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## Hyperpositive non-linear effects: enantiodivergence and modelling†

Yannick Geiger,<sup>1</sup> Thierry Achard,<sup>1</sup> Aline Maise-François and Stéphane Bellemin-Laponnaz<sup>1\*</sup>

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  $k_{\text{obs}}$  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  $k_{\text{obs}}$  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.

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## 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.<sup>1</sup> The first examples and models of such behavioural differences between scalemic and enantiomerically pure catalysts were established by Kagan in 1986.<sup>2</sup> 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<sup>2,3</sup> (*cf.* also reviews<sup>4,5</sup> and some recent examples<sup>6-9</sup>). 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.<sup>10</sup>

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*),<sup>11-13</sup>

although pure homochiral aggregation can also lead to (+)-NLEs in certain cases.<sup>14</sup> 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.<sup>15,16</sup> 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.<sup>13,17</sup>

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

Institut de Physique et Chimie des Matériaux de Strasbourg, Université de Strasbourg-CNRS, UMR 7504, Strasbourg, France. E-mail: bellemin@unistra.fr

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simulate catalyst order vs. catalyst loading-plots. (4) Finally, we will discuss the impact of the simulations in a more general way and compare them with the experimental results.

## Results & discussion

### Nonlinear effect in the presence of *N*-methylephedrine as a chiral ligand

The NME and NBE ligands only differ by the *N*-methyl group being changed by an *N*-benzyl group. Therefore, we suspected that NME might generate diastereomeric and aggregation-induced perturbations in the same way as in Fig. 1 for the same reaction. The ligand has been previously applied in asymmetric alkylations using  $\text{ZnEt}_2$  as the reagent<sup>18–21</sup> but, to the best of our knowledge,  $\text{ZnMe}_2$  has not been investigated so far. Knowing that the NBE ligand displays a more pronounced NLE with  $\text{ZnMe}_2$  than with  $\text{ZnEt}_2$ ,<sup>15</sup> we suspected that NME might show an NLE in conjunction with  $\text{ZnMe}_2$ , even though it had been shown previously that there is no apparent NLE with  $\text{ZnEt}_2$ .<sup>22</sup> Fig. 2a displays the correlation between the enantiomeric excess of the product ( $ee_p$ ) and the enantiomeric excess of the ligand ( $ee_L$ ) for the asymmetric addition of dimethylzinc to benzaldehyde using chiral (–)-NME (blue dots). Although its (1*R*,2*S*)-configuration is identical to the one of (–)-NBE, it surprisingly yielded mainly the *S*-product ( $P_S$ ) while (–)-NBE (orange crosses) gave the *R*-product ( $P_R$ ) under similar reaction conditions. The NME-dataset in Fig. 2a generates a negative non-linear effect [(–)-NLE], albeit in an apparently inverted manner when compared to common representations of (–)-NLEs (this is due to  $ee_p$  being defined here as the enantiomeric excess of  $P_R$ , which leads to negative  $ee_p$  values when  $P_S$  is predominant).

In parallel, we conducted a screening of the catalyst loading using enantiopure (–)-NME (Fig. 2b, blue dots). While a catalytic loading of 20 mol% (–)-NME gave the product in –11% ee ( $P_S$  being predominant), lowering the catalyst loading progressively displaced  $ee_p$  into the positive scale, giving  $P_R$  in +18% ee at 2.5 mol%. The shape of the curve was found similar to the one observed when using NBE (orange crosses), as well as the  $ee_p$  increase from 20 mol% to 2.5 mol% (NME: +31%; NBE: +33%).

Such behaviour with enantiopure NME, similar to what was observed with the NBE ligand, suggests that both systems follow an analogous catalytic scheme, where both monomeric and dimeric complexes are catalytically active. However, in contrast to NBE the catalytic runs with scalemic NME ligand were homogeneous with no apparent precipitate in the reaction mixture. This may account for the observed differences in NLE curves in Fig. 2a. While the hyperpositive NLE with NBE ligand was caused by the precipitation of the *RS*-dimer (leaving only *R* and *RR* complexes in solution and allowing high asymmetric amplification), the (–)-NLE with NME ligand might be the result of the presence of all catalytic species in solution (including *S*, *SS* and the meso dimer *RS*).

Moreover, the observed negative  $ee_p$  at high catalyst loading unambiguously indicates that the dimeric NME-catalyst is not only less enantioselective, it even yields mainly the opposite

enantiomeric product compared to the monomeric catalyst. Catalysis in which both enantiomeric products may be obtained from the same catalyst enantiomer is called enantiodivergent catalysis. It has attracted a lot of attention as a means to access easily both product enantiomers. Over the last two decades, many examples have been reported in which slight changes of the catalyst (substituent, metal, counter-ion, *etc.*) or of the reaction conditions (solvent, temperature, additive, ligand-to-metal ratio) have inverted the stereochemistry of the product.<sup>23–26</sup> In our case, the switch which allows toggling between both product enantiomers is the catalyst concentration, a factor which has not been discussed in this context so far.<sup>27</sup>

These results made us wonder whether it is possible to switch the product enantiomer's sign within an NLE curve, *i.e.* by varying  $ee_L$  instead of the catalyst loading. Such “enantiodivergent non-linear effect” has already been observed in other catalytic systems,<sup>28–30</sup> but their origin has never been studied; even the possible presence of two catalysts yielding opposite enantiomers has not been proposed.<sup>31</sup> Therefore, we continued our studies on NME by performing a temperature screening of the catalysis with the enantiopure ligand (Fig. 3a, blue dots) or only 50%  $ee_L$  (orange triangles). At low temperature (0 °C), the product ee of the enantiopure ligand was well below the  $ee_p$  of the scalemic sample, both being negative. Increasing the temperature increased  $ee_p$  in both cases but not in the same manner: the difference between 100% and 50%  $ee_L$  decreased progressively. At 40 °C the enantiopure ligand even surpassed the 50%  $ee_L$ -sample.

However, an interesting situation occurred at room temperature (20–25 °C): here, (–)-NME in 50% ee gave positive  $ee_p$ -values (*i.e.* *R* product), while the enantiopure ligand stayed negative (*i.e.* *S* product): this is nothing but the requirement for an enantiodivergent non-linear effect. The full NLE curve at room temperature (Fig. 3b, blue dots) confirmed this observation: the curve starts at 0%  $ee_L$  in the positive  $ee_p$ -range, reaches a maximum, then falls down to cross the  $ee_L$ -axis (at  $ee_L$  of ca. 80%) and ends up in the negative part of the  $ee_p$ -scale. The use of (+)-NME (red squares) gave the appropriate mirror image of this curve. Thus, going to room temperature changes the (–)-NLE to a hyperpositive NLE, which in addition is also enantiodivergent.

### Model studies: product ee vs. catalyst concentration (enantiopure system)

In the past, non-linear effects have been simulated and quantified using mathematical expressions of the considered models, such as the Kagan  $ML_n$  models (catalysis by the aggregate)<sup>11</sup> or the Noyori model (catalysis by the monomer, dimer acting as inactive reservoirs).<sup>13</sup> These models have been further extended (electron-rich substrates,<sup>32</sup> product inhibition<sup>33</sup> for the Noyori model; monomers as reservoir species with catalytically active homochiral aggregates by Kagan<sup>14</sup>). However, to the best of our knowledge there has been no attempt to unify both approaches and to consider both monomers and dimers being simultaneously catalytically active.<sup>34</sup> In order to fill this





Fig. 3 (a) ee<sub>P</sub> as a function of the reaction temperature (blue dots: 100% ee<sub>L</sub>; orange triangles: 50% ee<sub>L</sub>) and (b) NLE at room temperature of (-)-NME (blue dots) and (+)-NME (red squares) of the NME-catalysed enantioselective addition of ZnMe<sub>2</sub> 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<sub>P</sub> vs. catalyst concentration- and ee<sub>P</sub> vs. ee<sub>L</sub>-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*<sub>1</sub> and *k*<sub>2</sub>) and with different enantioselectivities (ee<sub>1</sub> and ee<sub>2</sub>), as shown in Fig. 4; [Cat<sub>tot</sub>]

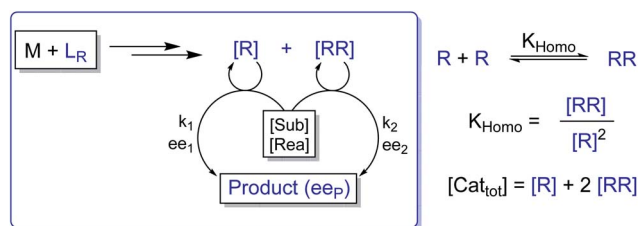


Fig. 4 Schematic representation of Model I, which consists of a monomeric (*R*) and a dimeric (*RR*) enantiopure catalyst both of which operate at a steady state and are linked through the equilibrium constant *K*<sub>Homo</sub>. The catalysts are issued from the reaction of a metal salt (*M*) with a chiral, enantiopure ligand (*L*<sub>R</sub>) and promote the reaction of a substrate (*Sub*) and a reactant (*Rea*) to form a chiral product with the overall enantiomeric excess ee<sub>P</sub>. The *R*- and *RR*-catalysts yield a product with a rate constant of *k*<sub>1</sub> and *k*<sub>2</sub>, respectively, and with an enantioselectivity of ee<sub>1</sub> and ee<sub>2</sub>.

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  $-d[\text{Sub}]/dt = k_i[\text{Cat}_i][\text{Sub}][\text{Rea}]$  (with *k*<sub>i</sub> and [Cat<sub>i</sub>] 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*<sub>Homo</sub>.<sup>35</sup> This makes Model I reminiscent of Kagan's ML<sub>n</sub> 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.

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

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

By combining the set of equations displayed in Fig. 4, it was possible to obtain eqn (1) and (2) which relate ee<sub>P</sub> to the parameters *k*<sub>2</sub>/*k*<sub>1</sub>, ee<sub>1</sub>, ee<sub>2</sub>, *K*<sub>Homo</sub> and [Cat<sub>tot</sub>], and allowed us to compute ee<sub>P</sub> vs. [Cat<sub>tot</sub>]-curves. Fig. 5a displays the evolution of ee<sub>P</sub> for selected values of ee<sub>2</sub> with fixed values of *K*<sub>Homo</sub>, *k*<sub>1</sub> and *k*<sub>2</sub>





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).<sup>13,36</sup> 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  $\alpha$  and  $\beta$ . Since  $\beta$  is itself a function of  $\alpha$  [*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 ( $ee = 0$ ).





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

**Influence of  $K_{\text{Homo}}$ ,  $[\text{Cat}_{\text{tot}}]$ ,  $k_2/k_1$  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  $ee_{\text{P}}$  for the enantiopure ligand ( $ee_{\text{P}}^{100}$ ). In Model II,  $ee_{\text{P}}^{100}$  will be strongly dependent on  $K_{\text{Homo}}$ ,  $[\text{Cat}_{\text{tot}}]$  and  $k_2/k_1$  (Fig. 7a–c): higher the  $K_{\text{Homo}}$ ,  $[\text{Cat}_{\text{tot}}]$  or  $k_2/k_1$ , lower the  $ee_{\text{P}}^{100}$ . This is consistent with a higher proportion and a higher activity of the low  $ee_{\text{P}}$ -yielding RR-catalyst over its monomeric counterpart.

In all representations in Fig. 7, we selected conditions in which  $ee_{\text{P}}^{100}$  could be negative and where the NLE curve crosses the  $ee_{\text{L}}$ -axis, making it an enantiodivergent NLE. Lower the  $ee_{\text{P}}^{100}$ , lower the crossing point at which  $ee_{\text{P}} = 0$  ( $ee_{\text{L}}^0$ ). At this point, the outcomes of all catalysts compensate each other to yield a racemic product.  $ee_{\text{P}}^{\text{max}}$  diminishes as  $ee_{\text{P}}^{100}$  decreases; the maximum's  $ee_{\text{L}}$ -value ( $ee_{\text{L}}^{\text{max}}$ ) is only slightly affected by  $K_{\text{Homo}}$  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,  $K_{\text{Homo}}$  is multiplied and  $[\text{Cat}_{\text{tot}}]$  divided by the same value:  $ee_{\text{P}}^{100}$  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  $ee_{\text{P}}^{100}$ : lower the  $ee_2$ , lower the  $ee_{\text{P}}^{100}$ . 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 ( $P_{\text{S}}$ , Fig. 7d, dashed curves); the same holds for the *R*-product ( $P_{\text{R}}$ ) if  $ee_1 \leq ee_2$  and if both are positive. In a similar way, very high  $K_{\text{Homo}}$ ,  $[\text{Cat}_{\text{tot}}]$  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  $K_{\text{Hetero}}$  and  $k_2'$ .** In contrast to the previously discussed parameters, an increase in  $K_{\text{Hetero}}$  (Fig. 7e) does not affect  $ee_{\text{P}}^{100}$  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  $ee_{\text{L}}^0$  is shifted to higher  $ee_{\text{L}}$  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  $ee_{\text{P}}^{100}$  and  $ee_{\text{L}}^0$  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  $ee_{\text{L}}$  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  $ee_{\text{L}}^0$  and  $ee_{\text{L}} = 100$  and push its appearance towards a classical (–)-NLE. As in Kagan's  $\text{ML}_2$ -model, a high activity of the meso catalyst leads to asymmetric depletion.

### Dynamic properties of models I and II

Apart from simulating  $ee_{\text{P}}$  vs.  $ee_{\text{L}}$ -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;<sup>37,38</sup> 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  $ee_{\text{P}}$  vs.  $ee_{\text{L}}$ -curves alone)<sup>39</sup> and verified the origin of the non-linearity in the Noyori model by a kinetic system based on differential equations.<sup>40</sup> 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  $k_{\text{obs}}$  (cf. ESI Methods† for the calculation details). For aggregate-free catalysed reactions, with 1<sup>st</sup> order in catalyst,  $k_{\text{obs}}$  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,  $k_{\text{obs}}$  depends on the parameters previously discussed: the (now absolute instead of relative) rate constants  $k_1$  and  $k_2$ ,  $K_{\text{Homo}}$  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  $ee_{\text{L}}$ ,  $k_2'$  and  $K_{\text{Hetero}}$  (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  $ee_{\text{L}}$ ):

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

with







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.

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