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Observation of hyperpositive non-linear effects in asymmetric catalysis.

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Asymmetric amplification is a curious phenomenon which is believed to play a key role in the emergence of biological homochirality, and thus of life itself. In asymmetric catalysis, it is achieved via positive non-linear effects, which allow high product enantiomeric excesses with a non-enantiopure catalyst. However, it has also been proposed that non-enantiopure catalysts may be even more enantioselective than their enantiopure counterparts, though such a case has never been experimentally observed to date. Here we show an example of such a hyperpositive non-linear effect in asymmetric catalysis. We found that addition of dialkylzinc reagents to benzaldehyde gave higher product e.e.s with only partially resolved chiral *N*-benzyl-ephedrine ligands. A mechanistic study was carried out and our results point toward a two-component catalysis, where mononuclear as well as aggregated catalysts are in equilibrium and in

competition. These results introduce an unprecedented class of asymmetric amplification in enantioselective catalysis.

Introduction

Asymmetric amplification, which coins the obtention of highly enantioenriched chiral products from material of low enantiomeric purity, is a phenomenon which has fascinated scientists for several decades as it probably plays an important role in the emergence of biological homochirality.^{1–10} In enantioselective catalysis, such asymmetric amplification is known as positive non-linear effect [(+)-NLE]^{11–14} since Kagan's pioneering work on non-linear relationships between product enantiomeric excess (e.e.) and catalyst e.e., which followed up on Wynberg and Feringa's study on e.e.-dependent chemical reactivity.¹⁵ A striking example is Noyori's DAIB-catalysed addition of dialkylzincs to benzaldehyde, where an only 15% e.e. ligand lead to a 95% e.e. product.¹⁶ In the case of the intriguing Soai reaction, it combines a positive non-linear effect with a reaction that proceeds autocatalytically, i.e. faster as more product – which is also the catalyst – is formed ('far-from-equilibrium' process).^{5,6} Kagan and co-workers were also the first to propose mathematical models which rationalise and quantify the appearance of NLEs that are the consequence of the presence of self-organised dimeric, trimeric and even tetrameric catalysts (i.e. ML₂, ML₃ and ML₄ models).¹¹ On the other hand, Noyori's group developed a model adapted to the DAIB ligand and the fluctuational nature of dialkylzinc chemistry, in which a monomeric DAIB-alkylzinc adduct catalyses the reaction, while homochiral and heterochiral dimeric aggregates act as resting species.^{17–19} In both models, (+)-NLEs are achieved when the aggregates consist preferably of both catalyst enantiomers in equal parts (heterochiral aggregate) and when those aggregates are less (or not at

all) catalytically active. Under those conditions, the active scalemic (i.e. nonenantiopure) catalyst may become as selective as the enantiopure one. Interestingly, Kagan also showed that it should be also possible to find chiral systems where the product e.e.s “take values much larger for partially resolved ligand than enantiomerically pure ligand!”.¹¹ They predicted this behaviour as a particular case of the ML_3 system, where both homochiral (RRR) and heterochiral catalyst trimers (RRS) catalyse, the latter being the most selective one, and coined the term of hyperpositive NLEs.¹¹ However, to the best of our knowledge, a concrete example of a hyperpositive NLE has never been observed.

Here we present a case of a hyperpositive NLE using an ephedrine-based ligand in the catalytic addition dialkylzincs to aldehydes. Correlation between the product e.e. (ee_P) and ligand e.e. (ee_L) for the asymmetric addition of dimethylzinc (or diethylzinc) to benzaldehyde using (1*R*,2*S*)-*N*-benzylephedrine [(-)-NBE] as chiral auxiliary ligand showed that an non-enantiopure ligand increased the product e.e. compared to the enantiopure ligand. A mechanistic study was carried out in which the influence of catalyst concentration and temperature were investigated and the reaction's kinetics analysed. Rationalisation points towards this system being different from the ML_3 -system theorized by Kagan, consisting of competition between both discrete and dimeric homochiral catalytic species, and therefore also differing from Noyori's model for aminoalcohol-catalysed dialkylzinc additions.

Results

Hyperpositive non-linear effect Fig. 1 displays the hyperpositive correlation between the product e.e. (ee_P) and ligand e.e. (ee_L) for the asymmetric addition of

71 dimethylzinc to benzaldehyde using (1*R*,2*S*)-*N*-benzylephedrine [(-)-NBE]²⁰ as chiral
72 auxiliary ligand. While the enantiopure ligand induces a very poor enantioselectivity
73 of only 16%, the progressive reduction of the enantiomeric excess of the ligand leads
74 to an approximately exponential growth of the product e.e., reaching a maximum of
75 53% e.e. with only 5% ee_L. Thus, using an enantio-impure ligand of only 5% e.e.
76 increased the product e.e. by 37% compared to the enantiopure ligand, which is
77 astonishing - when seeking a more stereoselective catalyst, typical logic would
78 suggest searching for alternative molecular structures of the ligand, but never to
79 reduce the enantiopurity of the ligand. The use of ZnEt₂ as the dialkylzinc reagent
80 leads to a less pronounced but still significant ee_P increase when decreasing ee_L (cf.
81 Supplementary Fig. 1). Kagan's ML₃ model implies that the NLE curve can be
82 hyperpositive only in the upper half of the ligand e.e. scale, which does not match
83 with our observations shown in Fig. 1.¹¹ Therefore, the ML₃ model is not applicable
84 here and we have to search for other explanations for this peculiar phenomenon.

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Fig. 1 | Hyperpositive non-linear effect. $(1R,2S)$ -*N*-benzylephedrine [(-)-NBE]-catalysed addition of ZnMe_2 to benzaldehyde. The reaction conditions and the experimental procedure can be found in the Supplementary Methods. Each point is the mean of three different experiments; the vertical bars depict standard deviations.

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Mechanistic investigations One striking difference between the use of enantiopure and scalemic ligand is that upon addition of the dialkyl zinc reagents, a white precipitate was observed in the latter case whereas enantiopure solutions stay clear. Filtration and hydrolysis of the precipitates obtained from 50% e.e. ligand samples yielded the starting ligand in its racemic form, which is most likely due to the formation of a heterochiral dimer. Thus, it becomes clear that in this case precipitation of an inactive heterochiral aggregate drives the overall system to a positive (+)-NLE, while leaving an enantioenriched Zn complex in solution.

Decreasing the e.e. of the ligand would thus generate more heterochiral – and inactive – dimer and therefore less catalytically active species (reservoir effect).¹¹ In other words, reducing the ee_L induces a decrease of the catalyst concentration. We hypothesized that the observed hyperpositive NLE could be related to the active catalyst concentration. To this end, we evaluated the product e.e. while varying the concentration of the enantiopure ligand (Fig. 2a). Indeed, a decrease of the catalyst loading led to an increase of ee_P. Interestingly, the shape of the curve is consistent with the one seen in Fig. 1, which made us compare the two datasets: assuming that the heterochiral aggregate fully precipitates and does not interfere in the catalytic process, a system with e. g. originally 20 mol% catalyst loading of a 50 % ee_L-ligand should be identical to a 10 mol% catalyst loading of enantiopure catalyst (cf. Supplementary Fig. 2 for a more detailed graphical representation). Thus, we could correlate the results from the enantiopure catalysts with a simulated e.e. if a scalemic ligand was used. The resulting graph from Fig. 2a was then superimposed with the hyperpositive NLE curve (Fig. 2b), leading to an excellent match between both curves. The catalyst loading screening models accurately the ee_P increase at lower ee_L and proves that the observed hyperpositive NLE in Fig. 1 is due to a change in the concentration of the soluble part of the catalyst. The same catalyst concentration effect was observed when using ZnEt₂ as reagent and a perfect correlation was obtained with the measured non-linear effect; dilution of the catalytic system while keeping the catalyst loading at 20 mol% also led to an ee_P increase (cf. Supplementary Fig. 3).

Fig. 2 | Impact of the catalyst loading in the enantiomeric excess of the product. a, Product e.e. as function of catalyst loading using enantiopure NBE. **b,** Superimposition of the two curves after conversion of a) to ee_P vs (simulated) ligand e.e. Each point is the mean of three different experiments; the vertical bars depict standard deviations.

The results point toward a possible participation of several active species with different enantioselectivities. In order to gain more insight into the system, we performed a temperature screening of the reaction, investigated the kinetic order in catalyst and studied the ee_P evolution over time. Increasing the reaction temperature at constant catalyst concentration lead to a surprising ee_P increase, both with the enantiopure and the 20% e.e. enantioenriched ligand (Fig. 3), which is an unusual inverse temperature dependence. This is obviously accompanied by a shift to the more enantioselective catalytic species, which overcompensates the usual ee_P loss at high temperature. This temperature effect is less pronounced with ZnEt_2 and correlates with its weaker hyperpositive NLE (cf. Supplementary Fig. 4).

Fig. 3 | Temperature-dependence study. Addition of ZnMe_2 to benzaldehyde in presence of (-)-NBE ligand as function of the temperature. ●: enantiopure (-)-NBE, ▲: (-)-NBE with 20% ee_L, otherwise standard reaction conditions as in Fig. 1. Each point is the mean of three different experiments; the vertical bars depict standard deviations.

The kinetic order in catalyst c was determined by Visual Time-Normalised Analysis (VTNA) of the kinetic profiles obtained from reactions with different catalyst loadings, monitored by FTIR (the dataset can be found in Supplementary Fig. 5).^{21–23} Simultaneous analysis of all kinetic profiles did not give a single value of c , which indicates a non-constant c . Therefore, a segmented analysis was conducted and the results are shown in Fig. 4. The plot c vs. catalyst loading gives an unusual, U-shaped curve which starts at $c = 1$ at low catalyst loading, which goes down to 0.4 (at 10–15 mol% catalyst) but then increases again at higher catalyst loading. Exponential or near-exponential curves have been observed in case of catalyst aggregation,

where either only the monomer or only the aggregate catalyses, but these do not contain minimum or maximum values.²¹

Fig. 4 | Catalyst order as function of the catalyst loading. (-)-NBE-catalysed addition of ZnMe_2 to benzaldehyde at 30 °C (otherwise standard reaction conditions as in Fig. 1). c is defined according to the standard rate equation $-\text{d}[\text{Benz}]/\text{dt} = k[\text{Cat}]^c[\text{Benz}]^a[\text{ZnMe}_2]^b$, with $[\text{Cat}]$ as the overall (-)-NBE- ZnMe concentration, $[\text{Benz}]$ as the benzaldehyde concentration, $[\text{ZnMe}_2]$ as the ZnMe_2 -concentration, a and b as the respective partial reactant orders and k as the rate constant. The horizontal bars on each dot indicate which two kinetic curves have been used to determine c via VTNA, which can be considered as a mean value over the respective $\Delta(\text{Catalyst loading})$.

In addition, the evolution of ee_P over the course of the reaction was investigated. Fig. 5 displays ee_P vs. time plots at an early stage of the reaction and with different catalyst loadings. For a given catalyst loading, the ee_P values are not constant but increase as the reaction proceeds, a result that is observed in all cases. These observations indicate, in addition to the fact that the ee_P is directly dependent on the catalyst loading, that the ratio of the different catalytic active species changes over time. Changing the catalyst loading seemingly does not affect significantly the way in

which this ratio evolves (at least in the early stage of the reaction) but it affects the initial distribution of the different catalysts.

Fig. 5 | Evolution of the product e.e. as function of time and at different catalyst loading. (-)-NBE-catalysed addition of ZnMe_2 to benzaldehyde at various catalyst loadings (standard reaction conditions as in Fig. 1). Some plots have been omitted for clarity; the full dataset can be found in Supplementary Fig. 6. Each point is the mean of three different experiments; the vertical bars depict standard deviations.

Discussion

We propose the reaction scheme shown in Fig. 6 that accounts for our observations. Our results indicate the presence of two different enantiodivergent pathways: a monomeric (-)-NBE- ZnMe -catalysed mechanism and a possible dimeric (-)-NBE- ZnMe -catalysed mechanism that operate at a steady state. Assuming that the ee_P produced by the monomer catalyst (ee_m) is higher than with the dimer (ee_d) and that both catalysts are in a dynamic equilibrium, then decreasing the catalyst concentration leads to an ee_P increase as the equilibrium is shifted to the more enantioselective monomer. Decreasing ee_L has the same effect as it causes the

lowering of the effective catalyst in solution (because of the precipitating heterochiral aggregate) and therefore gives rise to the observed hyperpositive NLE. This is evidenced by the following points: 1) Chiral alkylzinc aminoalkoxides, issued from dialkylzinc and a chiral aminoalcohol, are known to generate homochiral as well as heterochiral dimers.¹⁶ Since the latter are insoluble in our case, only monomeric and homochiral dimeric complexes (both consisting only of the major enantiomer) stay in solution. This was supported by ¹H DOSY NMR experiments^{24–27} of enantiopure (-)-NBE reacted with ZnMe₂ in toluene-*d*₈, which indicated that the complexes have a higher molecular weight (MW) than expected from monomeric (-)-NBE-ZnMe over a broad temperature range (cf. Supplementary Fig. 7). 2) The monomer/homochiral dimer equilibrium is necessarily affected by the overall catalyst concentration as well as by the reaction temperature. The higher the catalyst concentration and the lower the temperature, the more it aggregates. This is seen in the upwards slope in Fig. 1a and 3, considering the homochiral dimer less enantioselective than the monomeric catalyst. 3) The impact of the catalyst loading on the product e.e. is already visible at the initial stage of the reaction, where other potential aggregates (e. g. catalyst/product-aggregates) play a minor role and therefore are not likely to be the origin of the ee_P variation. 4) The intriguing catalyst order / catalyst loading dependence is also consistent with a model in which both monomer and homochiral dimer catalyse. If we consider both monomeric and dimeric catalysts to have an inherent first order kinetic behaviour – which is the case for monomeric DAIB-ZnMe^{16,18} – then we would expect first order behaviour at very low and at very high catalyst loading, when either only the monomeric or only the dimeric catalyst is present. In the intermediate regime, the observed order is expected to change because (i) the overall kinetic constant of the system varies as a function of the dimeric catalyst's kinetic constant (*k*₂) and the monomer's kinetic constant (*k*₁) ratio,

and (ii) because of the aggregation-induced decreasing amount of catalyst molecules. Both effects lead to a non-linear variation of the reaction rate and, therefore, to $c \neq 1$.

In the light of Noyori's model for aminoalcohol-catalysed addition of dialkylzinc to aldehyde, these findings are notable because catalysis by aggregates was always excluded (except in certain conditions where the model didn't fit experimental results) and this supposition has only been rarely questioned.^{28–30}

In conclusion, we have discovered an example of a hyperpositive NLE in the (-)-NBE-catalysed enantioselective addition of dialkylzincs to benzaldehyde. Catalyst loading screenings, temperature screenings, conversion vs time and ee_P vs time plots indicate that the catalytic system consists of two enantiodivergent pathways, in which both monomeric and homochiral dimeric (-)-NBE-ZnMe complexes catalyse the reaction, with different enantioselectivities. Further work is in progress to gain a deeper understanding of the mechanism of the catalyst system.

Fig. 6 | Proposed enantiodivergent model for the (-)-NBE-catalysed addition of dialkylzincs to benzaldehyde. The dimeric catalyst RR is depicted as being in equilibrium with higher-order aggregates like trimers or tetramers, which have been observed with ligands derived from ephedrine and other aminoalcohols^{31–34} and whose presence (and possible catalytic activity) we cannot fully exclude so far.

Data availability

Complete experimental procedures, compound characterisation data and kinetic rate profiles are available in the Supplementary Information.

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Author contributions

Y.G. performed the synthetic experiments and data analyses. A.M.F. and T.A. participated in data analyses. S.B.L. conceptualized and supervised the study, and wrote the manuscript with Y.G.

Competing interests

The authors declare no competing interests.

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