

Absolute autocatalytic amplification under heterogenous conditions involving subsequent hydride transfer and hemiacetal intermediate.

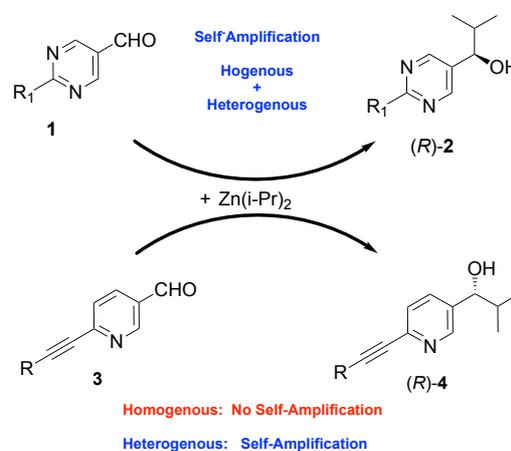
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Abstract: In contrast to homogenous phase, absolute asymmetric amplification of pyridine alkanol is observed under heterogenous conditions. Reaction of *i*Pr₂Zn vapor on solid powder of pyridine carbaldehyde induced anautocatalytic amplification of chirality providing enantiopurity up to 90% ee. In this study side products were identified and their formation is traced back to redox pathways involving hydride transfer, namely a chiral ester resulting most probably through a disproportionation of starting aldehyde into hemiacetal and subsequent hydride loss following a Claisen-Tishchenko mechanism. These observations provide new perspectives in the elucidation of the mechanism of amplification of chirality in the Soai reaction.

The origin of homochirality remains an intriguing scientific topic.^[1] Mechanisms for the rise of homochirality assume a three stages sequence: mirror symmetry breaking, followed by chiral amplification^[2] and finally propagation through subsequent asymmetric transformations. Although very few, recent work shows that enantioenrichment (*ee*) is achievable from achiral precursors without chiral catalysts, and reactants are obtained as single enantiomer crystals to be used in absolute asymmetric synthesis.^[3] Not only chiral, but also achiral molecules can crystallize in chiral crystals: in these cases, the chirality of the crystal structure arises from a chiral packing of the molecule. Single phase homochirality without counter enantiomer nucleation may also be accessed through crystallization, although no chemical transformation occurs throughout the processes. Kondepudi's total spontaneous resolution and Viedma's attrition enhanced deracemization of NaClO₃.^[4] Viedma ripening was shown on an intrinsically chiral molecule, an amino acid derivative racemizing in solution in presence of a strong base. It is believed that CPL induces crystal growth of a specific enantiomer by action of chiral side products.^[5] By Viedma ripening of organometallic complexes, six-coordinated Δ- and Λ- [Co(bpy)₃]²⁺ cations and tetrahedral Δ- and Λ- [Ag(PS)₂]⁺ cations (PS = (2-(methylthio)ethyl)-diphenylphosphine) were successfully obtained in enantiopure forms.^[6] However, chiral discrimination in

the solid state can only be archived with molecules that form conglomerate crystals, narrowing the scope of suitable substrates for this technique. Enantioenrichment may also be achieved by selective crystallization or sublimation.^[7]

To date, the Soai reaction offers the only example of an asymmetric autocatalytic reaction employing a catalyst with a very low enantiomeric excess (*ee*).^[8] Frank envisioned an asymmetric autocatalytic model,^[9] where one enantiomer catalyzes its own production and at the same time inhibits the formation of its opposite enantiomer, giving rise to high asymmetric amplification from extremely low enantiopurity.^[10] Thus, even classical statistical fluctuation in the enantiomeric ratio may lead to spontaneous asymmetric synthesis,^[11] by virtue of non-linear relationship (NLE) of catalyst-product pair, in the form of a homochiral dimer species.^[9, 12] This is key to propagation of asymmetric amplification during the course of a reaction.^[13] It was pointed out that the (+)-NLE must be working in parallel with autocatalysis to provide the asymmetric amplification.^[14]



Scheme 1. Scheme Caption.

We have recently reported on the combination of autocatalysis with asymmetric induction.^[17] Inspired by the work of Soai et al., we hypothesized whether this combination would also function under heterogenous conditions in the alkylation of aldehydes **1** and **3**. The work presented here establish that amplification of pyridine alkanol **4** can operate under heterogenous conditions and does not require the conjunction assistance of Soai autocatalyst **2**, in sharp contrast to homogenous phase. We also report on additional products, identified as ketone, alcohol, and esters. This work demonstrates that their formation is associated with episodes of hydride transfer involving a hemiacetal intermediate and may be key players in the amplification process.

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Soai revealed the enantioface selective addition of $i\text{Pr}_2\text{Zn}$ to pyrimidine-5-carbaldehyde **1**.^[15] By selecting one enantiotopic crystal face, the chiral secondary alcohol **2** was formed with the absolute configuration corresponding to the two-dimensional chirality at the crystal surface. They could predict the absolute configuration of alcohol **2** from the parallelogram face shape. Furthermore, the ee value of product **2** could be enhanced to greater than 99.5% by asymmetric autocatalysis with amplification of enantiomeric enrichment. An achiral pyrimidine-5-carbaldehyde that forms an achiral crystal (achiral space group $P\bar{1}$), with enantiotopic (001) and (00 $\bar{1}$) faces underwent enantioselective addition of $i\text{Pr}_2\text{Zn}$ to the single exposed enantiotopic surface to give highly enantiomerically enriched *S* and *R* secondary alcohols. The absolute configuration of the alcohol product correlated with the orientation of the prochiral aldehyde in the achiral crystal lattice. Just recently, this study was extended with an absolute asymmetric synthesis under kinetic control of vapor-solid phase of reaction of $i\text{Pr}_2\text{Zn}$ with aldehyde **1**.^[16]

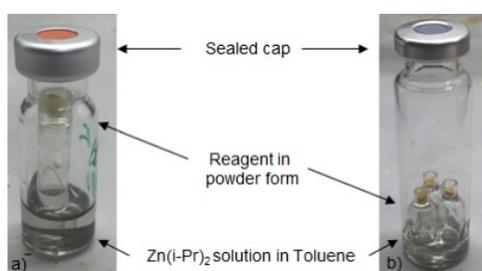


Figure 1. Figure Caption.

Initially, we examined the behavior of pyrimidine-5-carboxaldehyde **1** in presence of pyridine-3-carboxaldehyde **3** in a 1:1 stoichiometry. Five reactions with the setup of Fig. 1a were initiated simultaneously and stopped at fixed times. The final sample afforded alcohol (*R*)-**2** in 75% conversion and 81% ee, while alcohol (*R*)-**4** was formed in 91% ee and 36% yield. Monitoring the progress of the reaction revealed a sudden formation of alkanol **2** with very high ee from the first sample, (Figure 2: dashed red lines), while the enantiopurity of **4** slowly increased over time, in agreement with our previous report on delayed amplification for alkanol **4** in solution (see SI section 3).^[17c] At a catalytic loading of 10 mol% of **1** in presence of pyridine-3-carboxaldehyde **3** and vapor of diisopropyl zinc, the same experiment provided quantitatively alkanol **2** with 95% ee, while alkanol **4** was isolated in 73% ee and 29% yield. Thus, absolute asymmetric synthesis of two distinct products is achieved by action of alkylating reagent vapor on solid substrate.

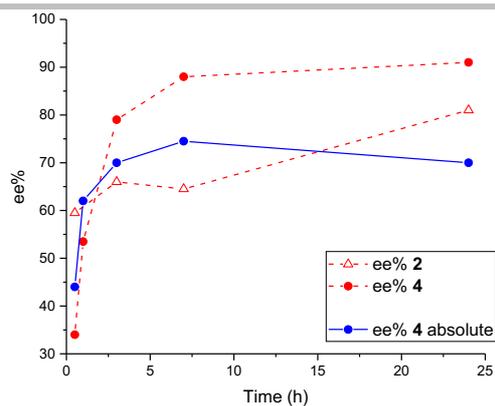


Figure 2. Progression of ee vs. time: of **2** and **4** under stoichiometric conditions (dashed red lines); of **4** under absolute conditions (solid blue line).

In our previous work, addition of $i\text{Pr}_2\text{Zn}$ to aldehyde **3** in solution in toluene produced alkanol **4** as a racemate, although the process is autocatalytic. Thus, there is no symmetry breaking by absolute asymmetric synthesis for **4** as it is usually the case for the Soai reaction. A key question was whether heterogeneous reaction conditions would provide settings for nucleation, by exposure of enantiotopic *Re* and *Si* faces, and thereby induce symmetry breaking in the alkylation of **3**. This hypothesis was tested by conducting several sets of experiments under heterogeneous condition, by subjecting aldehyde **3** powder to vapor of $i\text{Pr}_2\text{Zn}$. In absence of chiral trigger, the process operates as a spontaneous absolute asymmetric catalysis. Alkanol **4** was obtained with a final 75% ee and 21% conversion, as shown in Figure 2 (solid blue line), with a similar trend for evolution ee as in presence of **2** (see SI section 4).

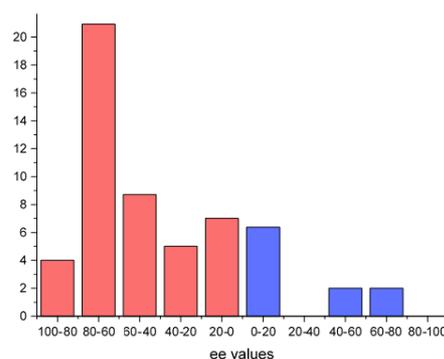
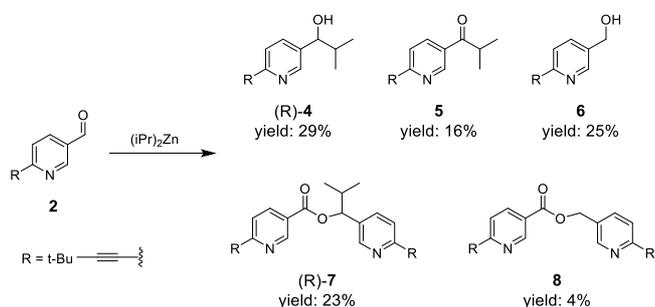


Figure 3. Frequency of ee and distribution of enantiomers of **4**.

Clearly, amplification of compound **4** under heterogeneous conditions operates independently from the action of autocatalyst **2**. Reactions are carried out in triplicates in the same container (Figure 1b), enantiomers of **4** are obtained at random as 2 times (*R*) and once (*S*) or the opposite, and often only (*R*) as summarized in Figure 3. Thus, in presence of a same $i\text{Pr}_2\text{Zn}$ atmosphere, amplification of alkanol **4** is not subject to a chiral trigger as shown previously.^[16]

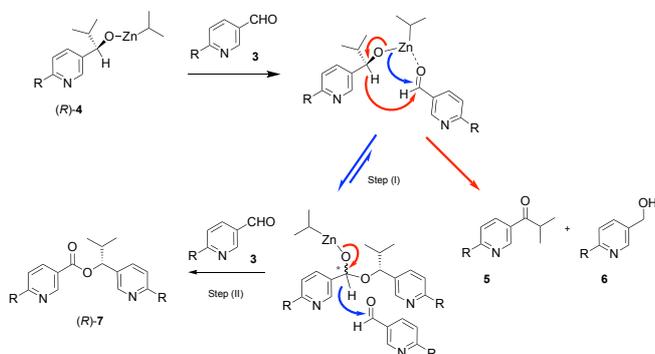
Closer analysis of crude material indicates the presence of ketone **5** and reduction alcohol **6**. Furthermore, and perhaps more interesting formation of chiral ester **7** and achiral **8** is also

observed (Scheme 2). Compounds **5** and **6** could be formed by a Meerwein-Ponndorf-Verley oxidation of alkanol **4** and reduction of aldehyde **3** during amplification process following.



Scheme 2. Products of the vapour solid reaction of **3** and $(iPr)_2Zn$.

On the other side, the only possible mechanism of formation of esters **7** and **8** is through a Claisen-Tishchenko reaction following a Cannizzaro disproportionation mechanism.^[18] The reaction pathway would involve key steps of the C-O bond formation and the hydride transfer which occur in the coordination sphere of the Zn metal as outlined in scheme 3. The proposed mechanism starts in step I with a nucleophilic addition of the chiral Zn-**4** alkoxide onto the carbonyl **3** to form a chiral Zn-hemiacetal. Step II can be viewed as analogous to the hydride transfer of the Meerwein-Ponndorf-Verley reaction of the Zn-hemiacetal intermediate to aldehyde **3** to produce chiral ester **7** and alkoxide Zn-**6**. The same reaction pathway involving Zn-**6** would lead to formation of achiral ester **8**.



Scheme 3. Suggested reaction mechanism for the formation of the reaction side products.

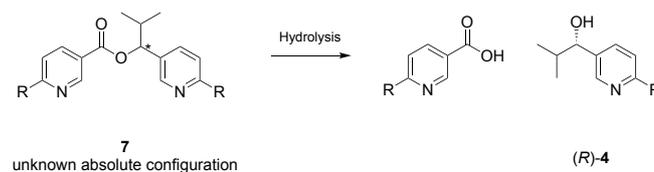
Chiral hemiacetals have been observed in intramolecular condensation of Zn-alkoxides as a result of a monoalkylation of dialdehyde with Et_2Zn .^[19] Further oxidation of hemiacetal would lead to the corresponding chiral ester.^[20] More recent work revealed an intra- and intermolecular Claisen-Tishchenko catalyzed by metallic zinc, although achiral.^[21] The existence of Zn-hemiacetal has been described as transient intermediate in recent NMR studies, which suggested its association in a transition state in the Soai reaction.^[22] This species, consisting of two alkoxides and one aldehyde, forms in the early stage of the amplification and last until complete consumption of aldehyde. Kinetic and DFT computations incorporating an acetal

mechanism were also investigated lately.^[23] The extent of formation of these side products is not yet understood but they are present in all runs above 0 °C, and in nearly similar proportions. Although high amplification of **4** coincides with the absence of side products, their role in the reaction remains to be clarified.

Reaction at 40 °C afforded compound **4** as racemate in 31% yield and 20% of ester **7** in 15% ee. The reaction also performs well at low temperatures. The highest amplification level is observed at 0 °C after 20h giving 20% of (*R*)-**4** with 90% ee and only 9 % of (*R*)-**7** in 86% ee. An even slower reaction at -15 °C provided only alkanol **4** in 32% with 83% ee, after 3 days. Interestingly, none of the other side products is detected at this temperature. Thus, formation of ester **7** remains dependent of chiral alkanol **4** and is also function of temperature.

Hypothesis: at higher temperature the vapor might consist of high portion of toluene, which would dissolve most of the solid **3**, making the reaction conditions more likely homogenous. Monitoring the reaction revealed a rapid onset of product optical activity at rt with 40 % ee after 30 min to peak at 74% ee within 5 hours. At -15 °C a longer induction period shows a low 18% ee in the first 10 hours followed by a rapid increase up to 83% ee. This shows that iPr_2Zn vapor reacts with solid **3** in small portions and limited toluene solvent. The overall process, may account for the observed amplification by keeping a constant flow of iPr_2Zn at low concentration throughout the reaction, but a much higher total concentration of both reagents than under homogenous conditions used in previous reports.

Moreover, in all cases HPLC on chiral stationary phase shows a constant trend in which absolute configuration of major enantiomer **7** follows that of **4**. The absolute configuration of ester **7** has been assigned to be the same as for alkanol **4**. For example, hydrolysis of ester (*R*)-**7** provided alcohol (*R*)-**4** (Scheme 4).



Scheme 4. Hydrolysis of ester **7**.

To examine the correlation of the amplification of **4** and **7**, triplicate experiments with the reaction setup of Fig. 1b, to a total of nine reactions, were performed and in all cases **4** and **7** were obtained with the same absolute configuration (*R*). Chiral amplification of **7** was often higher or comparable to that of **4** as shown in table 1. Analysis over time shows a steady ee increase for chiral **7** while alkanol **4** terminates with a remarkably lower ee (Figure 4). This could reasonably be interpreted as an amplification of chiral **7** at the expense of alkanol **4** through a reversible hemiacetal formation step I in scheme 3. Indeed, the hemiacetal may form as two diastereomers with a kinetically preferred intermediate for a hydride transfer converting into ester **7** (step II: thermodynamic sink), while the other diastereomer reverts back to starting alkoxide Zn-**4** and aldehyde **3**. It is not yet clear to which extent this hemiacetal intermediate may be implicated in the amplification process of **4** or even **7**.

Nevertheless, the Claisen-Tishchenko may represent a new chiral amplification process.

Table 1. Absolute asymmetric synthesis of **4** and **7** by reaction of vapor $i\text{Pr}_2\text{Zn}$ on solid **3**.

| Entry ^[a] | ee (R)- 4 | ee (R)- 7 ^[b] |
|----------------------|------------------|---------------------------------|
| 1 | 48 | 72 |
| 2 | 53 | 65 |
| 3 | 62 | 83 |
| 4 | 55 | 54 |
| 5 | 47 | 25 |
| 6 | 63 | 79 |
| 7 | 67 | 81 |
| 8 | 50 | 57 |
| 9 | 49 | 66 |

[a] Table Footnote. [b] ...

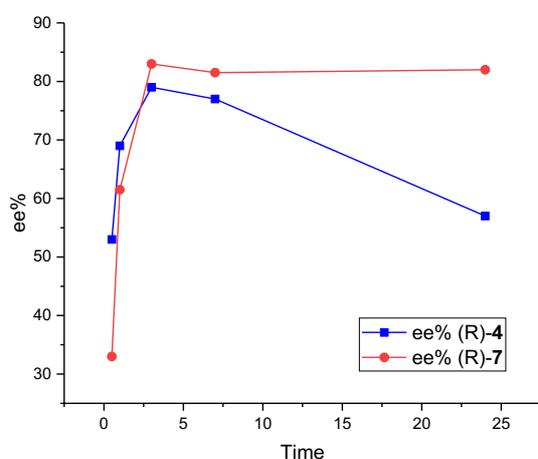


Figure 4. Asymmetric amplification of (R)-**4** (blue) and (R)-**7** (red) at rt.

Finally, other alkylzinc reagents, Et_2Zn and Me_2Zn were employed as solutions in hexane, heptane and toluene. Upon exposure to vapor of R_2Zn reagents alkylation was observed in all cases. None of Et_2Zn or Me_2Zn did provide amplification, and all products were isolated as racemates. Interestingly, no side products were isolated with these reagents.

In conclusion, this paper broadens the scope of autocatalytic amplification of chirality by an unprecedented phase alteration. We have demonstrated the realization of asymmetric amplification of pyridine alkanol **4** in heterogenous phase by the reaction of $i\text{Pr}_2\text{Zn}$ vapor on solid aldehyde **3**. Under these experimental conditions the presence of Soai autocatalyst **2** as chiral trigger is not necessary. This is in striking contrast to homogenous conditions, without autocatalytic amplification of alkanol **4** in solution. Actually, one could assume that even in a mixture, different pathways may be involved for amplification **2** and **4**. Clearly, autocatalysis is in action as shown by monitoring the progression of ee over time. However, this amplification is not observed for other zinc reagents and remains a characteristic of $i\text{Pr}_2\text{Zn}$, adding more intrigue to this unique reactivity.

First observation of side products provides new insight into possible amplification process. Their formation may find explanation through redox pathways involving hydride transfer following mechanisms for MPV and Claisen-Tishchenko reactions (*vide supra*), but these are not observed for the Soai reaction nor under homogenous conditions. The selective formation of chiral ester **7** emerges as evidence of a subsequent reactivity of a chiral hemiacetal intermediate, which may also have implications in the autocatalytic amplification of chirality, and provides new perspectives for the mechanism elucidation of the Soai reaction. Further studies are undertaken to examine the mechanism of their formation and its relation to amplification.

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