dominant enantiomer of **2**. Hence, the stereochemical control in this sequence of events is influenced by the chirality of the catalyst alcohol **2**, the transfer of the isopropyl group to form **3** being a stereospecific intramolecular S_N2 process. This implies that the minor enantiomer of **2** is also formed in an analogous stereospecific S_N2 process from the minor stereoisomer of **II** (not shown). (In fact, an analogous mirror-image sequence of reactions would occur, although relatively slowly, from the minor enantiomer of **2**.)

The above mechanism accords with the available kinetic evidence and indicates the energy profile in Scheme 2. The overall reaction can be kinetically analyzed by employing the steady state approximation as the first step is rate determining (not shown), although the profile in Scheme 3 captures the essence of the overall process. (Scheme 3: *G* represents the Gibbs energy; the dashed profile represents the above-discussed collapse of the minor stereoisomer of **III** to the minor enantiomer of **2**, leading to the overall enantioselectivity being < 100%.)

In fact, the fundamental basis of the observed autocatalysis appears to be the aggregation of the three reactants, **1**, **2** and (*i*-Pr)₂Zn, in the key transition state (cf. **III**), possibly indicating stacking interactions among the heterocyclic moieties as well.



Scheme 3

Conclusions

The single most important conclusion from the above analysis is that—generally—autocatalytic enhancements of ee are possible only in tandem with a process that enhances the ee of the “autocatalyst”, both at the beginning of the overall reaction and during its subsequent course. The enantioselectivity of the key step should be relatively high to maintain the overall yield correspondingly high. The most likely tandem process mentioned above would be the irreversible formation of a non-reacting racemic species (possibly aggregated), composed of both enantiomers of the “autocatalyst”. In the particular case of the Soai reaction the observed autocatalysis is likely the result of the aggregation of reactants and catalyst, aggregation also being the likely reason for the formation of the non-reacting racemic species. Thus, the Soai reaction is apparently enabled by an unusual concatenation of molecular mechanisms playing a cat-and-mouse game of sorts!

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