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# Observation of hyperpositive non-linear effect in asymmetric organozinc alkylation in presence of N-pyrrolidinyl norephedrine

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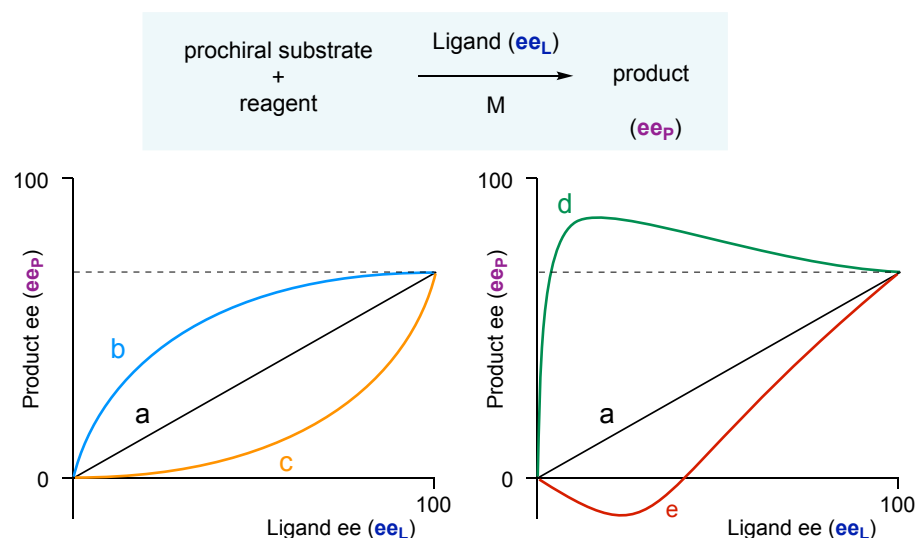
**Abstract:** Phenomena related to asymmetric amplification are considered to be key to understanding the emergence of homochirality in life. In asymmetric catalysis, theoretical and experimental models have been studied to understand such chiral amplification, in particular on the basis of non-linear effects. Three decades after the theoretical demonstration that a chiral catalyst, when not enantiopure, could be more enantioselective than its enantiopure counterpart, we show here a new experimental example of nonlinear hyperpositive effect. We report here our investigations in the enantioselective zinc-catalyzed alkylation of benzaldehyde with *N*-pyrrolidinyl norephedrine as partially resolved chiral ligand, which shows a significant hyperpositive non-linear effect. A study of the underlying mechanism has been conducted and allows us to confirm a mechanism that imply a monomeric and a dimeric complex both catalyzing the reaction at a steady state and giving different enantioselectivities.

**Keywords:** asymmetric catalysis; nonlinear effect; chiral amplification

## 1. Introduction

Asymmetric synthesis and catalysis are of paramount importance for obtaining enantiopure molecules, especially in the development of chiral drugs that are almost exclusively applied in the form of single enantiomers [1]. In asymmetric catalysis, a chiral auxiliary (most often a chiral ligand attached to a metal) is used ideally in its enantiomerically pure form to maximize the enantiomeric excess of the desired product ( $ee_P$ ). When the chiral auxiliary is not enantiopure, in most cases a linearity is observed between the optical purity of the product ( $ee_P$ ) and the reagent ( $ee_L$ ), as shown in Figure 1a. However, deviations from linearity between  $ee_P$  and  $ee_L$  can occur and are referred to as non-linear effects (NLEs) [2,3]. In the case of a positive non-linear effect (often called (+)-NLE), the  $ee_P$  can be much higher than the  $ee_L$ , resulting in asymmetric amplification (Figure 1b). The opposite is also possible, called negative non-linear effect ((-)-NLE) (Figure 1c).

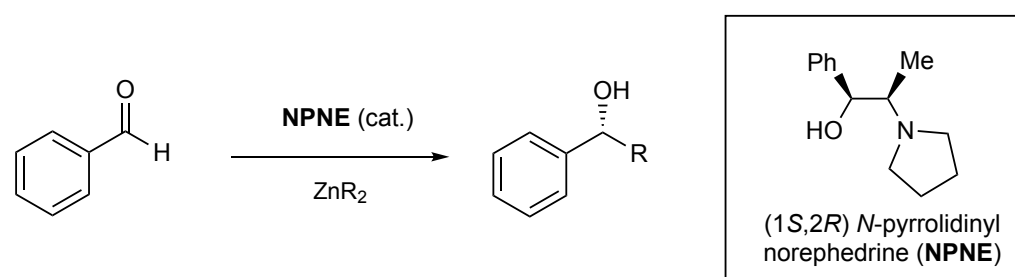
Recently, we observed that a chiral catalyst, when not enantiopure, can be more enantioselective than its enantiopure counterpart (Figure 1d) [4]. Such unusual, "hyperpositive" NLE was first suggested by Kagan in the mid-90's [2,5,6]. This was observed in the zinc-catalyzed alkylation of aldehyde in the presence of *N*-benzyl ephedrine and we rationalized the hyperpositive NLE by introducing a monomer-dimer competition model where both monomers and dimers are catalytically active [4,7,8,9]. Such model also allows to describe enantiodivergent NLEs, that is when a catalyst can generate one enantiomer or its opposite by simply varying the ligand  $ee$  (see Figure 1e) which was observed with *N*-methyl ephedrine as ligand [10].



**Figure 1.** Product ee vs ligand ee-graphs of catalytic asymmetric reactions showing examples for a) no NLE, b) a positive NLE [(+)-NLE], c) a negative NLE [(-)-NLE] d) a hyperpositive NLE and e) a enantiodivergent NLE.

Since chiral ligands based on ephedrine or norephedrine have been and still are widely used in asymmetric catalysis, it appeared important to study other derivatives of this family in the context of non-linear effect. Among all the derivatives, *N*-pyrrolidinyl norephedrine (NPNE) attracted our attention [11,12] in part because it is one of the most enantioselective ligands in ephedrine-based catalytic organozinc additions.

Herein, we wish to report our investigations in the enantioselective zinc-catalyzed alkylation of benzaldehyde with NPNE as partially resolved chiral ligand. A hyperpositive non-linear effect was observed with diethylzinc or dimethylzinc as reagent, which was found to be more pronounced at low temperatures. The results were rationalized by studying the effect of temperature and concentration and also on the basis of our previous studies with *N*-benzyl ephedrine. Overall, this system concurs with the previously proposed monomer-dimer competition model, where a monomeric species is in equilibrium with a dimeric species, both being active and competing to generate the product albeit with different enantioselectivity.



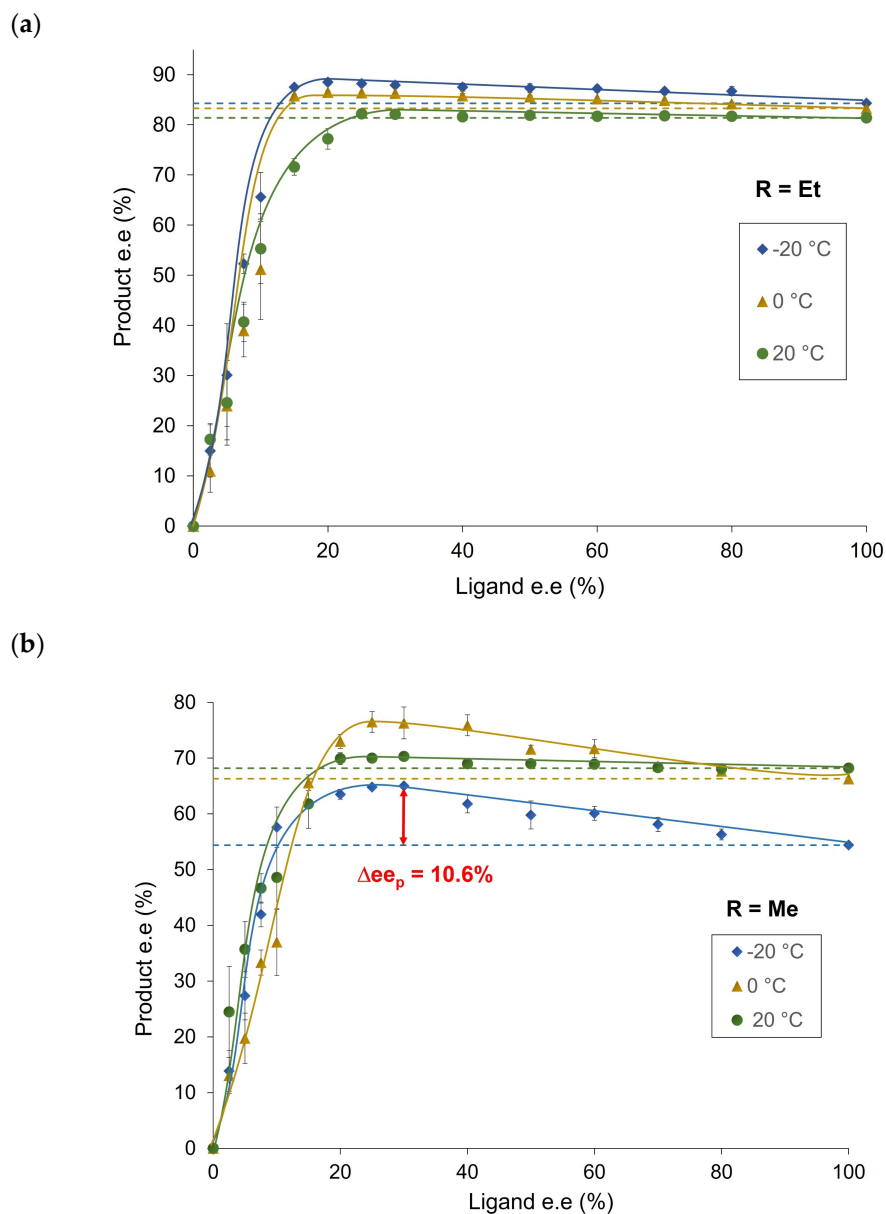
**Figure 1.** Catalytic enantioselective addition of dialkylzinc to benzaldehyde, catalyzed by *N*-pyrrolidinyl norephedrine.

## 2. Results

### 2.1. Non-linear studies

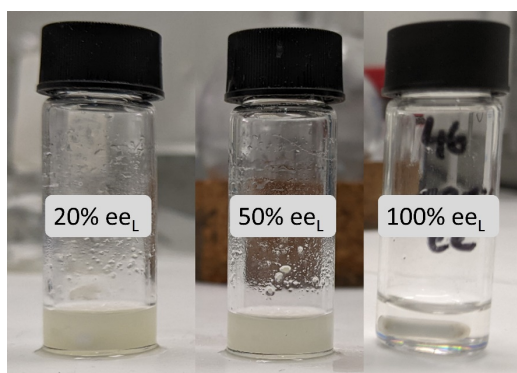
The zinc-catalyzed alkylation of benzaldehyde was investigated with partially resolved chiral *N*-pyrrolidinyl norephedrine ligand (NPNE). Figure 2 displays the results with diethylzinc (a) or dimethylzinc (b) as reagent. The catalyst loading was fixed at 20 mol% and toluene was used as solvent. The reactions were carried out at 20 °C, 0 °C and -20 °C.

In case (a), at room temperature the product was isolated in 81.4% ee when the enantiopure ligand was used (green curve). A strong positive non-linear effect occurred with essentially no change of the product enantiopurity up to ee<sub>L</sub> of 25%. The lowering of the reaction temperature induced a slight increase in the optical purity of the product and the appearance of a hyperpositive effect that is more significant at -20 °C than 0 °C ( $\Delta ee$  of 4.2% and 3.2%, respectively). In contrast, in case (b) the best enantioselectivity in presence of the enantiopure ligand was observed at room temperature (68.2% ee), since the lowering of the reaction temperature caused an opposite result than before. The three curves showed a hyperpositive effect that intensified with decreasing temperature. Here, the highest  $\Delta ee$  was found to be 10.6%.



**Figure 2.** Optical purity of the product as a function of the enantiomeric excess of NPNE ligand (20 mol%) at different temperatures. (a) with ZnEt<sub>2</sub> as reagent; (b) with ZnMe<sub>2</sub> as reagent. The reaction conditions and experimental procedure are described in the Supplementary Methods. Each point is the mean of three different experiments. The vertical error bars depict standard deviations. The dashed line represents the product e.e. of the enantiopure compound; the full line is a free-hand drawing, which serves as a guideline.

During the catalytic investigations, we detected that, when the partially resolved ligand was used, upon addition of the dialkylzinc reagent a precipitate was observed. This was in contrast to the use of the enantiopure ligand which gave a clear solution. Figure 3 displays three selected catalytic samples at 20%, 50% and 100% ee<sub>L</sub> (from left to right) that clearly illustrates the differences. Additional experiments were carried out to identify the nature of the precipitate. Analyses of the hydrolyzed precipitate obtained from 20% ee NPNE ligand sample revealed the free ligand in its racemic form, as deduced from the measurement of the optical rotatory power.

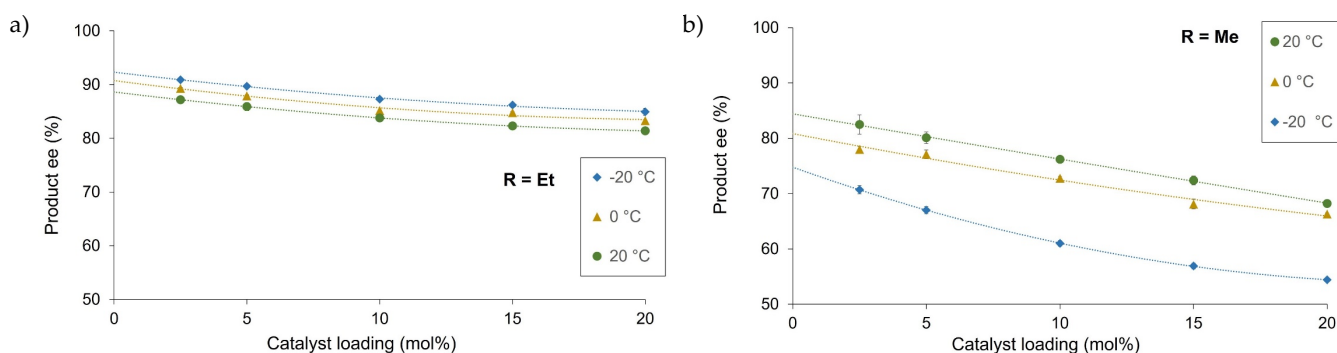


**Figure 3.** Reaction medium (Ligand, substrate, diethylzinc, toluene) as function of the optical purity of the NPNE ligand. From left to right: 20% ee<sub>L</sub>; 50% ee<sub>L</sub>; 100% ee<sub>L</sub>.

### 2.2. Impact of catalyst loading

The enantioselective reaction was evaluated by varying the catalyst loading of the enantiopure NPNE ligand with diethylzinc (Figure 4, a) or dimethylzinc (Figure 4, b) as reagent. In both cases, the results showed that a decrease in catalyst loading resulted in an increase in the enantiomeric excess of the product.

All curves show the same trend, the major difference between the two reagents lies in the temperature effect as already observed in the previous NLE studies.

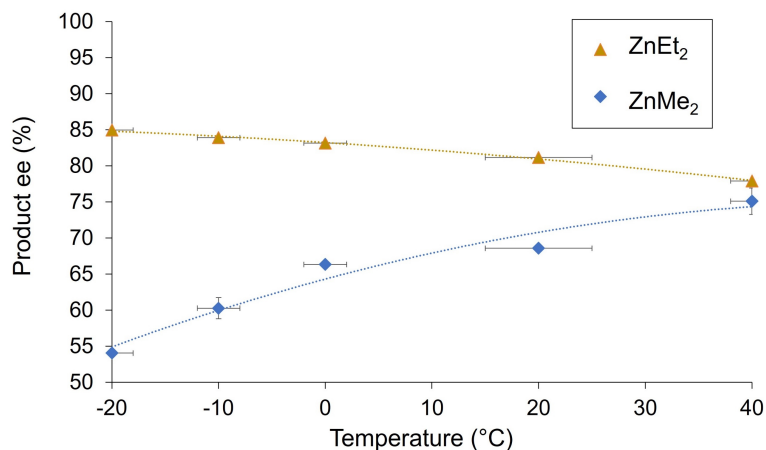


**Figure 4.** Optical purity of the product as a function of the catalyst loading of NPNE ligand (enantiopure 1*S*-2*R* form) at different temperatures. (a) with ZnEt<sub>2</sub> as reagent; (b) with ZnMe<sub>2</sub> as reagent. The reaction conditions and experimental procedure are described in the Supplementary Methods. Each point is the mean of three different experiments. The vertical error bars depict standard deviations. The dotted trendlines are second-order polynomial fits, which serve as guidelines.

### 2.3. Impact of temperature

The impact of the reaction temperature on the product enantioselectivity was investigated. Figure 5 displays the results ranging from -20 °C to 40 °C with diethylzinc (yellow triangle) or with dimethylzinc (blue square) as reagent. With diethylzinc, the product ee

went down from 84.4% at -20 °C to 77.8% at 40 °C. In contrast, the product ee increased from 54.4% at -20 °C to 72.4% at 40 °C with dimethylzinc.



**Figure 5.** Optical purity of the product as a function of the temperature. Orange triangles correspond to the reaction with ZnEt<sub>2</sub> as reagent; Blue squares correspond to the reaction with ZnMe<sub>2</sub> as reagent. The reaction conditions and experimental procedure are described in the Supplementary Methods. Each point is the mean of three different experiments. The horizontal error bars depict temperature variation during the reaction. The vertical error bars depict standard deviations. The dotted trend-lines are second-order polynomial fits, which serve as guidelines.

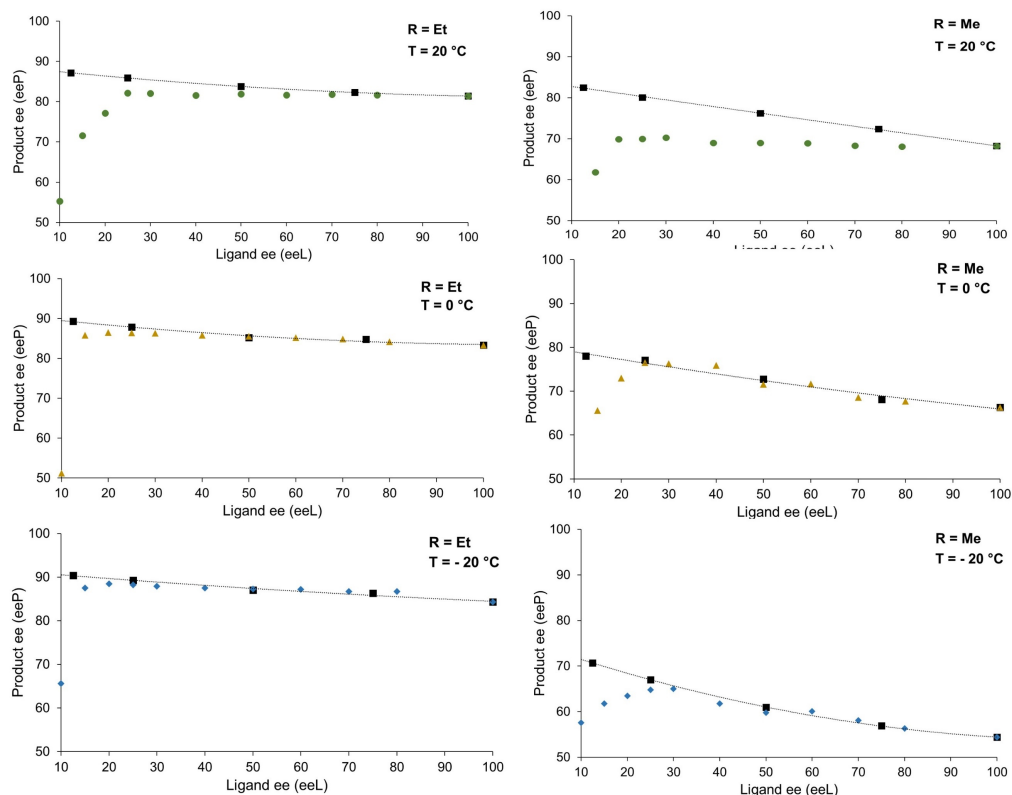
### 3. Discussion

The norephedrine skeleton has been used extensively for the development of efficient chiral auxiliaries in asymmetric synthesis and asymmetric catalysis, mostly with zinc as active metal [13]. Enantioselectivities greater than 90% ee were often reported in the alkylation (or alkynylation) of carbonyl or imine compounds [14,15,16]. Additionally, Efavirenz, an industrially produced drug for the treatment of Human Immunodeficiency Virus (HIV), includes an enantioselective transformation mediated by *N*-pyrrolidinyl norephedrine (NPNE) [17]. We therefore decided to focus NLE studies with NPNE ligand to better understand the nature of the catalytically active species.

Investigations of the product ee ( $ee_P$ ) as function of ligand ee ( $ee_L$ ) with NPNE revealed a hyperpositive NLE in the zinc-catalyzed alkylation reaction (Figure 2). Such behavior is similar to what was observed previously with the *N*-benzyl ephedrine ligand [4]. Interestingly, using ZnMe<sub>2</sub> as reagent the enantioselectivities are more pronounced than with the NBE ligand. The hyperpositive NLE effects (i. e. the difference between the highest  $ee_P$  obtained and the  $ee_P$  with enantiopure ligand) with NPNE ligand are relatively small at room temperature and more pronounced at lower temperature (0 and -20 °C).

Similar to what was observed with the NBE system, a zinc aggregate precipitated when the ligand was not enantiopure, as shown in Figure 3 [18]. A measurement of the rotatory power of the ligand contained in the aggregate revealed that the ligand was in its racemic form. Therefore, the precipitate is an overall racemic mixture of NPNE-complexes, as previously observed with NBE as ligand, most likely as a heterochiral dimer or co-precipitated RRS-RSS trimer adduct (trimeric adducts were observed in solution with the parent ligand *N*-methyl ephedrine) [8]. Such precipitation of racemic ligand causes a strong positive non-linear effect to emerge, as it enantioenriches the zinc species left in solution (i.e. Kagan's *reservoir effect*) [3]. Trapping the ligand in a racemic form implies that when decreasing the enantiomeric excess of the ligand, we generate more racemic inactive aggregates and thus less catalytically active species. Figure 4 displays the evolution of product ee as function of the catalyst loading of the enantiopure NPNE. In all cases, a decrease of the catalyst loading led to an increase of the product ee.

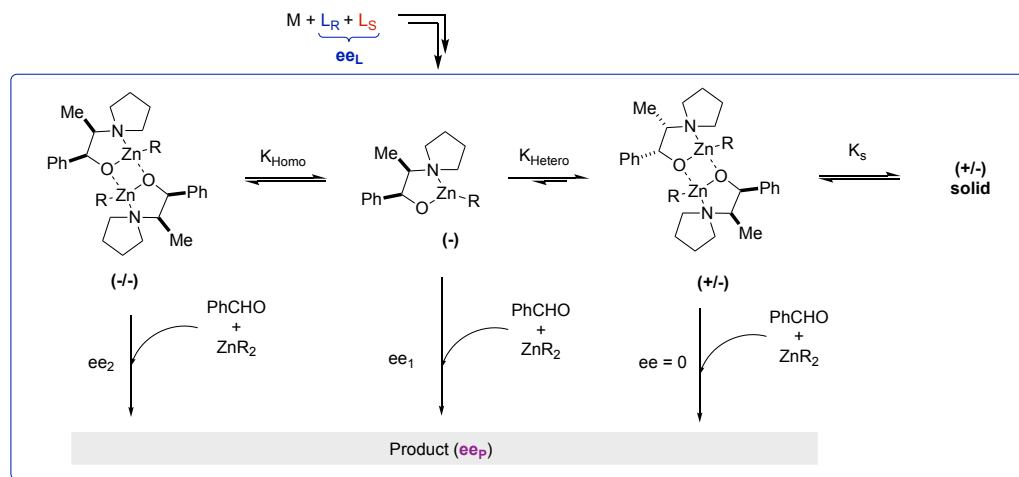
The catalytic loading effect with the enantiopure ligand and the non-linear effects were correlated. Considering that the reservoir effect on the racemic species is optimal in these systems, we could correlate the data points from the catalyst loading effect with a virtual enantiomeric excess if a scalemic ligand was used. The plots were superimposed with the NLE curves and are displayed in Figure 7 below [4]. At -20 °C and 0 °C, good agreement was observed but not at room temperature.



**Figure 7.** Colored dots: Non-linear studies (from Figure 2). Black dots: Superimposition of  $ee_P$  as function of catalyst loading, which was previously converted to  $ee_L$  vs. simulated ligand  $ee$  assuming a complete trapping of the racemic ligand (from Figure 4).

Altogether, these results indicate a monomer-dimer mechanism as proposed in Figure 8 [19]. Two different enantiodivergent pathways are present in the system: a monomeric (-)-NPNE-ZnR-catalyzed mechanism and a dimeric (-)-NPNE-ZnR-catalyzed mechanism that operate at a steady state. Since the overall  $ee$  (and yield) of the product is the combination of the two catalysts, if (i) the monomeric catalyst is more enantioselective than the dimeric catalyst (i.e.  $ee_1 > ee_2$ ), (ii) the two chiral catalysts are in dynamic equilibrium, and (iii) the minor enantiomer is trapped in the form of an inactive species such as a solid heterochiral dimer, then a hyperpositive non-linear effect is possible. Indeed, decreasing  $ee_L$  leads to an increase of  $ee_P$  because the equilibrium should be shifted to the monomeric catalyst. Decreasing the catalyst loading should have the same effect.





**Figure 8.** Proposed enantiodivergent model with  $(-)$ -NPNE as major enantiomer.

However, this hyperpositive non-linear effect will only be possible if the reservoir effect is highly efficient, trapping the minor enantiomer. This is the case at low temperatures ( $0^\circ\text{C}$  and  $-20^\circ\text{C}$ ). On the other hand, at room temperature we observe essentially a “classical” positive non-linear effect although the study of the catalysis revealed an increase of  $ee_P$  as function of the catalyst loading (Figure 4). This suggests that at room temperature a portion of the heterochiral dimer is soluble and lowers the overall  $ee_P$  by allowing for the formation of the minor enantiomer catalyst, or by being catalytically active itself and generating racemic product.

In asymmetric catalysis, the enantioselectivity is determined by the relative rates of the enantiodifferentiating step (i.e.  $\Delta\Delta G^\ddagger$ ), which is temperature-dependent. As a result, the enantioselectivity is greater at lower temperature. Here, we also investigated the effect of the temperature on the overall product  $ee$  of the reaction (Figure 5). With diethylzinc as reagent,  $ee_P$  goes from 84.2% at  $-20^\circ\text{C}$  to 77.8% at  $40^\circ\text{C}$ , a variation that is very little given the temperature range. With dimethylzinc, the enantiomeric excess of the product was significantly increased (from 54.4% to 75.1%) which is an unusual inverse temperature dependence. Altogether, this is consistent with an equilibrium between a monomeric species and a dimeric species, which is shifted towards the more enantioselective monomer at higher temperature.

#### 4. Materials and Methods

Synthetic procedures as well as additional data for experimental catalytic runs can be found in the supplementary information section. Detailed experimental data (reactant quantities, reaction conditions, raw and treated results for all catalytic runs).

#### 5. Conclusions

In asymmetric synthesis or catalysis, the NPNE ligand is one of the most used in the family of ephedrine-based ligands usually generating products with high enantiocontrol. The study of the  $ee$  of the product versus the  $ee$  with this ligand in the asymmetric organozinc alkylation demonstrated that the chiral catalyst, when not enantiopure, is more enantioselective than its enantiopure counterpart. Mechanistic studies show that the system follows the same pattern as that with *N*-benzyl ephedrine or *N*-methyl ephedrine ligands: with NPNE ligand, we noticed the presence of an insoluble racemic aggregate that allowed to trap the minor enantiomer catalyst. The remaining enantioenriched active species consist in a two-component system, where a monomeric catalyst is in equilibrium with a dimeric catalyst. The equilibrium between the catalytic species is dependent on the total concentration of species in solution which depends on the enantiomeric excess of the ligand used in the reaction. Evidence for this model has been found by varying the catalyst



loading, or the reaction temperature. A correlation between the catalytic loading effect with the enantiopure ligand and the non-linear effects suggested that part of the racemic aggregate could catalyze the reaction and reduce the magnitude of the observed hyperpositive non-linear effect at higher temperature.

**Supplementary Materials:** Additional information of this research is included in Tables S1–S13, which are available online. Synthetic procedures are also included.

**Author Contributions:** Conceptualization and methodology, T.T., Y.G. and S.B.L.; investigation, T.T. and Y.G.; writing—original draft preparation S.B.L.; writing—review and editing, T.T., Y.G. and S.B.L; supervision, S.B.L.; project administration, S.B.L.; funding acquisition, S.B.L. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** Data is contained within the article and Supplementary Materials.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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