Non-linear Effects in Asymmetric Catalysis: Whys and Wherefores

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ABSTRACT It is argued that the titled non-linear effects (NLE) may arise whenever the order of the reaction in the chiral catalyst in greater than 1. In a fundamental departure from previous approaches, this is mathematically elaborated for the second order case. (NLE may also be observed if the chiral catalyst forms non-reacting dimers in a competing equilibrium; practically, however, this implies the *in situ* resolution of the catalyst.) The amplification of enantiomeric excess by NLE implies a relative (although modest) reduction in the entropy of mixing. The consequent increase in free energy apparently indicates a non-equilibrium process. It is suggested, based on arguments involving the chemical potential, that kinetically-controlled reactions lead to a state of "quasi-equilibrium": in this, although overall equilibrium is attained, the product-spread is far from equilibrium. Thus, both the linear and NLE cases of chiral catalysis represent departures from equilibrium (which requires that the product e.e. = 0). Interesting similarities exist with models of non-equilibrium systems, the NLE cases apparently being analogs of open systems just after the bifurcation point has been crossed.

INTRODUCTION

The enhancement of enantiomeric excess (e.e.) is justly a cause for jubilation, but sometimes, for concern too! Whilst asymmetric syntheses clearly aim for the highest possible e.e.'s, unsolicited enhancements of e.e. raise intriguing conceptual issues. Thermodynamic stability is represented by e.e. = 0, and a departure from this theoretical comfort zone implies a higher level of order: it is then incumbent on the investigator to explain the origin of the apparent increase in free energy content, and the nature of the intervention that brought it about.

The phenomenon of non-linear effects in asymmetric catalysis (NLEAC) burst upon the scene of asymmetric synthesis relatively recently.[1-6] NLEAC is predicated on the reasonable assumption that in a reaction that is catalysed by a chiral catalyst, the e.e. of the product cannot be greater than the e.e. of the catalyst itself. A lower product e.e., relative to the catalyst, can be accommodated by assuming correspondingly poor enantioselectivity. (This represents a drift towards the comfort zone of e.e. = 0, so can be dismissed as another failed asymmetric synthesis!) The caveat, however, is that the observed lower e.e. should be in constant proportion to the catalyst e.e.

Intriguing conceptual questions arise, however, when either the above constant proportion is not maintained, or worse still, the e.e. of the product is greater than that of the catalyst! (In the latter case too, proportionality may not be maintained.) Typical plots of the product e.e. (P_{ee}) *vs.* the catalyst e.e. (C_{ee}), representing these cases ("asymmetric depletion and amplification" respectively), are shown in Fig. 1.

Fig. 1

Scheme 1

Interestingly, such examples can be mediated by complexation of two molecules of the chiral catalyst – usually with a metal ion – prior to the reaction (Scheme 1). This leads to the formation of all three diastereomeric dimeric complexes (C_R and C_S are the enantiomeric catalysts, and M a metal ion): $C_\mathrm{R}MC_\mathrm{R}$, $C_\mathrm{S}MC_\mathrm{S}$ and $C_\mathrm{R}MC_\mathrm{S}$. These are, in fact, the effective catalytic species in the reaction.

Current treatments are apparently successful in explaining the observed NLEAC on the basis of the pre-equilibrium formation of the above diastereomeric complexes. However, a rigorous formulation would be based on a kinetic treatment of the formation of the enantiomeric products, as discussed at length below. [This differs fundamentally from previous approaches, reviewed critically in the Supplementary Information (S.I.) section.]

Also, NLEAC may manifest itself under other mechanistic conditions, particularly when the non-racemic catalyst forms a relatively unreactive meso dimer species.[3] A variant of this is preferential diastereomer formation between chiral catalyst and chiral product (as occurs in certain cases of homogeneous amino acid catalysis).[4] These cases, however, apparently involve a prior *in situ* resolution of the catalyst, and are hence considered only briefly further below.

RESULTS AND DISCUSSION

The rates of formation (v_R and v_S) of the two enantiomeric products, P_R and P_S (respectively) in the reaction in Scheme 1, would be given by eqs. 1 and 2. (We note that two molecules of catalyst are involved in the reaction, hence the second order dependence, the k's being rate constants; the treatment extends previous ones as explained in the S.I. section.)[1,2] For the sake of simplicity, at this stage, it is assumed that the reaction of (achiral) substrate (S) with C_R yields only P_R, and with C_S only P_S, *i.e.* 100% enantioselectivity; also, C_R and C_S do not act in concert. (All this implies that only C_RMC_R and C_SMC_S react with total selectivity, and that C_RMC_S is completely unreactive.)

$$v_R = \mathrm{d}[P_R]/\mathrm{dt} = k_R[S][M][C_R]^2 \tag{1}$$

$$v_S = \mathrm{d}[P_S]/\mathrm{dt} = k_S[S][M][C_S]^2 \tag{2}$$

The e.e. of the product (P_{ee}) would then be given by eq. 3, that of the catalyst (C_{ee}) by eq. 4 ($[C_R] > [C_S]$). It is also assumed that the yield of each product, at a given time (t), bears the same proportion to its rate of formation, *i.e.* $v_R = \alpha[P_R]$ and $v_S = \alpha[P_S]$, α being a proportionality constant.

$$P_{ee} = ([P_R]-[P_S])/([P_R]+[P_S]) = (v_R-v_S)/(v_R+v_S) =$$

$$([C_R]^2-[C_S]^2)/([C_R]^2+[C_S]^2) \tag{3}$$

$$C_{ee} = ([C_R]-[C_S])/([C_R]+[C_S]) \tag{4}$$

$$P_{ee} = ([C_R]-[C_S])/\{([C_R]+[C_S])-2[C_R][C_S]/([C_R]+[C_S])\} \tag{5}$$

This is valid as the catalyst is regenerated, so $[C_R]$ and $[C_S]$ remain constant during the course of the reaction; also, S and M are achiral precursors common to the two pathways. (In an achiral medium, $k_R = k_S$.) It is particularly noteworthy that this mechanism thus gives rise to the “real” NLEAC, and differs fundamentally from cases involving a prior *in situ* resolution of catalyst (discussed further below).

Furthermore, eq. 3 can be reduced to eq. 5, which can be compared with eq. 4: it is seen that since $\{[C_R][C_S]/([C_R] +[C_S])\} > 0$, the denominator of eq. 5 would be less than that of eq. 4. Clearly, therefore, P_{ee} would be enhanced relative to C_{ee}. This enhancement, of course, is a direct consequence of the fact that the reaction is second order in the catalyst. [Note: 10^2 x $P_{ee} = P_{ee}(\%)$;10^2 x $C_{ee} = C_{ee}(\%)$.]

$$v_R = d[P_R]/dt = k_R[S][M][C_R]^2 + k_{RS}[S][M][C_R][C_S] \quad (6)$$

$$v_S = d[P_S]/dt = k_S[S][M][C_S]^2 + k_{RS}[S][M][C_R][C_S] \quad (7)$$

$$P_{ee} = ([C_R]^2-[C_S]^2)/([C_R]^2+[C_S]^2+2(k_{RS}/k_R)[C_R][C_S]) \quad (8)$$

$$P_{ee} = ([C_R]-[C_S])/\{([C_R]+[C_S])+2(\omega-1)[C_R][C_S]/([C_R]+[C_S])\} \quad (9)$$

In contrast to this amplification, depletion would be observed when the meso complex, C_RMC_S, is more reactive than its chiral diastereomers. (The meso diastereomer would produce equal amounts of P_R and P_S). For then, the rates of formation of P_R and P_S would be given by eqs. 6 and 7 (k_{RS} being the rate constant corresponding to the meso catalyst, noting that $k_{RS} > k_R$, k_S). P_{ee} is now given by eq. 8; reduction of this to eq. 9 (where $\omega = k_{RS}/k_R$) sets it up for analogous arguments as with eq. 5 above. In this case, the denominator would be greater than that of eq. 4, as $\omega > 1$ and $(2(k_{RS}/k_R)[C_R][C_S]/([C_R]+[C_S]) > 0$, so $P_{ee} < C_{ee}$. (Note that $[C_R]/([C_R]+[C_S])$ and $[C_S]/([C_R]+[C_S])$ are the mole fractions of C_R and C_S respectively.)

The above simplified treatment can evolve to represent real-life scenarios by the inclusion of a factor for the enantioselectivity (χ_{es}) and the (very real!) possibility that all three diastereomeric complexes (C_RMC_R, C_SMC_S and C_RMC_S) react concurrently (*vide infra*).

This was considered above for the case of depletion of e.e., with $k_{RS} >> k_R$, $k_S \neq 0$; however, for the case of amplification, it was assumed that $k_{RS} = 0$. (Note that for the case $k_{RS} >> k_R$, $k_S = 0$, $P_{ee} = 0$.) In fact, it is quite likely that k_R, $k_S >> k_{RS} \neq 0$: this would moderate the observed amplification of e.e. Thus, $C_R M C_R$ and $C_S M C_S$ would have identical reactivity (*via* analogous transition states), but $C_R M C_S$ may be either more or less reactive than them. (These two cases would lead to depletion or moderated amplification of e.e. respectively.)

$$P_{ee} = ([C_R]-[C_S])/\{([C_R]+[C_S])-2(1-\omega)[C_R][C_S]/([C_R]+[C_S])\} \tag{10}$$

$$P_{ee} = (\chi_{es})([C_R]-[C_S])/\{([C_R]+[C_S])-2(1-\omega)[C_R][C_S]/([C_R]+[C_S])\} \tag{11}$$

Fig. 2

The case of moderated amplification (k_R, $k_S >> k_{RS} \neq 0$) may be dealt with analogously as the derivation of eq. 9, but now $\omega < 1$, so eq. 9 may be rewritten as eq. 10: comparison with eq. 4 clearly shows that P_{ee} would be enhanced but not to the same extent as in eq. 5. Plots of P_{ee} (eqs. 5 and 10) *vs.* C_{ee} (eq. 4) can thus be generated and are shown in Fig. 2. The inclusion of the enantioselectivity term, χ_{es}, leads to eq. 11 (*cf.* S.I. for details).

Thus, the above kinetic treatment succeeds in reproducing the observed NLEAC for the case of the intermediate formation of dimeric complexes.

Case of Non-reactive Dimers in Equilibrium[3,4]

Scheme 2

An interesting variant of the above phenomena, which also apparently displays NLEAC, is shown in Scheme 2. In this, the reactive form of the chiral catalyst is a monomer, which, however, is in equilibrium with non-reacting dimeric species. (This variant was originally observed in the addition of diethylzinc to aldehydes, catalysed by chiral amino alcohols.[3] An analogous case was discovered in certain proline-catalysed aldol condensations.[4]) In fact, these systems can also be described by equations analogous to eqs. 5-11 above. (However, there is no second order dependence with the catalyst concentration in these cases. Eqs. 12-17 specifically refer to the diethylzinc addition case;[3] the proline-catalysis case can be treated analogously.)

$$v_R = d[P_R]/dt = k_R[S][C_R] \tag{12}$$

$$v_S = d[P_S]/dt = k_S[S][C_S] \tag{13}$$

$$[C_R] = [C_R]_o - (2[C_R]^2/K_R) - ([C_R][C_S]/K_{RS}) \tag{14}$$

$$[C_S] = [C_S]_o - (2[C_S]^2/K_S) - ([C_R][C_S]/K_{RS}) \tag{15}$$

$$\mathrm{C}_{ee} = ([C_R]_o - [C_S]_o)/([C_R]_o + [C_S]_o) \tag{16}$$

$$\mathrm{P}_{ee} = \{([C_R]_o - [C_S]_o) - 2([C_R]^2 - [C_S]^2)/K_R\}/\{([C_R]_o + [C_S]_o) - (2([C_R]^2 + [C_S]^2)/K_R) - 2([C_R][C_S]/K_{RS})\} \tag{17}$$

Thus, the rates of formation of enantiomeric products follow the rate laws in eqs. 12 and 13. (For simplicity, total stereoselectivity is assumed.) Now, however, the concentrations of the reactive monomeric species are governed by the equilibrium constants (K_R, K_S and K_{SR}, *cf.* Scheme 2) for the formation of the three diastereomeric dimer species, *viz.* C_R-C_R, C_S-C_S and C_S-C_R. Eqs. 14-17 follow, analogously to eqs. 3-8 above. ($[C_R]_o$ and $[C_S]_o$ refer to total catalyst concentrations; note that $k_R = k_S$ and $K_R = K_S$; an enantioselectivity term, χ_{es}, can be included in eq. 17, as in eq. 11 above.)

Comparison of eqs. 16 and 17 indicates that amplification is to be expected when K_R, $K_S >> K_{RS}$. This is because the terms $([C_R]^2 - [C_S]^2)/K_R$ and $([C_R]^2 + [C_S]^2)/K_R << ([C_R][C_S]/K_{RS})$ for large K_R, K_S, so may be neglected. Also then, since $([C_R][C_S]/K_{RS}) > 0$, the denominator of eq. 17 would be less than that of eq. 16.

The case for depletion is less straightforward, but obtains for K_R, K_S << K_{RS} as follows. Firstly, $([C_R][C_S]/K_{RS})$ may be neglected. Furthermore, as $[C_R] > [C_S]$, $[C_R]^2 >> [C_S]^2$, so $([C_R]^2 - [C_S]^2)$ and $([C_R]^2 + [C_S]^2) \sim [C_R]^2$. Thus, eq. 17 now reduces to $P_{ee} \sim \{([C_R]_o - [C_S]_o) - 2([C_R]^2/K_R)\}/\{([C_R]_o + [C_S]_o) - 2([C_R]^2/K_R)\}$. Comparing this with C_{ee} (eq. 16) indicates that both its numerator and denominator have been reduced by an equal quantity $(2([C_R]^2/K_R)$. However, since $C_{ee} < 1$, the numerator has been reduced by a greater fraction of itself than has the denominator. Hence, $P_{ee} < C_{ee}$, leading to depletion.

For both large K_R, K_S and K_{RS}, *i.e.* insignificant formation of the dimers, linearity would be observed between C_{ee} and P_{ee}: $P_{ee} = \chi_{es}C_{ee}$ (χ_{es} being the enantioselectivity as defined above). This, then, represents the transition between amplification and depletion.

Interestingly, these systems are analogs of a precedented phenomenon. Thus, it is known that, when a racemic compound is crystallized from its enantiomerically-enriched solution, the supernatant solution displays an enhanced e.e.[7] The preferred formation of the meso dimer (C_R-C_S) above is the analog of crystalline racemic-compound formation. Also, for amplification of e.e. to be observed, the analog of conglomerate formation, *i.e.* the formation of C_S-C_S and C_R-C_R, needs to be avoided or suppressed: this condition obtains when K_R, K_S >> K_{RS}. Thus, the condition K_R, K_S << K_{RS} (leading to depletion) is analogous to the conglomerate form being more stable than the racemic compound form. (In this case the crystalline phase would be enantiomerically enriched.)

It is also noteworthy that, for NLEAC to be observed in these cases, the reverse of the "favored" equilibrium needs to be much slower than the rate of the overall reaction. If not, the suppression would not be "kinetically effective" even if the equilibrium constant favors the formation of the dimer. Ideally, therefore, the meso dimer should be formed irreversibly, for maximal amplification to be achieved.

Furthermore, this practically implies the *in situ* resolution of the chiral catalyst. In this sense, perhaps, these cases (that are mediated by competing dimer formation) cannot strictly be considered as NLEAC.

Thermodynamic Considerations

The above kinetic treatment provides a model that explains the manner in which the observed NLEAC arise. However, the fundamental origin of the effects remains intriguing, as a singular thermodynamic stumbling block still needs to be addressed. This is because the phenomenon of NLEAC, in proposing that a product of higher e.e. can be obtained from a catalyst of lower e.e., implies the creation of a higher level of order from a lower one, apparently without additional input of energy.

A racemate is known to possess an entropy of mixing (S_{mix}) by virtue of the presence of both the enantiomers (eq. 18, n being the number of moles of the racemate present and R the gas constant).[8] S_{mix} is modest in magnitude, contributing ~ 0.4 kcals/mol in the Gibbs free energy, towards stabilizing the racemate relative to an enantiomer (whose $S_{\mathrm{mix}} = 0$). A “partial racemate”, *i.e.* an enantiomerically enriched mixture, would thus possess S_{mix} in between 0 and $R\ln2$, which would but contribute marginally in terms of the Gibbs free energy of stabilization (relative to e.e. of 100%).

The relation between S_{mix} and e.e. can be derived in a straightforward manner (eqs. 19-20, N being the total number of moles of the sample). Eq. 20 – which shows that higher e.e. implies a lower S_{mix} – follows (*cf.* S.I. for details).

$$S_{\mathrm{mix}} = nR\ln2 \tag{18}$$

$$n = N[1\text{-}(\text{e.e.}/100)] \quad (19)$$

$$S_{\text{mix}} = N[1\text{-}(\text{e.e.}/100)]R\ln 2 \quad (20)$$

$$\Delta S_{\text{mix}} = NR\ln 2(\Delta\text{e.e.}/100) \quad (21)$$

$$\Delta G^{\text{o}}{}_{\text{mix}} = -T\Delta S^{\text{o}}{}_{\text{mix}} \quad (22)$$

In the case of NLEAC, the entropy of mixing (S_{mix}) of the reaction product would be different from the (hypothetical) case in which the relationship between the catalyst and product e.e.'s is linear. The corresponding change in the entropy of mixing (ΔS_{mix}) in terms of the change in the e.e. of the product relative to the catalyst (Δe.e.) is given by eq. 21. This leads to eq. 22, in which $\Delta G^{\text{o}}{}_{\text{mix}}$ is the change in the standard Gibbs free energy corresponding to the change in the standard entropy of mixing of $\Delta S^{\text{o}}{}_{\text{mix}}$ (T is the absolute temperature).[8] In the case of a positive NLEAC, the S_{mix} would be lower relative to the linear case, so $\Delta S^{\text{o}}{}_{\text{mix}}$ would be negative and $\Delta G^{\text{o}}{}_{\text{mix}}$ would be positive.

However, the marginal magnitude of $\Delta G^{\text{o}}{}_{\text{mix}}$ (at least at normal temperatures) belies the overwhelming stability of a racemate (e.e. = 0) relative to an enantiomer (e.e. = 100%), as is generally observed. Thus $\Delta G^{\text{o}}{}_{\text{mix}} = RT\ln 2$ (from eqs. 18 and 22, per mole of racemate), which implies that the free energy difference associated with S_{mix} is even less than the average thermal energy (RT).[9] However, it is noteworthy that a racemate is never known to spontaneously convert to an enantiomerically enriched form (in an achiral environment in free solution).

The reason for this apparent paradox, of course, is that there are two enantiomeric species of equal energy (ignoring parity violation,[10] deemed undetectable generally). Thus, the probability of disequilibration of a racemate to either enantiomer is identical, so the racemate form prevails. Conversely, an observed disequilibration – defined to include any enhancement of e.e. – would represent a departure from the above norm, clearly challenging cherished assumptions in stereochemical practice!

It is also noteworthy that the above thermodynamic quantities, *viz.* free energy, enthalpy and entropy, are scalar quantities (*i.e.* invariant to reflection).[11] Hence, they cannot be used to distinguish between chiral possibilities. In the above case of enantiomers possessing identical free energy content, the entropic difference between one enantiomer and the racemate should perhaps be double that were both the enantiomers taken into account. This is because, in considering only one of the enantiomers, only half of the available energy states is being taken into account. Based on this argument, the $\Delta S^{o}_{\mathrm{mix}}$ between the racemate and an enantiomer would be $2R\ln2$, and the corresponding $\Delta G^{o}_{\mathrm{mix}} = 2RT\ln2$ (~ 0.8 kcal/mol at normal temperatures).

This is still a modest difference in free energy, although perhaps not insubstantial (being discernibly > RT). However, it does serve to bolster that argument that any “spontaneous” enhancement of e.e. needs to be justified in thermodynamic terms. It is also noteworthy that the fact that a chiral catalyst is regenerated does not confer an exemption from the above thermodynamic strictures. (The catalyst is thus analogous to a template.)

The e.e. of the product would reflect the e.e. of the catalyst (in a characteristic way). As the rate constants for the formation of the enantiomeric products are identical, the Gibbs free energy contents of the enantiomeric transition states would also be identical. Thus, the enhanced e.e.’s observed in NLEAC represent a purely concentration effect. An amplified product e.e., relative to the catalyst e.e., then implies – in effect – a correspondingly selective reaction of one of the catalyst enantiomers.

However the play of catalyst e.e., *i.e.* relative enantiomer concentrations, on the product e.e. is explained in kinetic terms, it remains a thermodynamic enigma. The following arguments are noteworthy in this context.

Kinetic Control and "Quasi-equilibrium"

Even apart from the NLEAC cases, processes involving the enhancement of e.e., including the spontaneous generation of optical activity, have been well-documented (but remain controversial in some cases). Thus, several examples of second-order asymmetric transformation are known, which are crystallization-driven processes resulting in the spontaneous generation of optical activity.[12] The enhancement of e.e. merely by recrystallization is also known;[7] this, however, does not imply an absolute increase in the e.e., as the enhancement results from the preferential crystallization (hence does not apply to the whole sample, *i.e.* there is no change in the total S_{mix}). An analog of this process, based on compound formation with an achiral but "bis-functionalized" auxiliary, is also well-exemplified.[13]

Perhaps the most intriguing and spectacular examples of enhancement of e.e., are those resulting from autocatalytic amplification reported by Soai and coworkers.[14,15] These represent the only known reaction analogs of the crystallization-driven processes mentioned above. Also, the Soai reactions are capable of spontaneous generation of optical activity, *i.e.* without any initial enrichment.[16,17]

Theoretically, however, any spontaneous increase in e.e. – crystallization-driven or not – remains enigmatic (certainly so when there is a change in the total S_{mix}). Current approaches view these phenomena in the light of non-equilibrium theory and irreversibility.[18,19] These approaches essentially make a distinction between conventional "static" stability, on one hand, and a dynamic stability achieved as a steady state in an open system, on the other. The racemate represents stability in the static sense, but can be countervailed under suitable conditions of matter flow, particularly involving the removal or recycling of product. Under these conditions, two enantiomerically-related steady states develop, the system then evolving irreversibly to one of them. Under the inexorable influence of autocatalytic loops and processes effecting mutual destruction of the enantiomers, the system careens into a state that is both dynamically stable and far from thermodynamic equilibrium.

Thus, enhancement of e.e. is the result of the interplay of two seemingly incompatible conditions – stability and disequilibrium. It is interesting to note that an analogous combination is to be found in the case of kinetically-controlled reactions. These reactions are driven to completion by a highly favorable equilibrium constant, although the ratios of the various products that may be formed need not reflect their thermodynamic stability. In other words, despite the large equilibrium constant in favor of products, equilibrium between the various products themselves is not attained.

This appears to represent a state of "quasi-equilibrium", which is, of course, the result of the fact that the reverse of the overall reaction is extremely (often immeasurably) slow. Given sufficient time, however, the reaction – in principle – could be reversed, thus leading to the various products attaining mutual thermodynamic equilibrium.

In the case of a reaction occurring under chiral catalysis, this would correspond to racemic products. (This may appear intriguing, but it should be noted that a catalyst –

chiral or achiral – cannot alter the equilibrium constant between enantiomers, which perforce equals 1.) Therefore, the obtention of non-racemic products under chiral catalysis implies a non-equilibrium state. This is true even if the relationship between catalyst and product e.e.'s is linear. The NLEAC case, then, would represent an extension of the non-equilbrium state (beyond the linear case), the origins of which can be addressed as below.

To reiterate, the abnormally high e.e. observed in the case of NLEAC (asymmetric amplification) represents a state of apparent stability (reaction being driven to completion), although not of overall equilibrium (e.e. being non-zero). According to current theory, apparently, two conditions are necessary for the manifestation of the non-racemic state: non-equilibrium and autocatalysis. For the emergence of chiral states from a totally racemic one, autocatalysis is apparently *de rigueur*.[18] However, for the transformation of a previously chiral state to another chiral state, experience indicates that autocatalysis need not be mechanistically involved. (This applies to any of the myriad examples of asymmetric synthesis, whether involving chiral auxiliaries or catalysts.) In the case of NLEAC, autocatalysis is also not a necessity.

These arguments seem to indicate that the NLEAC cases represent states that are farther from equilibrium than the cases in which the catalyst and product e.e.'s are linearly related. The origins of this "extended non-equilibrium" lie both in the kinetic characteristics of NLEAC phenomena and in the nature of the non-equilibrium state. Thus, as has been discussed at length above, NLEAC arise when the overall kinetic order is greater than one. This also has an interesting consequence on the manner in which the non-equilibrium state is attained.

Thus, it is believed that a non-equilibrium state can be attained and maintained in an open system, in which there is a continuous inflow of reactants and outflow of products. This ensures that the chemical potential (μ) of reactants remains high relative to the products, thus avoiding the state of conventional thermodynamic equilibrium (characterized by $\Delta\mu = 0$). These conditions are also conducive to the maintenance of non-racemic states. Also, a relatively high $\Delta\mu$ between products and reactants, apparently, may lead to a non-equilibrium state that is correspondingly farther from equilibrium, as discussed below.

$$\mu_{\mathrm{R}} = \mu_{\mathrm{o(R)}} + RT\ln([S][M][C_{\mathrm{R}}]^2) \tag{23}$$

$$\mu_{\mathrm{S}} = \mu_{\mathrm{o(S)}} + RT\ln([S][M][C_{\mathrm{S}}]^2) \tag{24}$$

Now, the chemical potentials of the reactants (μ_{R} and μ_{S}) relating to eqs. 1 and 2 (Scheme 1) are given by eqs. 23 and 24.[20] The μ_{o}'s are the standard potentials, noting that $\mu_{\mathrm{o(R)}} = \mu_{\mathrm{o(S)}}$. The fact that the reactions are second order in catalyst (C_{R} and C_{S}) means that μ_{R} and μ_{S} are also correspondingly greater, relative to the (hypothetical) first order case. Interestingly, this is analogous to the high chemical potential of the reactants in the case of open systems, which prevents a reversal of the reaction and the attainment of equilibrium.

In the NLEAC cases, the reactions are essentially driven by a large equilibrium constant in favor of products, arising from a correspondingly large difference in the standard potential between products and reactants ($\Delta\mu_{\mathrm{o}}$). The second order concentration terms, therefore, also contribute to a raised ground state, *i.e.* high ($\mu_{\mathrm{R}} + \mu_{\mathrm{S}}$). (This would not affect the overall equilibrium as the reverse reaction would also be second order in the catalyst; however, the effect would be important under kinetic control, *i.e.* away from equilibrium.)

Also, the second order dependence of the concentration terms in eqs. 23 and 24 leads to a correspondingly greater enantioselectivity, by virtue of a greater difference in the ground state energy (in terms of μ_R and μ_S) for the two parallel routes. The enhanced enantioselectivity in NLEAC (amplification) indicates a state of non-equilibrium, and the relatively high chemical potentials of the reactants apparently enable the phenomenon.

Furthermore, the equilibrium condition of $\Delta\mu = 0$ is compatible with both a "quasi-equilibrium" or total equilibrium. "Quasi-equilibrium" is achieved under kinetic control, with the product-spread being unrelated to relative stability. Total equilibrium, however, implies that the products are present in proportion to their thermodynamic stability. Thus, if there are two products P_1 and P_2 that are formed, the chemical potential of the product (μ_P) is given by eq. 25, wherein $\mu_{\mathrm{P(1)}}$ and $\mu_{\mathrm{P(2)}}$ are the chemical potentials of P_1 and P_2 respectively. The $\mu_{\mathrm{P(1)}}$ and $\mu_{\mathrm{P(2)}}$ can be represented in terms of their standard potentials ($\mu_{\mathrm{oP(1)}}$ and $\mu_{\mathrm{oP(2)}}$) by eqs. 26 and 27, respectively. If the sum total of the reactant (Rt) chemical potentials be μ_Rt, this is given by eq. 28 (μ_oRt being the corresponding standard potential). The equilibrium condition is given by eq. 29. Involving eqs. 25-27 in eq. 29 leads to eq. 30, thence by rearrangement to eq. 31.

$$\mu_\mathrm{P} = \mu_{\mathrm{P(1)}} + \mu_{\mathrm{P(2)}} \tag{25}$$

$$\mu_{\mathrm{P(1)}} = \mu_{\mathrm{oP(1)}} + RT\,\ln[P_1] \tag{26}$$

$$\mu_{\mathrm{P(2)}} = \mu_{\mathrm{oP(2)}} + RT\,\ln[P_2] \tag{27}$$

$$\mu_\mathrm{Rt} = \mu_\mathrm{oRt} + RT\,\ln[Rt] \tag{28}$$

$$\Delta\mu = (\mu_{\mathrm{P}} - \mu_{\mathrm{Rt}}) = (\mu_{\mathrm{P(1)}} + \mu_{\mathrm{P(2)}} - \mu_{\mathrm{Rt}}) = 0 \tag{29}$$

$$\Delta\mu = (\mu_{\mathrm{oP(1)}} + \mu_{\mathrm{oP(2)}} + RT\ln([P_1][P_2])) - (\mu_{\mathrm{oRt}} + RT\ln[Rt]) = 0 \tag{30}$$

$$(\mu_{\mathrm{oP(1)}} + \mu_{\mathrm{oP(2)}}) - (\mu_{\mathrm{oRt}} + RT\ln[Rt]) = -RT\ln([P_1][P_2]) \tag{31}$$

$$K = ([P_1][P_2])/[Rt] \tag{32}$$

$$\Delta\mu_{\mathrm{oP}} = (\mu_{\mathrm{oP(1)}} - \mu_{\mathrm{oP(2)}}) = -RT\ln([P_1]/[P_2]) \tag{33}$$

The left hand side of eq. 31 is a constant at given values of [*Rt*] and *T*, noting that the μ_{o}'s are constants at given standard states. The product ($[P_1][P_2]$) on the right hand side would then also be a constant, <u>although $[P_1]$ and $[P_2]$ themselves may vary</u>. (A similar conclusion may be reached, perhaps more simply, by involving the equilibrium constant *K*, as defined in eq. 32; however, the chemical potentials apparently relate better to non-equilibrium theory, as discussed above.)

Eqs. 31 and 32 thus show that the fundamental equilibrium condition ($\Delta\mu = 0$, or *K* constant) may be satisfied for either the case of “quasi-equilibrium” or that of total equilibrium: “quasi-equilibrium” represents kinetic control, the ratio ($[P_1]/[P_2]$) reflecting only the relative rates of formation; in total equilibrium, however, ($[P_1]/[P_2]$) would reflect relative stabilities.

Also, total equilibrium implies the condition $\mu_{\mathrm{P(1)}} = \mu_{\mathrm{P(2)}}$ which, along with eqs. 26 and 27, leads to eq. 33. (Thus, ($[P_1]/[P_2]$) is now a constant.) In the context of asymmetric catalysis, this implies that the product is a racemate, *i.e.* ($[P_1]/[P_2]$) = 1. Indeed, it is against this absolute standard that the e.e.'s observed in asymmetric catalysis, whether linear or not, have to be judged. To reiterate, both NLEAC and the linear cases represent departures from the equilibrium case, which must lead to racemic product. NLEAC, however, represents an extended departure from reversibility and equilibrium.

NLEAC and Non-equilibrium

It is interesting to compare NLEAC with current models of non-equilibrium processes. These models, of course, are based on open systems (with autocatalysis);[18] the normally observed NLEAC cases are closed ones (generally without autocatalysis). However (to reiterate), the latter are driven by the irreversibility of the reactions, which apparently ensures a measure of non-equilibrium.

Interestingly, the existence of three possible transition states in the NLEAC case (2 chiral and 1 meso) finds a resonance in the open system models of non-equilibrium. These, too, postulate the formation of three states, two chiral and one racemic, which coexist at the steady state. The further evolution of such systems away from the racemic state towards one of the chiral ones is believed to occur when there is a continuous flow of matter, which ensures a large difference in chemical potential between reactants and products. This, in turn, ensures irreversibility, thus avoiding the racemic equilibrium state.

In the NLEAC cases, however, a naturally large difference in standard potentials ensures irreversibility (as discussed above). Also, NLEAC requires a selective traversing of the three possible transition states. This is *per se* a condition of non-equilibrium, as equal traverse along the three transition states would lead to racemic products: indeed, this is the analog of the equilibrium state achieved in an open system.

It is also noteworthy that the maximal departure from linearity observed in NLEAC corresponds to a catalyst e.e. of ~ 25%.[1-6] This indicates a relatively enhanced sensitivity of the product e.e. towards changes in the catalyst e.e., in the low catalyst e.e. regime. This is, of course, explicable with reference to eqs. 5 and 9, the term $\{[C_R][C_S]/([C_R]+[C_S])\}$ being greater at lower e.e.'s (as may be gleaned by assigning values to $[C_R]$ and $[C_S]$). Interestingly, however, this is also reminiscent of the hypersensitivity of open systems at the bifurcation point, which is also a state with e.e. ~ 0, and marks the beginning of the non-equilibrium regime.

An important difference between NLEAC and open systems is that, in NLEAC the chiral outcome is predetermined by the e.e. of the catalyst, whereas the open systems are totally achiral to begin with. Thus, NLEAC apparently corresponds to the regime beyond the bifurcation point in open systems, after chirality has evolved and a choice made between the two possible chiral states. The low e.e. regime in NLEAC would thus be analogous to an open system which has just crossed the bifurcation point, when the system is still at its most sensitive: indeed, the curve for the evolution of chirality [in terms of α, corresponding to ($[P_R]$-$[P_S]$ in Scheme 1)] is not unlike that seen for NLEAC!

In fact, the former represents the evolution of α in relation to reactant chemical potential μ. Interestingly, α relates to P_{ee}, and the μ to C_{ee}, in the NLEAC representation (Fig. 2), noting that a higher C_{ee} relates to a higher μ. Therefore, although the analogy between an open system and NLEAC should not be belabored, it does appear that NLEAC resonates to at least some of the ideas of non-equilibrium theory!

CONCLUSIONS

The phenomenon of non-linear effects in asymmetric catalysis (NLEAC) has been rigorously addressed by a kinetic treatment. When the chiral catalyst forms dimeric reactive intermediates, NLEAC apparently arises from the second-order dependence of the overall rates on the concentration of the catalyst. When the chiral catalyst forms non-reactive dimers reversibly, NLEAC arises from the competition between this equilibrium and the overall rates. The thermodynamic origins of NLEAC are intriguing, although they are apparently a manifestation of the “quasi-equilibrium” status of kinetic control. (“Quasi-equilibrium” possesses some of the characteristics of both equilibrium and non-equilibrium.) Analogies possibly exist between NLEAC and irreversible processes in open systems (in particular, apparently, after the bifurcation point has been crossed).

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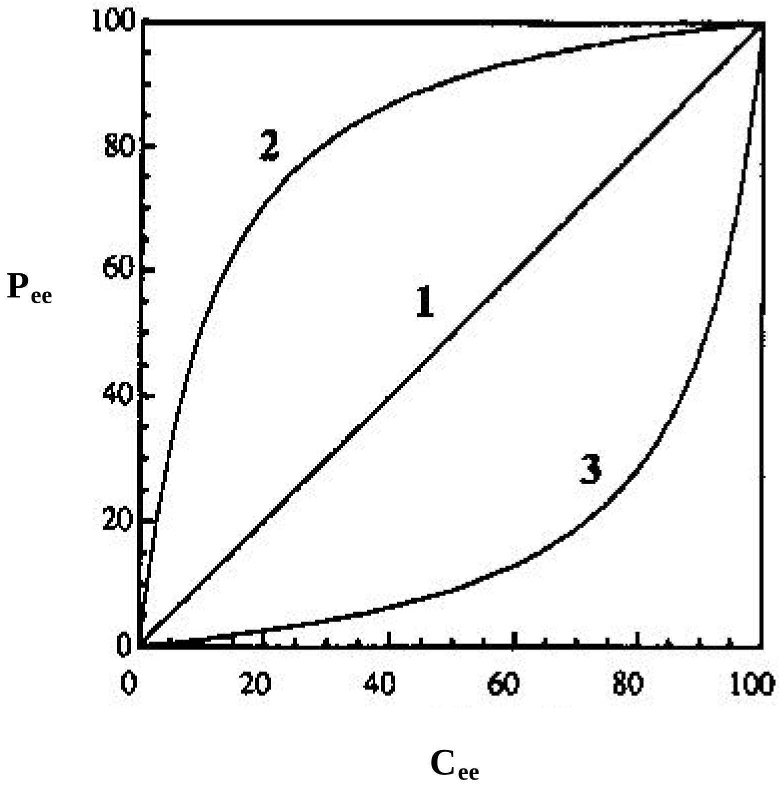


Fig. 1. Graphical illustration of NLEAC, indicating amplification (curve 2) and depletion (curve 3), as seen against the expected linear relationship (curve 1). (Adapted from ref. 3.)

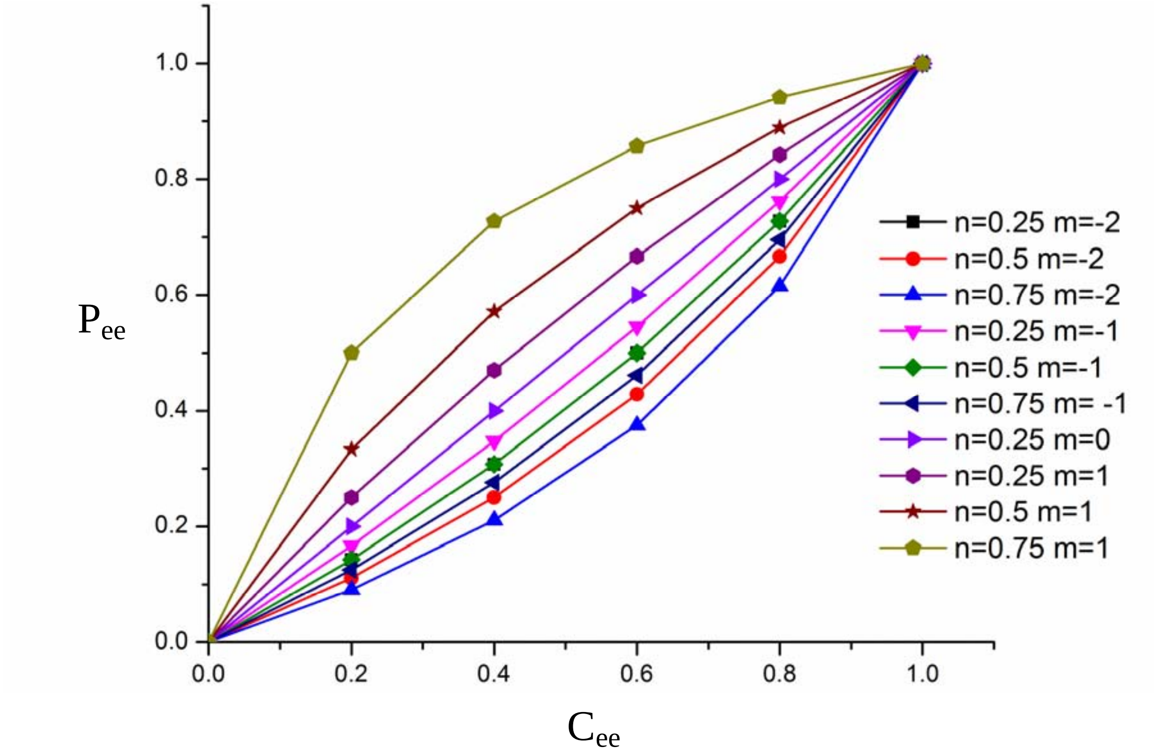


Fig. 2. Graphical representation of eq. 10, for various values of ‘m’ (1-ω) and ‘n’ (mole fraction of C_R). C_R and C_S have been varied concurrently from 0-100% and 100-0% respectively; the m = 1 cases represent eq. 5. (P_{ee} and C_{ee} should be multiplied by 10^2 for comparison with Fig. 1.) The plots were generated with the software program Origin (OriginLab, Northampton, MA).

$$M + 2C_\mathrm{R} \overset{K_\mathrm{R}}{\rightleftharpoons} C_\mathrm{R}\text{-}M\text{-}C_\mathrm{R} \qquad K_R = [C_\mathrm{R}MC_\mathrm{R}]/([M][C_\mathrm{R}]^2)$$

$$C_\mathrm{R}\text{-}M\text{-}C_\mathrm{R} + S \xrightarrow{k_{(\mathrm{R})}} P_\mathrm{R} \qquad v_\mathrm{R} = k_{(\mathrm{R})}[C_\mathrm{R}\text{-}M\text{-}C_\mathrm{R}][S] = k_{(\mathrm{R})}K_\mathrm{R}[S][M][C_\mathrm{R}]^2$$

$$= \underline{k_\mathrm{R}[S][M][C_\mathrm{R}]^2}$$

$$M + 2C_\mathrm{S} \overset{K_\mathrm{S}}{\rightleftharpoons} C_\mathrm{S}\text{-}M\text{-}C_\mathrm{S} \qquad K_\mathrm{S} = [C_\mathrm{S}MC_\mathrm{S}]/([M][C_\mathrm{S}]^2)$$

$$C_\mathrm{S}\text{-}M\text{-}C_\mathrm{S} + S \xrightarrow{k_{(\mathrm{S})}} P_\mathrm{S} \qquad v_\mathrm{S} = k_{(\mathrm{S})}[C_\mathrm{S}\text{-}M\text{-}C_\mathrm{S}][S] = k_{(\mathrm{S})}K_\mathrm{S}[S][M][C_\mathrm{S}]^2$$

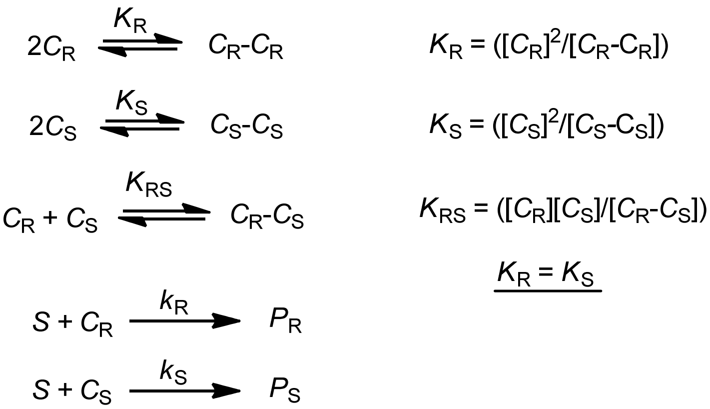
$$= \underline{k_\mathrm{S}[S][M][C_\mathrm{S}]^2}$$

$$M + C_\mathrm{R} + C_\mathrm{S} \overset{K_\mathrm{RS}}{\rightleftharpoons} C_\mathrm{R}\text{-}M\text{-}C_\mathrm{S} \qquad K_\mathrm{RS} = [C_\mathrm{R}MC_\mathrm{S}]/([M][C_\mathrm{R}][C_\mathrm{S}])$$

$$C_\mathrm{R}\text{-}M\text{-}C_\mathrm{S} + S \xrightarrow{k_{(\mathrm{RS})}} (P_\mathrm{R}+P_\mathrm{S})/2 \qquad v_\mathrm{RS} = k_{(\mathrm{RS})}[C_\mathrm{R}\text{-}M\text{-}C_\mathrm{S}][S] = k_{(\mathrm{RS})}K_\mathrm{RS}[S][M][C_\mathrm{R}][C_\mathrm{S}]$$

$$= \underline{k_\mathrm{RS}[S][M][C_\mathrm{R}][C_\mathrm{S}]}$$

Scheme 1. The reactions mediating the catalytic conversion of an achiral substrate S to enantiomeric products P_R and P_S. The enantiomeric catalysts C_R and C_S react *via* their diastereomeric complex with M. The K_R, K_S and K_RS are equilibrium constants as defined; v_R, v_S and v_RS are overall reaction rates; $k_{(\mathrm{R})}$, $k_{(\mathrm{S})}$ and $k_{(\mathrm{RS})}$ are rate constants for the indicated steps, while k_R, k_S and k_RS are overall rate constants.



$$2C_R \overset{K_R}{\rightleftharpoons} C_R\text{-}C_R \qquad K_R = ([C_R]^2/[C_R\text{-}C_R])$$

$$2C_S \overset{K_S}{\rightleftharpoons} C_S\text{-}C_S \qquad K_S = ([C_S]^2/[C_S\text{-}C_S])$$

$$C_R + C_S \overset{K_{RS}}{\rightleftharpoons} C_R\text{-}C_S \qquad K_{RS} = ([C_R][C_S]/[C_R\text{-}C_S])$$

$$\underline{K_R = K_S}$$

$$S + C_R \xrightarrow{k_R} P_R$$

$$S + C_S \xrightarrow{k_S} P_S$$

Scheme 2. The reactions mediating the conversion of an achiral substrate S to enantiomeric products P_R and P_S, with enantiomeric catalysts C_R and C_S. These react *per se*, although they are in equilibrium with non-reactive dimeric forms C_R-C_R, C_S-C_S and C_R-C_S. The K_R, K_S and K_{RS} are equilibrium constants as defined, while k_R, k_S and k_{RS} are rate constants for the indicated reactions.

SUPPLEMENTARY INFORMATION

A Critical Assessment of Previous Approaches

There are two previous models (not involving autocatalysis) based on the pre-equilibrium formation of reactive complexes.[1-3] However, these models end up implying that all of the catalyst is converted to the complexes. This is because the starting substrates, reactants and (uncomplexed) catalyst do not appear in the final rate equations that are employed to arrive at the product e.e. In other words, the rate equations are derived with the intermediates themselves as initial reactants. This, and other inaccuracies as discussed below, suggest that these approaches now need to be abandoned.

The first of these is based on the intermediate formation of dimeric diastereomeric complexes; (*cf.* Scheme 1 above, and Fig. 2 of ref. 2; symbols used in eqs. I-IV below are from ref. 2, unless stated otherwise).[1,2] However, the e.e. of the catalyst (termed "$\mathrm{ee_{aux}}$") is defined inaccurately (eq. I). This definition implies (apparently inadvertently) that all the original catalyst has been converted to the complexed forms. In fact, eq. I would not be valid even in that case, as the concentration of the meso form (z) is included in the total concentration (denominator).

$$\mathrm{ee_{aux}} = (x-y)/(x+y+z) \qquad \text{(I)}$$

$$\mathrm{ee_{aux}} = \{([L_\mathrm{R}]+2x)-([L_\mathrm{S}]+2y)\}/\{([L_\mathrm{R}]+[L_\mathrm{S}])+2(x+y+z)\} \qquad \text{(II)}$$

$$\mathrm{ee_{comp}} = (x-y)/(x+y) \qquad \text{(III)}$$

$$\mathrm{EE_{prod}} = EE_0(x-y)/(x+y+gz) \qquad \text{(IV)}$$

The definition of e.e. involves only the concentrations of the chiral forms of the particular compound in question, and excludes those of all other species. Thus, the e.e. of the starting catalyst would be given by eq. II. (This follows the original treatment in assuming, apparently, that the probability of forming the meso complex is twice that of the chiral ones.) The e.e. of the complexes (termed $\mathrm{ee_{comp}}$ herein) in mobile equilibrium with unreacted catalyst would be given by eq. III.

The $\mathrm{ee_{aux}}$ of eq. I was plotted (abscissa) *vs.* "$\mathrm{EE_{prod}}$" (ordinate).[2] Clearly, however, $\mathrm{ee_{aux}} \neq \mathrm{ee_{comp}}$ in the general case; the view that $\mathrm{ee_{aux}} = \mathrm{ee_{comp}}$ stems from their erroneous definition. (Indeed, if $\mathrm{ee_{aux}} = \mathrm{ee_{comp}}$, there should be neither amplification nor depletion!)

Note that eq. I relates the original e.e. of the catalyst (prior to complexation) to the concentrations of the three dimeric species (*i.e.* upon their irreversible formation); however, this is irrelevant to the purported steady-state condition assumed in the derivation.

The problems of eq. I are then carried over to the definition of the product e.e. [eq. IV, where $g = (k_{RS}/k_{RR})$]. Thus, when $\mathrm{ee_{aux}}$ (eq. I) is plotted *vs.* $\mathrm{EE_{prod}}$ (eq. IV): apparently, amplification arises for the case of $g < 1$ (meso form less reactive), and depletion for the case of $g > 1$ (meso form more reactive). These results are hence fortuitous, the observed correlation merely reflecting the same errors present in both eqs. I and IV.

In point of fact, once $\mathrm{ee_{aux}}$ is defined as in eq. 1, $\mathrm{EE_{prod}}$ (eq. 4) follows, based on the stereospecific reactions of the enantiomeric complexes. Also, any definition of $\mathrm{ee_{aux}}$ as in eq. 1, with a two-parameter numerator and a corresponding three-parameter denominator, along with appropriate weighting of one of the denominator terms, would then lead to the derived plots. However, this *per se* does not validate the approach.

It may be noted that this approach essentially implies the resolution of the catalyst *via* the formation of the diastereomeric dimeric complexes. This is analogous to the precedented case of formation of “bis-functionalized” auxiliaries discussed above.[13]

In another related approach (Scheme 2),[3] the dimeric diastereomeric complexes act as a reservoir (rather than as intermediates) in equilibrium with the monomeric chiral species. The reaction then proceeds through these, *via* the intermediate formation of reactive complexes with a substrate and a reagent. The competition between the above equilibrium and the rates of formation of products is described in a complex mathematical formalism. However, the arguments appear lost in the algebraic detail, with key equations being dubious. In particular, two relations appear to be in error. (The symbols below have the same significance as in the original paper.)[3]

Thus, $ee_{C(total)}$ (relating to the original chiral catalyst) is defined by eq. V, whereas it should be as in eq. VI:

$$ee_{C(total)} = \{(2\alpha/K_{homo}) + 1 + K_{assoc}[Rea][Sub](\alpha^2\text{-}4\beta)^{0.5}\}/[C_{tot}] \qquad \text{(V)}$$

$$ee_{C(total)} = (\alpha^2\text{-}4\beta)^{0.5}\{(2\alpha/K_{homo}) + 1 + K_{assoc}[Rea][Sub]\}/[C_{tot}] \qquad \text{(VI)}$$

Furthermore, the key relation $(\alpha^2\text{-}4\beta)$ is defined as in eq. VII:

$$(\alpha^2\text{-}4\beta) = \{(K_{homo}+2K_{hetero})\alpha^2 + 2K_{homo}K_{hetero}(1+K_{assoc}[Rea][Sub])\alpha - 2K_{homo}K_{hetero}[C_{tot}])\}/(K_{homo} - 2K_{hetero}) \qquad \text{(VII)}$$

There are indeed several problems with this relation. Firstly, for the condition $K_{homo} = 2K_{hetero}$, the denominator equals zero, so $(\alpha^2\text{-}4\beta) = \infty$. [In point of fact, $(\alpha^2\text{-}4\beta)^{0.5} = ([S]\text{-}[R])$, $[S]$ and $[R]$ being the concentrations of uncomplexed catalyst enantiomers.] Also, when $K_{homo} < 2K_{hetero}$, $(\alpha^2\text{-}4\beta)$ would appear to change sign; if so, this would turn

$(\alpha^2\text{-}4\beta)^{0.5}$ [= ([S]-[R]), *vide supra*] into an imaginary quantity. In fact, the numerator of eq. VII can be rewritten as in eq. VIII:

$$\{(K_{\text{homo}}+2K_{\text{hetero}})\alpha^2 + 2K_{\text{homo}}K_{\text{hetero}}(1+K_{\text{assoc}}[\text{Rea}][\text{Sub}]\alpha - [\text{C}_{\text{tot}}])\} \quad \text{(VIII)}$$

It appears that this would remain > 0, even when $K_{\text{homo}} < 2K_{\text{hetero}}$. The only other variable in it is α (= [S]+[R]); although this is itself a function of K_{homo} and K_{hetero}, it seems possible (under some conditions) that α remains nearly constant although K_{homo} and K_{hetero} vary. Thus, the condition $K_{\text{homo}} < 2K_{\text{hetero}}$ is unlikely to substantially alter the term $(1+K_{\text{assoc}}[\text{Rea}][\text{Sub}]\alpha)$ in eqs. VII and VIII. In other words, the numerator of eq. VII would remain > 0, even when the denominator < 0, so the condition $(\alpha^2\text{-}4\beta) > 0$ is unlikely to be generally fulfilled.

These arguments indicate that the key relation (eq. VII) is unlikely to be valid, which throws into doubt the successive derivations and arguments. In fact, eqs. 14 and 15 are quadratic equations, which – in principle – can be solved to arrive at [C_{R}] and [C_{S}] in terms of $[C_{\text{R}}]_{\text{o}}$, $[C_{\text{S}}]_{\text{o}}$, K_{R} and K_{RS}. (These would then lead to P_{ee} *via* eq. 17.) However, the final equations (eqs. IX and X, $a = 2/K_{\text{R}}$ and $b = 1/K_{\text{RS}}$) are apparently not easily tractable (certainly not manually).

$$[C_{\text{S}}] = \{\pm[(b[C_{\text{R}}] + 1)^2 + 4a[C_{\text{S}}]_{\text{o}}]^{0.5} - (b[C_{\text{R}}] + 1)\}/2a \qquad \text{(IX)}$$

$$a[C_{\text{R}}]^2 + [C_{\text{R}}](1 + b[C_{\text{S}}]) - [C_{\text{R}}]_{\text{o}}) = 0 \qquad \text{(X)}$$

Thus, substituting [C_{S}] from eq. IX into eq. X, and solving the resulting quadratic equation would lead to [C_{R}] in terms of $[C_{\text{R}}]_{\text{o}}$, $[C_{\text{S}}]_{\text{o}}$, K_{R} and K_{RS}. (Eq. IX above can be derived by solving eq. 15 by standard methods, *e.g.* see: Clar LM, Hart JA. Mathematics for the technologies. Englewood Cliffs, NJ: Prentice-Hall; 1978. p 389. Eq. X derives from rearranging eq. 14.)

However, as briefly mentioned in the main paper, this system represents a case wherein the catalyst effectively undergoes an *in situ* resolution (upon formation of the non-reactive dimers). They also apparently represent analogs of previously known crystallization phenomena, involving enhancement of e.e.[7] In view of this, as also the above discussed mathematical complexity, these systems have not been considered further in this work. (Qualitative justification for the observed amplification and depletion has been provided in the main paper.)

Notes on the Derivation of Eqs. 5, 11 and 19

Derivation of eq. 5. The transformation of eq. 3 to eq. 5 is based on the following well-known relations: $(a - b)(a + b) = (a^2 - b^2)$ and $(a + b)^2 = (a^2 + 2ab + b^2)$. The former is applied to the numerator, and the latter to the denominator of eq. 3. Further rearrangement and simplification, noting that $[(a + b)^2 - 2ab] = (a^2 + b^2)$, leads to eq. 5.

Derivation of eq. 11. The stereoselectivity factor χ_{es} may be introduced into eq. 10, in order to obtain eq. 11, as follows. The rates of formation of P_R and P_S are now defined to include the formation of the alternative enantiomer as a (minor) side product. Thus, eqs. 1 and 2 transform to eq. XI and XII:

$$v_R = d[P_R]/dt = k_R[S][M][C_R]^2 + k_R'[S][M][C_S]^2 \quad \text{(XI)}$$

$$v_S = d[P_S]/dt = k_S[S][M][C_S]^2 + k_S'[S][M][C_R]^2 \quad \text{(XII)}$$

In these, k_R' is the rate constant for the formation of P_R by C_S; likewise k_S' is the rate constant for the formation of P_S by C_R. Note that $k_R' = k_S'$, as they represent enantiomeric transition states. P_{ee} is now defined by eq. XIII, derived analogously to eq. 5.

$$P_{ee} = \{(k_R[C_R]^2 + k_R'[C_S]^2) - (k_S[C_S]^2 + k_S'[C_R]^2)\}/\{(k_R[C_R]^2 + k_R'[C_S]^2) +$$

$$(k_S[C_S]^2 + k_S'[C_R]^2)\} \quad \text{(XIII)}$$

$$P_{ee} = \{([C_R]^2 - [C_S]^2)(k_R - k_R')\}/\{([C_R]^2 + [C_S]^2)(k_R + k_R')\} \quad \text{(XIV)}$$

$$P_{ee} = \chi_{es}([C_R]^2 - [C_S]^2)/([C_R]^2 + [C_S]^2) \quad \text{(XV)}$$

$$\chi_{es} = (k_R - k_R')/(k_R + k_R') \quad \text{(XVI)}$$

Eq. XIII rearranges to eq. XIV, bearing in mind that $k_R = k_S$ and $k_R' = k_S'$. This is the analog of eq. 3, and can be rewritten as eq. XV by involving the enantioselectivity factor χ_{es} (defined as in eq. XVI). The χ_{es} is an index of the inherent enantioselectivity of the reaction, and will be less than 100% as long as k_R', $k_S' > 0$.

Derivation of eq. 19. This follows from the definition of e.e. (as a percentage), exemplified for the case of the product in question, in eq. XVII ($[P_R] > [P_S]$):

$$\text{e.e.} = 100([P_R] - [P_S])/([P_R] + [P_S]) \quad \text{(XVII)}$$

$$[1\text{-(e.e./100)}] = 1 - \{([P_R] - [P_S])/([P_R] + [P_S])\} = 2[P_S]/([P_R] + [P_S]) = m_r \quad \text{(XVIII)}$$

Eq. XVII can be rearranged to eq. XVIII, in which $2[P_S]/([P_R] + [P_S])$ represents twice the mole fraction of the minor enantiomer present in the mixture. This is the mole fraction of the racemate (m_r), so multiplying this by the total concentration $\{N = ([P_R] + [P_S])\}$ yields the concentration of the racemate present in an enantiomerically enriched sample. Thus, cross-multiplication transforms eq. XVIII to eq. XIX:

$$[1\text{-(e.e./100)}]([P_R] + [P_S]) = 2[P_S] = m_rN = n \quad \text{(XIX)}$$

Also, e.e. (eq. XVII) can equally be defined in terms of number of moles of the enantiomers present in a given sample of fixed volume (rather than concentrations). Then, m_rN above would represent the number of moles of the racemate (n in eq. 19).

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