

Cite this: *Chem. Sci.*, 2020, **11**, 12453

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Hyperpositive non-linear effects: enantiodivergence and modelling†

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The chiral ligand *N*-methylephedrine (NME) was found to catalyse the addition of dimethylzinc to benzaldehyde in an enantiodivergent way, with a monomeric and a homochiral dimeric complex both catalysing the reaction at a steady state and giving opposite product enantiomers. A change in the sign of the enantiomeric product was thus possible by simply varying the catalyst loading or the ligand ee, giving rise to an enantiodivergent non-linear effect. Simulations using a mathematical model confirmed the possibility of such behaviour and showed that this can lead to situations where a reaction gives racemic products, although the system is composed only of highly enantioselective individual catalysts. Furthermore, depending on the dimer's degree of participation in the catalytic conversion, enantiodivergence may or may not be observed experimentally, which raises questions about the possibility of enantiodivergence in other monomer/dimer-catalysed systems. Simulations of the reaction kinetics showed that the observed kinetic constant k_{obs} is highly dependent on user-controlled parameters, such as the catalyst concentration and the ligand ee, and may thus vary in a distinct way from one experimental setup to another. This unusual dependency of k_{obs} allowed us to confirm that a previously observed U-shaped catalyst order vs. catalyst loading-plot is linked to the simultaneous catalytic activity of both monomeric and dimeric complexes.

Received 27th August 2020
Accepted 7th October 2020

DOI: 10.1039/d0sc04724d

rsc.li/chemical-science

Introduction

Non-linear effects (NLEs) in asymmetric catalysis refer to cases in which the enantiomeric excess of the product does not scale linearly with the enantiomeric excess of the catalyst.¹ The first examples and models of such behavioural differences between scalemic and enantiomerically pure catalysts were established by Kagan in 1986.² Since then NLEs are considered as ubiquitous phenomena that provide additional information regarding the aggregation state of the catalyst or the formation of multi-ligand species^{2,3} (*cf.* also reviews^{4,5} and some recent examples⁶⁻⁹). Not only being indicative of the catalytic system, NLEs also give clues to discussions on the origin of molecular homochirality in biology which is related to the origin of life.¹⁰

Several models for NLEs have been described and discussed in the literature, all of them being the results of interactions between the enantiomers of the chiral catalyst thus generating diastereomeric perturbations of the entire system. A positive non-linear effect (*i.e.* asymmetric amplification, (+)-NLE) is essentially generated by the presence of a reservoir of racemic ideally catalytically inactive hetero-aggregate (*meso*),¹¹⁻¹³

although pure homochiral aggregation can also lead to (+)-NLEs in certain cases.¹⁴ Amongst these models, Kagan established a hypothetical case wherein an unprecedented phenomenon could occur – that is, the chiral catalyst [would] be much more efficient when partially resolved than when enantiomerically pure. We recently have observed such a case, known as hyperpositive NLE, in the enantioselective addition of dialkylzincs to benzaldehyde when catalysed by the chiral *N*-benzylephedrine (NBE) ligand.^{15,16} Subsequent mechanistic investigations pointed towards a two-component catalysis where monomeric as well as homochiral dimeric catalysts are in equilibrium and in competition: both catalyse the reaction with different enantioselectivities, the dimeric catalyst being the less enantioselective one (Fig. 1). Through the precipitation of a heterochiral aggregate, variation of the ligand ee leads to a change of the overall catalyst concentration and, therefore, to a change of the monomer–dimer equilibrium. This favours the more enantioselective monomeric catalyst at low ligand ee and gives rise to the hyperpositive non-linear effect (Fig. 2a, orange crosses). These findings challenge the widely applied Noyori model for asymmetric dialkylzinc additions, where only monomers are catalytically active, and shows how complex systems with concurrent catalytic cycles can emerge from a minimum of components.^{13,17}

In line with our studies on NLEs, we have explored additional ephedrine-based ligands in dialkylzinc addition reactions. The

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc04724d



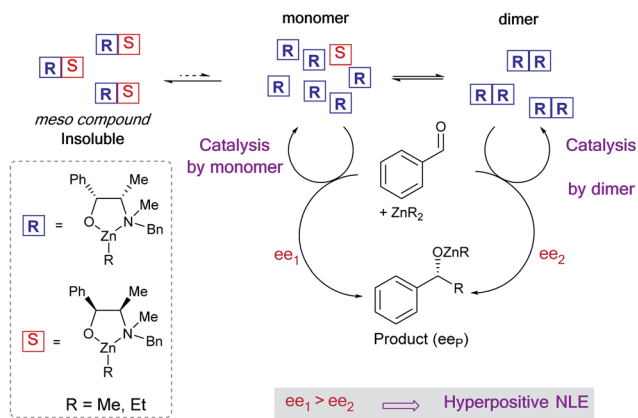


Fig. 1 Competitive reaction pathway of a monomeric and a dimeric catalyst in an enantioselective reaction that accounts for a hyperpositive non-linear effect: the case of NBE-catalysed enantioselective addition of dialkylzinc to benzaldehyde.

results presented in this work show that *N*-methylephedrine ligand (NME) follows the same model as the related NBE ligand, with monomer and dimer both catalysing the reaction, the only difference being that no meso aggregate precipitates in the case of NME. However, the homochiral dimer catalyst not only yields the product with a lower ee than the monomer catalyst, it selectively gives the opposite enantiomeric product. This

enantiodivergent behaviour allowed us to switch between the preference for either enantiomer of the product, just by varying the catalyst loading. Variation of the enantiomeric excess of the ligand also allowed switching the selectivity of the product formation, leading to an enantiodivergent non-linear effect. In addition, we developed a theoretical model giving a closed mathematical expression which takes into account the concomitant catalysis by monomeric and dimeric species. From this we simulated [product ee vs. catalyst concentration] and [product ee vs. ligand ee]-plots which allowed us to gain a better understanding of the two-component catalytic system. Furthermore, the model also allowed us to analyse the reaction kinetics. Simulations showed that the observed kinetic constant of the system k_{obs} is indeed not unique for each catalytic system, but depends on user-controlled parameters such as the total catalyst concentration and the ligand ee. This has confirmed the hypotheses made earlier and allowed the simulation of a U-shaped catalyst order vs. catalyst-curve, which had been previously observed experimentally in the NBE-catalysed reaction.¹⁵

The paper is organised as follows: we will (1) first present the experimental results obtained from the NME ligand, showing enantiodivergence in product ee (ee_P) vs. ligand ee (ee_L)- and ee_P vs. catalyst loading-plots, (2) then go on to a theoretical analysis where we present the mathematical model and discuss ee_P vs. catalyst concentration- and ee_P vs. ee_L -plots, (3) this is followed by a kinetic analysis of the system in which we investigate the relationship of k_{obs} with the catalyst concentration and ee_L and

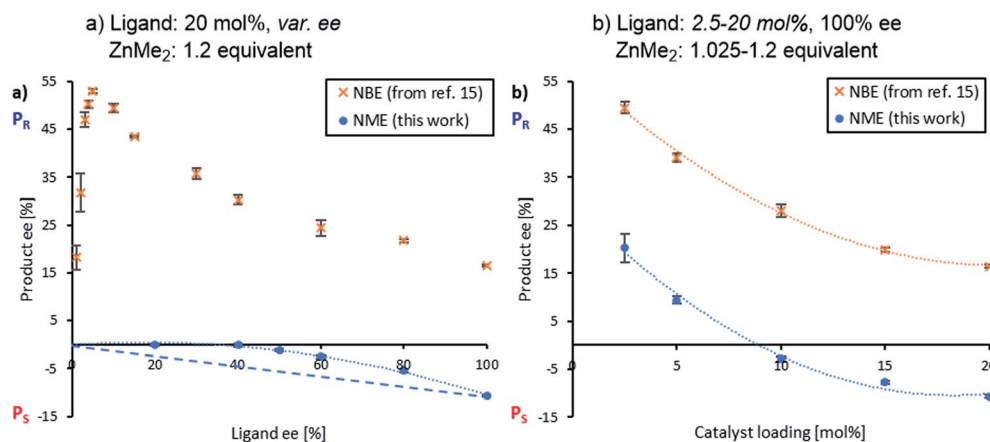


Fig. 2 (a) NLE-curve and (b) ee_P vs. catalyst loading-plot of the (–)-NME- (blue dots) and (–)-NBE- (orange crosses, from ref. 11) catalyzed enantioselective addition of $ZnMe_2$ to benzaldehyde at 0 °C. Each point is the mean of three independent experiments; the vertical bars depict standard deviations. The second-order polynomial fits (dotted lines) serve as visual guidelines. The dashed line in (a) simulates a linear ee_P/ee_L relationship for the NME-catalysed reaction. The product ee is defined as $(P_R - P_S)/(P_R + P_S)$.





Fig. 3 (a) ee_P as a function of the reaction temperature (blue dots: 100% ee_L ; orange triangles: 50% ee_L) and (b) NLE at room temperature of (-)-NME (blue dots) and (+)-NME (red squares) of the NME-catalysed enantioselective addition of ZnMe₂ to benzaldehyde. Each point is the mean of three different experiments; the vertical bars depict standard deviations. The second-order polynomial fits (dotted lines) serve as visual guidelines. The product ee is defined as $(P_R - P_S)/(P_R + P_S)$.

gap and to get a better understanding of hyperpositive and, in particular, enantiodivergent NLEs, we developed mathematical models which allow us to simulate ee_P vs. catalyst concentration- and ee_P vs. ee_L -plots. We begin with Model I, which is based on an enantiopure system where an enantiopure ligand reacts with a metal to give monomeric and dimeric homochiral complexes (R and RR , respectively) both of which catalyse the reaction at different rates (k_1 and k_2) and with different enantioselectivities (ee_1 and ee_2), as shown in Fig. 4; $[Cat_{tot}]$

represents the total catalyst concentration. For the sake of simplicity, we assume that both R and RR -catalysts follow a similar mechanism with a rate law of type $-d[Sub]/dt = k_i[Cat_i][Sub][Rea]$ (with k_i and $[Cat_i]$ being the respective rate constants and catalyst concentrations, $[Sub]$ and $[Rea]$ the substrate and reactant concentrations; all species are first-order). We also assume that the $[RR]/[R]$ -ratio stays constant over the course of the reaction and depends only on the homochiral dimerization constant K_{Homo} .³⁵ This makes Model I reminiscent of Kagan's ML_n model, which also considers the ratio between different catalytic species to be constant over time. The case of a time-dependent $[RR]/[R]$ -ratio will be discussed at the end of this study.



Fig. 4 Schematic representation of Model I, which consists of a monomeric (R) and a dimeric (RR) enantiopure catalyst both of which operate at a steady state and are linked through the equilibrium constant K_{Homo} . The catalysts are issued from the reaction of a metal salt (M) with a chiral, enantiopure ligand (L_R) and promote the reaction of a substrate (Sub) and a reactant (Rea) to form a chiral product with the overall enantiomeric excess ee_P . The R - and RR -catalysts yield a product with a rate constant of k_1 and k_2 , respectively, and with an enantioselectivity of ee_1 and ee_2 .

$$ee_P = \frac{ee_1 + \gamma \frac{k_2}{k_1} ee_2}{1 + \gamma \frac{k_2}{k_1}} \quad (1)$$

$$\gamma = \frac{\sqrt{1 + 8K_{Homo}[Cat_{tot}]} - 1}{4} \quad (2)$$

By combining the set of equations displayed in Fig. 4, it was possible to obtain eqn (1) and (2) which relate ee_P to the parameters k_2/k_1 , ee_1 , ee_2 , K_{Homo} and $[Cat_{tot}]$, and allowed us to compute ee_P vs. $[Cat_{tot}]$ -curves. Fig. 5a displays the evolution of ee_P for selected values of ee_2 with fixed values of K_{Homo} , k_1 and k_2





Fig. 5 Simulation of the relationship between ee_p and $[Cat_{tot}]$ according to eqn (1) and (2). The basic set of parameters is $ee_1 = 100$, $ee_2 = -100$, $K_{Homo} = 33$ and $k_2/k_1 = 1$. Each panel shows curves where one of the parameters has been varied: (a) ee_2 , (b) K_{Homo} , (c) k_2/k_1 . The product ee is defined as $(P_R - P_S)/(P_R + P_S)$.

(k_2/k_1 was set to 1, ee_1 to 100% and K_{Homo} to 33, which corresponds to the association constant of DAIB-ZnMe).^{13,36} The graphs show that an enantiodivergent behaviour can indeed be

observed by varying $[Cat_{tot}]$, as long as ee_2 has a sufficiently low and negative value. This is further favoured by high values of K_{Homo} (Fig. 5b) and k_2/k_1 (Fig. 5c): the more the dimeric complex prevails over the monomer and the higher its relative activity, the more the curve becomes hyperbolic, pushing the point at which it crosses the $[Cat_{tot}]$ -axis (*i.e.* $ee_p = 0$, labelled $[Cat_{tot}]^0$) to lower $[Cat_{tot}]$. $[Cat_{tot}]^0$ corresponds to an overall catalytic system where R and RR catalysts compensate each other to yield an overall racemic product – even if both give independently enantiopure products.

Model studies: product ee vs. ligand ee (scalemic system)

In order to also simulate NLE curves, we expanded Model I to non-enantiopure ligands, as shown in Fig. 6. The resulting system (Model II) now includes the catalytic species S and SS (which, like their enantiomeric counterparts, are linked through K_{Homo} and catalyse with the kinetic constants k_1 and k_2) and also the heterochiral dimer RS , which is related to R and S through the dimerization constant K_{Hetero} and may generate racemic products with a rate constant k_2' . Thus, a single scalemic ligand gives rise to 5 different catalytic species. To derive closed mathematical expressions, we followed the approach used by Noyori for the DAIB-model which consists in introducing $\alpha = [R] + [S]$ and $\beta = [R][S]$ to simplify the equations. ee_p and ee_L are then given by eqn (3) and (4) as functions of α and β . Since β is itself a function of α [*cf.* eqn (5)], ee_p and ee_L are linked



Fig. 6 Schematic representation of Model II, which consists of monomeric (R , S) and both homo- (RR , SS) and heterochiral (RS) dimeric catalysts that all operate at a steady state and are linked through the equilibrium constants K_{Homo} and K_{Hetero} . The catalysts are issued from the reaction of a metal salt (M) with a mixture of both ligand enantiomers (L_R and L_S) with an enantiomeric excess of ee_L . They promote the reaction of a substrate (Sub) and a reactant (Rea) to form a chiral product with the overall enantiomeric excess ee_p . The monomeric, the homochiral dimeric and heterochiral dimeric catalysts yield a product with a rate constant of k_1 , k_2 , and k_2' , respectively, and with an enantioselectivity of ee_1 and ee_2 (R and RR) or $-ee_1$ and $-ee_2$ (S and SS). The RS dimer yields a racemic product ($ee = 0$).



through α and depend only on the parameters K_{Homo} , K_{Hetero} , k_1 , k_2 , k'_2 , ee_1 , ee_2 and $[\text{Cat}_{\text{tot}}]$. After defining these parameters, ee_{P} vs. ee_{L} -datasets could be obtained by choosing appropriate values for α (cf. ESI Methods† for the details of the calculations and the general expressions for the upper and lower limits of α). For this study, we will focus on the cases where the NLE is hyperpositive and potentially enantiodivergent – that is with $K_{\text{Hetero}} > 2K_{\text{Homo}}$ which is, as in the Noyori model, a necessary condition to obtain (+)-NLEs – and $ee_1 > ee_2$.¹³ Fig. 7 shows

several cases computed from Model II. To simplify the discussion we have set $k'_2 = 0$ in all simulations except in Fig. 7f.

$$ee_{\text{P}} = \frac{\sqrt{\alpha^2 - 4\beta} \left(ee_1 + \alpha K_{\text{Homo}} \frac{k_2}{k_1} ee_2 \right)}{\alpha + (\alpha^2 - 2\beta) K_{\text{Homo}} \frac{k_2}{k_1} + \beta K_{\text{Hetero}} \frac{k'_2}{k_1}} \quad (3)$$

$$ee_{\text{L}} = \frac{\sqrt{\alpha^2 - 4\beta} (1 + 2\alpha K_{\text{Homo}})}{[\text{Cat}_{\text{tot}}]} \quad (4)$$

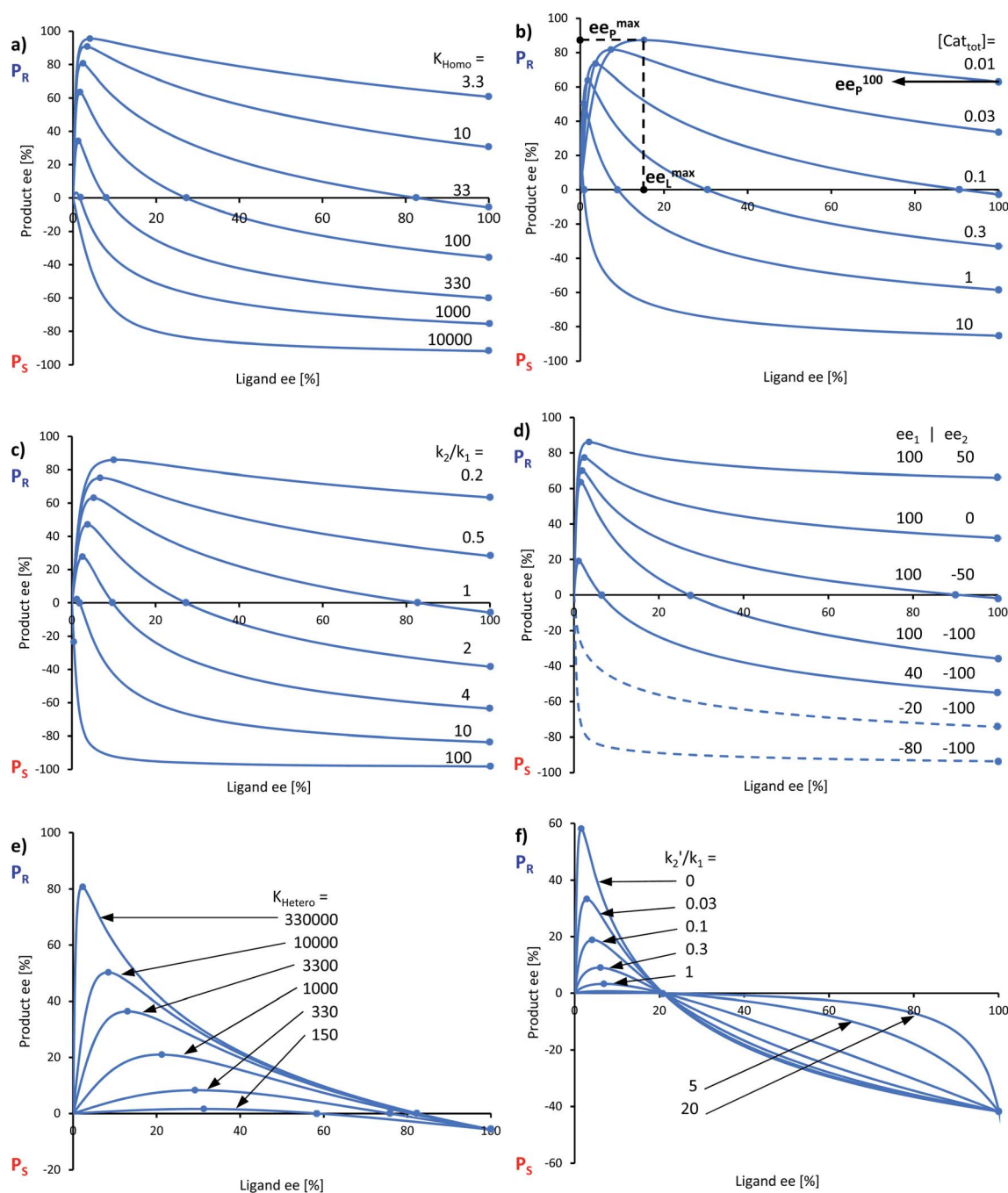


Fig. 7 Simulation of NLEs with Model II, varying parameters (a) K_{Homo} , (b) $[\text{Cat}_{\text{tot}}]$, (c) k_2/k_1 , (d) ee_1 and ee_2 , (e) K_{Hetero} and (f) k'_2/k_1 . Fixed parameters: $[\text{Cat}_{\text{tot}}] = 0.11$, $k_2/k_1 = 1$, $ee_1 = 100$, $ee_2 = -100$ and $k'_2/k_1 = 0$ in all curves except where the corresponding parameter is varied; $K_{\text{Homo}} = 33$ (b, c, e), 100 (d) and 130 (f); $K_{\text{Hetero}} = 330\,000$ (a, d, f), 100\,000 (b) and 33\,000 (c). The product ee is defined as $(P_{\text{R}} - P_{\text{S}})/(P_{\text{R}} + P_{\text{S}})$.



$$\beta = \frac{(\alpha + 2K_{\text{Homo}}\alpha^2 - [\text{Cat}_{\text{tot}}])}{4K_{\text{Homo}} - 2K_{\text{Hetero}}} \quad (5)$$

Influence of K_{Homo} , $[\text{Cat}_{\text{tot}}]$, k_2/k_1 and $ee_{1/2}$. A non-linear effect is hyperpositive as long as the highest product ee (labelled $ee_{\text{P}}^{\text{max}}$) is different from the ee_{P} for the enantiopure ligand (ee_{P}^{100}). In Model II, ee_{P}^{100} will be strongly dependent on K_{Homo} , $[\text{Cat}_{\text{tot}}]$ and k_2/k_1 (Fig. 7a–c): higher the K_{Homo} , $[\text{Cat}_{\text{tot}}]$ or k_2/k_1 , lower the ee_{P}^{100} . This is consistent with a higher proportion and a higher activity of the low ee_{P} -yielding RR-catalyst over its monomeric counterpart.

In all representations in Fig. 7, we selected conditions in which ee_{P}^{100} could be negative and where the NLE curve crosses the ee_{L} -axis, making it an enantiodivergent NLE. Lower the ee_{P}^{100} , lower the crossing point at which $ee_{\text{P}} = 0$ (ee_{L}^0). At this point, the outcomes of all catalysts compensate each other to yield a racemic product. $ee_{\text{P}}^{\text{max}}$ diminishes as ee_{P}^{100} decreases; the maximum's ee_{L} -value ($ee_{\text{L}}^{\text{max}}$) is only slightly affected by K_{Homo} and, to a somewhat greater extent, by $[\text{Cat}_{\text{tot}}]$ and k_2/k_1 . This is seen nicely if, for a given set of parameters, K_{Homo} is multiplied and $[\text{Cat}_{\text{tot}}]$ divided by the same value: ee_{P}^{100} remains unchanged but $ee_{\text{P}}^{\text{max}}$ and $ee_{\text{L}}^{\text{max}}$ do not (cf. ESI Fig. 1†). Fig. 7d shows the impact of ee_1 and ee_2 on ee_{P}^{100} : lower the ee_2 , lower the ee_{P}^{100} . This is also true for ee_1 ; however, if both ee_1 and ee_2 are negative, the enantiodivergent NLE curve becomes a classic (+)-NLE for the *S*-product (P_{S} , Fig. 7d, dashed curves); the same holds for the *R*-product (P_{R}) if $ee_1 \leq ee_2$ and if both are positive. In a similar way, very high K_{Homo} , $[\text{Cat}_{\text{tot}}]$ or k_2/k_1 -values lead to apparent (+)-NLEs as $ee_{\text{P}}^{\text{max}}$ and $ee_{\text{L}}^{\text{max}}$ become exceedingly close to 0. Lowering the absolute amount of both a positive ee_1 and a negative ee_2 leads to a compression of the spectra (cf. ESI Fig. 2†).

Influence of K_{Hetero} and k_2' . In contrast to the previously discussed parameters, an increase in K_{Hetero} (Fig. 7e) does not affect ee_{P}^{100} but has a great impact on the hyperpositive maximum, which is shifted to higher $ee_{\text{P}}^{\text{max}}$ and lower $ee_{\text{L}}^{\text{max}}$ values. Consequently, the ee_{L}^0 is shifted to higher ee_{L} values under the same conditions. However, this is only true if the meso dimer is catalytically inactive: *RS* performing racemic catalysis ($k_2'/k_1 \neq 0$, Fig. 6f) leads to the inverse effect, namely a compacting of the curve. The values of ee_{P}^{100} and ee_{L}^0 remain unchanged, the latter being an isobestic point. The value of $ee_{\text{P}}^{\text{max}}$ decreases significantly even at low k_2'/k_1 as the concentration of RS at low ee_{L} is particularly high. k_2'/k_1 -values higher than k_2/k_1 ($k_2'/k_1 > 1$ in Fig. 7f) additionally lead to a contraction of the curve between ee_{L}^0 and $ee_{\text{L}} = 100$ and push its appearance towards a classical (–)-NLE. As in Kagan's ML_2 -model, a high activity of the meso catalyst leads to asymmetric depletion.

Dynamic properties of models I and II

Apart from simulating ee_{P} vs. ee_{L} -curves, NLE models have also been used to study the kinetic properties of the systems. This can be useful as some kinetic features may be characteristic for one or the other model, and thus be used as an additional probe to support the validity of a model for a specific catalytic

reaction. Blackmond showed this in conjunction with the Kagan and Noyori models;^{37,38} Micheau and co-workers even built a toolset, using the different kinetic properties of both systems, which allows an easy distinction between monomer- and dimer-catalysed enantioselective systems (which is not necessarily possible on the basis of ee_{P} vs. ee_{L} -curves alone)³⁹ and verified the origin of the non-linearity in the Noyori model by a kinetic system based on differential equations.⁴⁰ This prompted us to extend our work on Models I and II to a kinetic study.

The mathematical expressions of the rate laws based on Models I and II turned out to correspond to a standard second-order rate law (eqn (6) and (7)), albeit with a more complex term for k_{obs} (cf. ESI Methods† for the calculation details). For aggregate-free catalysed reactions, with 1st order in catalyst, k_{obs} is the product of $[\text{Cat}_{\text{tot}}]$ and the rate constant k_1 (eqn (8)). According to Model I, where the monomer and dimer coexist and both of which are catalytically active, k_{obs} depends on the parameters previously discussed: the (now absolute instead of relative) rate constants k_1 and k_2 , K_{Homo} and $[\text{Cat}_{\text{tot}}]$ (eqn (9)). This holds for chiral, enantiopure catalysts as well as for achiral ones, since we consider only the system's kinetic behaviour and not a possible product ee. Non-enantiopure catalytic systems following Model II additionally depend on ee_{L} , k_2' and K_{Hetero} (eqn (10)). For the sake of simplicity, we will consider here only the second-order rate law where the substrate and reactant concentrations are equal ($[\text{Sub}] = [\text{Rea}]$), however the following discussion applies also to its more general form where both differ from each other.

General second-order rate law (if $[\text{Sub}] = [\text{Rea}]$):

$$-\frac{d[\text{Sub}]}{dt} = k_{\text{obs}}[\text{Sub}]^2 \quad (6)$$

Integrated form of the second-order rate law:

$$[\text{Sub}]_t = \left(\frac{1}{[\text{Sub}]_0} + k_{\text{obs}}t \right)^{-1} \quad (7)$$

If only monomers exist:

$$k_{\text{obs}} = k_1[\text{Cat}_{\text{tot}}] \quad (8)$$

If monomers and dimers catalyse (Model I, achiral or enantiopure catalyst):

$$k_{\text{obs}} = k_1 \frac{\sqrt{1 + 8K_{\text{Homo}}[\text{Cat}_{\text{tot}}]} - 1}{4K_{\text{Homo}}} + k_2 \frac{(\sqrt{1 + 8K_{\text{Homo}}[\text{Cat}_{\text{tot}}]} - 1)^2}{16K_{\text{Homo}}} \quad (9)$$

If monomers and dimers catalyse (Model II, chiral catalyst with any ee_{L}):

$$k_{\text{obs}} = k_1\alpha + k_2K_{\text{Homo}}(\alpha^2 - 2\beta) + k_2'K_{\text{Hetero}}\beta \quad (10)$$

with



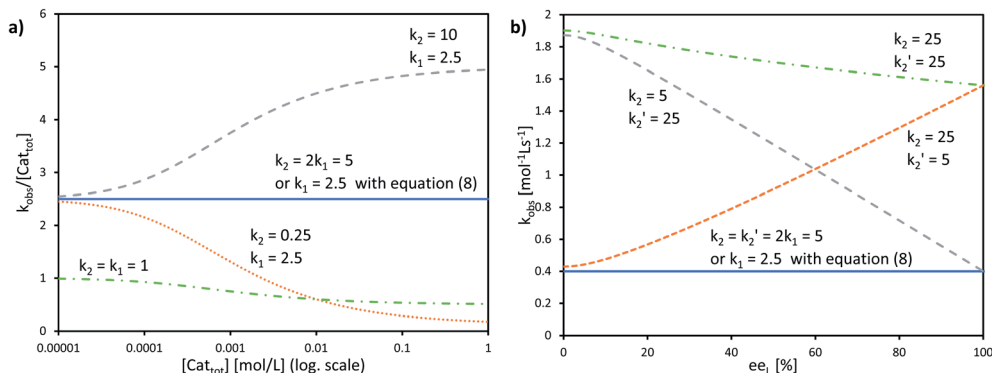


Fig. 8 (a) Simulated $k_{\text{obs}}/[\text{Cat}_{\text{tot}}]$ vs. $[\text{Cat}_{\text{tot}}]$ -plots computed from eqn (9) ($K_{\text{Homo}} = 1000$, k_1 and k_2 as indicated) and (b) simulated k_{obs} vs. ee_L plots computed from eqn (10), (4) and (5) ($K_{\text{Homo}} = 30$, $K_{\text{Hetero}} = 3000$, $[\text{Cat}_{\text{tot}}] = 0.16$, $k_1 = 2.5$, k_2 and k_2' as indicated). The full blue lines in a) and b) can also be obtained from eqn (8) (i.e. no aggregates are present in the system, the monomer is the only catalyst) using the indicated k_1 value.

$$ee_L = \frac{\sqrt{\alpha^2 - 4\beta(1 + 2\alpha K_{\text{Homo}})}}{[\text{Cat}_{\text{tot}}]} \quad (4)$$

and

$$\beta = \frac{(\alpha + 2K_{\text{Homo}}\alpha^2 - [\text{Cat}_{\text{tot}}])}{4K_{\text{Homo}} - 2K_{\text{Hetero}}}. \quad (5)$$

The interesting point here is that $[\text{Cat}_{\text{tot}}]$ and ee_L are user-controlled parameters, whose variation leads to singular changes in k_{obs} . This can be seen in simulated $k_{\text{obs}}/[\text{Cat}_{\text{tot}}]$ vs. $[\text{Cat}_{\text{tot}}]$ -plots: in the case of aggregate-free catalysed reactions (cf. eqn (8)) such a plot results in a flat line, whose y-intercept is equal to k_1 (Fig. 8a, blue line). The same is observed for Model I (eqn (9)) in a special case that is when $k_2/k_1 = 2$: the loss of monomeric catalyst upon increase of $[\text{Cat}_{\text{tot}}]$, because of dimeric aggregation, is then perfectly compensated by the higher activity of the dimer catalyst. Otherwise, an increase in $[\text{Cat}_{\text{tot}}]$ leads to a significant change of $k_{\text{obs}}/[\text{Cat}_{\text{tot}}]$: it increases if $k_2/k_1 > 2$ (grey dashed line) or decreases if $k_2/k_1 < 2$ (orange dotted line), which is symptomatic of the changing $[\text{RR}]/[\text{R}]$ -ratio. At very low $[\text{Cat}_{\text{tot}}]$ the amount of RR -catalyst becomes negligible and $k_{\text{obs}}/[\text{Cat}_{\text{tot}}]$ becomes equal to k_1 ; on the other hand, $k_{\text{obs}}/[\text{Cat}_{\text{tot}}] = 0.5k_2$ at very high $[\text{Cat}_{\text{tot}}]$ because of the prevalence of the dimeric catalyst. Thus, $k_{\text{obs}}/[\text{Cat}_{\text{tot}}]$ varies over changing $[\text{Cat}_{\text{tot}}]$ even if R and RR catalyse with the same rate ($k_1 = k_2$, green dashed/dotted line). With non-enantiopure ligands $k_{\text{obs}}/[\text{Cat}_{\text{tot}}]$ varies in a similar way to that in Fig. 7a and depends, in addition, also on k_2' (cf. ESI Fig. 3† for a commented example with $ee_L = 0$).

The other user-controlled parameter, ee_L , also influences k_{obs} (at constant $[\text{Cat}_{\text{tot}}]$) as seen in k_{obs} vs. ee_L plots (Fig. 8b, computed from eqn (10)). k_{obs} is constant if $k_2/k_1 = k_2'/k_1 = 2$ (blue full line). The case of k_2/k_1 -values higher than 2 leads to an increase in k_{obs} especially at high ee_L , where the concentration of the homochiral dimers is also higher, and results in a positive slope (orange dotted line). On the other hand, increasing k_2'/k_1 gives a negative slope as it affects k_{obs} mostly at low ee_L , where the proportion of RS -dimers is highest (grey dashed line). A simultaneous increase of k_2'/k_1 and k_2/k_1 by the same amount

also yields a negative slope if $K_{\text{Hetero}} > 2K_{\text{Homo}}$ (green dashed/dotted line). If the $K_{\text{Hetero}}/K_{\text{Homo}}$ -relationship is inverted then a positive slope is obtained, cf. ESI Fig. 4.†

In our previous study, we also determined the catalyst order c of the NBE-catalysed reaction when considering the system to follow the rate law $-d[\text{Sub}]/dt = k[\text{Cat}_{\text{tot}}]^c[\text{Sub}]^a[\text{Rea}]^b$.¹⁵ For this, we had determined the catalyst order c using Variable Time-Normalised Analysis (VTNA)^{41–44} of rate profiles obtained from enantiopure NBE at different catalyst loadings. Plotting catalyst order c vs. catalyst loading gave an unusual U-shaped plot which we postulated to originate in a $[\text{Cat}_{\text{tot}}]$ -induced change of k_{obs} . The present kinetic model now allows us to verify this assumption, since Fig. 8a shows that k_{obs} does indeed change with varying $[\text{Cat}_{\text{tot}}]$. To this end, we generated sets of rate profiles from eqn (7) and (9) by varying $[\text{Cat}_{\text{tot}}]$ and leaving all other parameters unchanged. Then, c was determined from two different rate profiles at a time using VTNA; the results are shown



Fig. 9 Simulated c vs. catalyst loading plot of a catalytic system following the kinetics of Model I and treated as if following the rate law $-d[\text{Sub}]/dt = k[\text{Cat}_{\text{tot}}]^c[\text{Sub}]^a[\text{Rea}]^b$, with c as a variable partial order in catalyst, with undetermined rate constant k and partial substrate/reactant order a and b . Each datapoint relates the c -value obtained from two Model I-rate profiles via VTNA (from eqn (7) and (9), with $[\text{Sub}]_0 = 0.833$, $k_1 = 2.5$, K_{Homo} and k_2 as indicated, var. $[\text{Cat}_{\text{tot}}]$) with the mean of their catalyst loading values; the procedure is described in the ESI Methods†. The full lines are free-hand drawings which serve as visual guidelines.



respective excel files (SI_experimental_Data.xlsx, SI_Simulated_NLE.xlsx, SI_kinetic_model.xlsx).

Author contributions

Y. G. performed the synthetic experiments and developed the catalytic models, along with their mathematical expressions. 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.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was funded by the French National Research Agency (ANR) through the Programme d'Investissement d'Avenir under contract ANR-11-LABX-0058_NIE within the Investissement d'Avenir program ANR-10-IDEX-0002-02.

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