Supporting Information

Kinetic Rationalization of Nonlinear Effects in Asymmetric Catalytic Cascade Reactions Under Curtin-Hammett Conditions

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1. General remarks

All kinetic modelling was conducted using Complex Pathway Simulator (COPASI) software. The values used in each kinetic model are provided, as well as the corresponding COPASI files. The data of the nonlinear effects used in the simulations have been extracted from the experimental data reported by Jørgensen in ACS catalysis 2020 for the reaction in Scheme S1. The reaction involves a catalyzed reaction between 1 and 2, producing intermediate II, which cyclises in a catalyzed reaction to from the final product 4. All the conditions used for the COPASI modelling were extracted from page S64 in the supporting information of Ref. (SI) unless stated otherwise. Within our COPASI models, we refer to 1, 2, and 3 as A, B, and cat respectively.

Scheme S1. Organocatalytic cycloaddition of 1 and 2 to form 4 via intermediate II.

2. Kinetic analysis of the nonlinear effects of the reaction network in Scheme 2

We derived an equation for ee₄ by applying the steady-state approximation to the reaction intermediates II(SS) and II(RR). We will use the following equations and definitions:

Enantiomeric ratio of product 4:

$$\sigma_4 = \frac{[4(SSSS)]}{[4(RRRR)]}$$  (1)

Rate of formation of 4(SSSS):

$$r_{4(SSSS)} = (k_3[3^R]+k_4[3^S])[II(SS)]$$  (2)

Rate of formation of 4(RRRR):

$$r_{4(RRRR)} = (k_3[3^R]+k_4[3^S])[II(RR)]$$  (3)

Steady-state approximation for II(SS):

$$(k_1[3^R]+k_2[3^S])[1][2] - (k_{-1}[3^R]+k_{-2}[3^S]+k_3[3^R]+k_4[3^S])[II(SS)] \approx 0$$  (4)

Steady-state approximation for II(RR):

$$(k_1[3^R]+k_2[3^S])[1][2] - (k_{-1}[3^R]+k_{-2}[3^S]+k_3[3^R]+k_4[3^S])[II(RR)] \approx 0$$  (5)
From the equilibrium of 1 and 2 with II(SS):

\[
\frac{[\text{II(SS)}]_{eq}[3^\gamma]_{eq}}{[1]_{eq}[2]_{eq}[3^\alpha]_{eq}} = \frac{k_1}{k_{-1}} = \frac{k_2}{k_{-2}} \quad \text{and therefore:} \quad k_{-2} = \frac{k_2 k_{-1}}{k_1}
\]  \hspace{1cm} (6)

Enantioselectivity of the first step:

\[
\alpha = \frac{k_1}{k_2}
\]  \hspace{1cm} (7)

Selectivity factor of the second step (analogous to the selectivity factor of kinetic resolutions):

\[
\beta = \frac{k_3}{k_4}
\]  \hspace{1cm} (8)

Enantiomeric ratio and enantiomeric excess of catalyst 3:

As \(e_{r3} = \frac{[3^\gamma]}{[3^\alpha]} \) and \(e_{e3} = \frac{[3^\gamma] - [3^\alpha]}{[3^\gamma] + [3^\alpha]} \), then

\[
\frac{[3^\gamma]}{[3^\alpha]} = 1 + e_{e3}
\]  \hspace{1cm} (9)

Enantiomeric excess of product 4:

\[
e_{e4} = \frac{[4(\text{SSSS})] - [4(\text{RRRR})]}{[4(\text{SSSS})] + [4(\text{RRRR})]} = \frac{e_{r4} - 1}{e_{r4} + 1}
\]  \hspace{1cm} (10)

From equations (1), (2) and (3):

\[
e_{r4} = \frac{(k_2[3^\gamma] + k_4[3^\alpha])}[1(\text{SS})] \quad \frac{(k_3[3^\gamma] + k_4[3^\alpha])}[1(\text{RR})]
\]  \hspace{1cm} (11)

From equations (11), (4) and (5):

\[
e_{r4} = \frac{(k_3[3^\gamma] + k_4[3^\alpha])(k_1[3^\gamma] + k_2[3^\alpha])}{(k_3[3^\gamma] + k_4[3^\alpha])(k_1[3^\gamma] + k_2[3^\alpha])} \frac{(k_1[3^\gamma] + k_2[3^\alpha])}{[1(\text{SS})][1(\text{RR})]}
\]  \hspace{1cm} (12)

From equations (12) and (6):

\[
e_{r4} = \frac{(k_3[3^\gamma] + k_4[3^\alpha])(k_1[3^\gamma] + k_2[3^\alpha])}{(k_3[3^\gamma] + k_4[3^\alpha])(k_1[3^\gamma] + k_2[3^\alpha])} \frac{(k_1[3^\gamma] + k_2[3^\alpha])}{[1(\text{SS})][1(\text{RR})]}
\]  \hspace{1cm} (13)

From equation (13) we derive the \(e_{r4}\) when using enantiomerically pure catalyst 3\(^{5}\) (\(e_{r4}^{\alpha} = \gamma\)):

\[
e_{r4}^{\alpha} = \gamma = \frac{k_1 k_3 k_2 k_{-1} + k_2 k_4}{k_2 k_4 k_3(k_{-1} + k_3)}
\]  \hspace{1cm} (14)

From equation (14), and definitions (7) and (8):

\[
\gamma = \frac{k_2 k_{-1} + k_1 k_4}{k_1(k_{-1} + k_3)}
\]  \hspace{1cm} (15)
From equations (13), (15) and definitions (7) and (8):

$$er_4 = \frac{(k_4[3\beta]+k_4[3\gamma])(k_4[3\beta] + k_4[3\gamma]) \left[ 3\gamma \frac{r}{ap} + 3\gamma \right]}{(k_4[3\beta]+k_4[3\gamma])(k_4[3\beta] + k_4[3\gamma]) \left[ 3\gamma \frac{r}{ap} + 3\gamma \right]}$$

$$er_4 = \frac{(\beta[3\gamma] + [3\gamma])(\alpha[3\beta] + [3\gamma])(3\gamma\gamma + \alpha\beta[3\gamma])}{(\beta[3\gamma] + [3\gamma])(\alpha[3\beta] + [3\gamma])(3\gamma\gamma + \alpha\beta[3\gamma])}$$

(16)

From equations (16) and (9):

$$er_4 = \frac{\beta \left[ \frac{3\gamma}{3\beta} + 1 \right] \left( \alpha \left[ \frac{3\gamma}{3\beta} + 1 \right] \right) \left( [3\gamma] \gamma + \alpha \beta \right)}{\left( \beta + [3\gamma] \right) \left( \alpha + [3\gamma] \right) \left( [3\gamma] \gamma + \alpha \beta \right)}$$

$$er_4 = \frac{\beta \left( \frac{1 + ee_3 + 1}{1 - ee_3} \right) \left( \frac{1 + ee_3 + 1}{1 - ee_3} \right) \left( 1 + ee_3 \gamma + \alpha \beta \right)}{\left( \beta + \frac{1 + ee_3}{1 - ee_3} \right) \left( \alpha + \frac{1 + ee_3}{1 - ee_3} \right) \left( 1 + ee_3 \gamma + \alpha \beta \right)}$$

(17)

From equations (17) and (10):

$$ee_4 = \frac{\left( \beta \left[ \frac{3\gamma}{3\beta} + 1 \right] \left( \alpha \left[ \frac{3\gamma}{3\beta} + 1 \right] \right) \left( [3\gamma] \gamma + \alpha \beta \right) - 1}{\left( \beta + [3\gamma] \right) \left( \alpha + [3\gamma] \right) \left( [3\gamma] \gamma + \alpha \beta \right) + 1}$$

$$ee_4 = \frac{ee_3\alpha\beta(3 + \alpha + \beta - \alpha\beta) + ee_3^3(\alpha - 1)(\beta - 1)(\beta - 1)(\gamma - 1) - ee_3\gamma(\alpha + \beta + 3\alpha\beta - 1)}{ee_3(\alpha + \beta + 3\alpha\beta - 3)(\alpha + 1)(\beta + 1) - \gamma(1 + \alpha + \beta + \alpha\beta + ee_3^2(3\beta - 1) - \beta - 1)}$$

(18)

Equation (18) allows us to rationalize the appearance of NLE and its sense (summarized in Figure S1).

1. If $\alpha\beta = 1$:

$$ee_4 = \frac{ee_3\alpha\beta(3 + \alpha + \beta - \alpha\beta) + ee_3^3(\alpha - 1)(\beta - 1)(\beta - 1)(\gamma - 1) - ee_3\gamma(\alpha + \beta + 3\alpha\beta - 1)}{ee_3(\alpha + \beta + 3\alpha\beta - 3)(\alpha + 1)(\beta + 1) - \gamma(1 + \alpha + \beta + \alpha\beta + ee_3^2(3\beta - 1) - \beta - 1)}$$

(18)

$$ee_4 = \frac{ee_3 \left( 3 + \frac{1}{\alpha} + 1 - \frac{1}{\alpha} \right) + ee_3^3(\alpha - 1) \left( \frac{1}{\alpha} - 1 \right) (1 - \gamma) - ee_3\gamma(\alpha + \frac{1}{\alpha} + 3 - 1)}{ee_3^2(\alpha + \frac{1}{\alpha} + 1 - 3) - (\alpha + 1) \left( \frac{1}{\alpha} + 1 \right) - \gamma(1 + \alpha + \frac{1}{\alpha} + 1 + ee_3^2(\alpha + \frac{3}{\alpha} - 1) - \frac{1}{\alpha} - 1)}$$

$$ee_4 = \frac{\gamma - 1}{1 + ee_3} = ee_4^{ee_3}$$

In this scenario, the selectivity of the first step ($\alpha$) is the inverse of the selectivity of the second step ($\beta$) and therefore they cancel each other. The result is a linear dependency of the $ee$ of the product ($ee_4$) with respect to the $ee$ of the catalyst ($ee_3$, Figure S1).
2. If $\alpha = \gamma$:

\[
 ee_4 = \frac{ee_3 \alpha (3 + \alpha + \beta - \alpha \beta) + ee_3^3 (\alpha - 1)(\beta - 1)(\alpha \beta - \gamma) - ee_3 \gamma (\alpha + \beta + 3 \alpha \beta - 1)}{\alpha (ee_3^2 (\alpha + \beta + \alpha \beta - 3) - (\alpha + 1)(\beta + 1)) - \gamma (1 + \alpha + \beta + \alpha \beta + ee_3^2 (\alpha (3 \beta - 1) - \beta - 1))}
\]

\[
 ee_4 = \frac{ee_3 \alpha (3 + \alpha + \beta - \alpha \beta) + ee_3^3 (\alpha - 1)(\beta - 1)(\alpha \beta - \alpha) - ee_3 \alpha (\alpha + \beta + 3 \alpha \beta - 1)}{\alpha (ee_3^2 (\alpha + \beta + \alpha \beta - 3) - (\alpha + 1)(\beta + 1)) - \alpha (1 + \alpha + \beta + \alpha \beta + ee_3^2 (\alpha (3 \beta - 1) - \beta - 1))}
\]

\[
 ee_4 = \frac{\gamma - 1}{\gamma + 1} ee_3 = ee_4^{ep} ee_3
\]

In this scenario, the result is a linear dependency of the $ee$ of the product ($ee_4$) with respect to the $ee$ of the catalyst ($ee_3$) (Figure S1), which may be due to different reasons. To understand the different reasons, we have used equation (14) and definitions (7) and (8) to derive the following equation:

\[
 \gamma = \frac{k_{-1} \beta + k_3 \alpha}{k_{-1} + k_3} = \frac{k_{-1} \beta + \alpha}{k_{-1} + 1}; \text{ as } \alpha = \gamma: \quad \alpha = \frac{k_{-1} \beta + \alpha}{k_{-1} + 1} \rightarrow \frac{k_{-1} \alpha}{k_{-1} + 1} = \frac{k_{-1} \beta}{k_{-1}}
\]

Which means that either the first step is practically irreversible ($k_{-1}/k_3 \approx 0$), or that both steps have identical selectivity ($\alpha = \beta$) (Figure S1).

3. $\beta = \gamma$:

\[
 ee_4 = \frac{ee_3 \alpha (3 + \alpha + \beta - \alpha \beta) + ee_3^3 (\alpha - 1)(\beta - 1)(\alpha \beta - \gamma) - ee_3 \gamma (\alpha + \beta + 3 \alpha \beta - 1)}{\alpha (ee_3^2 (\alpha + \beta + \alpha \beta - 3) - (\alpha + 1)(\beta + 1)) - \gamma (1 + \alpha + \beta + \alpha \beta + ee_3^2 (\alpha (3 \beta - 1) - \beta - 1))}
\]

\[
 ee_4 = \frac{ee_3 \alpha (3 + \alpha + \beta - \alpha \beta) + ee_3^3 (\alpha - 1)(\beta - 1)(\alpha \beta - \alpha) - ee_3 \alpha (\alpha + \beta + 3 \alpha \beta - 1)}{\alpha (ee_3^2 (\alpha + \beta + \alpha \beta - 3) - (\alpha + 1)(\beta + 1)) - \alpha (1 + \alpha + \beta + \alpha \beta + ee_3^2 (\alpha (3 \beta - 1) - \beta - 1))}
\]

\[
 ee_4 = \frac{\gamma - 1}{\gamma + 1} ee_3 = ee_4^{ep} ee_3
\]

In this scenario, the result is a linear dependency of the $ee$ of the product ($ee_4$) with respect to the $ee$ of the catalyst ($ee_3$) (Figure S1), which may be due to different reasons. To understand the different reasons, we have used equation (14) and definitions (7) and (8) to derive the following equation:

\[
 \gamma = \frac{k_{-1} \beta + k_3 \alpha}{k_{-1} + k_3} = \frac{\beta + \frac{k_3}{k_{-1}} \alpha}{1 + \frac{k_3}{k_{-1}}}; \text{ as } \beta = \gamma: \quad \beta = \frac{\beta + \frac{k_3}{k_{-1}} \alpha}{1 + \frac{k_3}{k_{-1}}} \rightarrow \frac{k_3}{k_{-1}} \alpha = \frac{k_3}{k_{-1}} \beta
\]

Which means that either the first step is in quasi-equilibrium (because $k_3/k_{-1} \approx 0$) or that both steps have identical selectivity ($\alpha = \beta$) (Figure S1).
4. $\beta < \gamma < \alpha$:

$$ee_4 = \frac{ee_2\alpha\beta(3 + \alpha + \beta - a\beta) + ee_3^2(\alpha - 1)(\beta - 1)(a\beta - \gamma) - ee_4(\alpha + \beta + 3a\beta - 1)}{a\beta(ee_2^2(a + \beta + a\beta - 3) - (\alpha + 1)(\beta + 1)) - \gamma(1 + \alpha + \beta + a\beta + ee_3^2(\alpha(3\beta - 1) - \beta - 1))}$$  \hspace{1cm} (18)$$

As in the absence of NLE: $ee_4(linear) = \frac{\gamma - 1}{\gamma + 1} ee_3$, then the difference between $ee_4$ and $ee_4(linear)$ is:

$$ee_4 - ee_4(linear) = \frac{ee_2\alpha\beta(3 + \alpha + \beta - a\beta) + ee_3^2(\alpha - 1)(\beta - 1)(a\beta - \gamma) - ee_4(\alpha + \beta + 3a\beta - 1)}{a\beta(ee_2^2(a + \beta + a\beta - 3) - (\alpha + 1)(\beta + 1)) - \gamma(1 + \alpha + \beta + a\beta + ee_3^2(\alpha(3\beta - 1) - \beta - 1))} \cdot \frac{\gamma - 1}{\gamma + 1} ee_3$$

$$ee_4 - ee_4(linear) = \frac{2ee_3(1 - ee_2^2)(\alpha - \gamma)(\gamma - \beta)(1 - a\beta)}{\delta - \varepsilon},$$

where:

$$\delta = a\beta(1 + \alpha + \beta + a\beta) + \gamma(1 + \alpha + \beta + 2a\beta + a^2\beta + a\beta^2 + a^2\beta^2) + \gamma^2(1 + \alpha + \beta + a\beta) + 3ee_3a\beta(1 + 2\gamma + \gamma^2)$$

$$\varepsilon = ee_3^2(\alpha(\alpha + \beta + a\beta) + \gamma(1 + \alpha + \beta + a^2\beta + a\beta^2 + a^2\beta^2) + \gamma^2(1 + \alpha + \beta))$$

As $1 \geq ee_2 \geq 0$ and the other parameters are positive: $\delta > \varepsilon$, and therefore, the denominator of (19) is positive.

As $1 \geq ee_2 \geq 0$, the term $2ee_2(1 - ee_2^2)$ of the numerator of (19) is positive.

As $\beta < \gamma < \alpha$, the term $(\alpha - \gamma)(\gamma - \beta)$ of the numerator of (19) is positive.

Therefore, the sign of the equation (19) depends on the value of $(1 - a\beta)$:

- If $a\beta > 1$, the sign of (19) is negative and there is (--)NLE (Figure S1).
- If $a\beta = 1$, (19) is zero and the system has a linear behaviour (see point 1 in page S-3 and Figure S1).
- If $a\beta < 1$, the sign of (19) is positive and there is (+)NLE (Figure S1).

5. $\beta > \gamma > \alpha$:

$$ee_4 = \frac{ee_2\alpha\beta(3 + \alpha + \beta - a\beta) + ee_3^2(\alpha - 1)(\beta - 1)(a\beta - \gamma) - ee_4(\alpha + \beta + 3a\beta - 1)}{a\beta(ee_2^2(a + \beta + a\beta - 3) - (\alpha + 1)(\beta + 1)) - \gamma(1 + \alpha + \beta + a\beta + ee_3^2(\alpha(3\beta - 1) - \beta - 1))}$$  \hspace{1cm} (18)$$

As in the absence of NLE: $ee_4(linear) = \frac{\gamma - 1}{\gamma + 1} ee_3$, then the difference between $ee_4$ and $ee_4(linear)$ is:

$$ee_4 - ee_4(linear) = \frac{ee_2\alpha\beta(3 + \alpha + \beta - a\beta) + ee_3^2(\alpha - 1)(\beta - 1)(a\beta - \gamma) - ee_4(\alpha + \beta + 3a\beta - 1)}{a\beta(ee_2^2(a + \beta + a\beta - 3) - (\alpha + 1)(\beta + 1)) - \gamma(1 + \alpha + \beta + a\beta + ee_3^2(\alpha(3\beta - 1) - \beta - 1))} \cdot \frac{\gamma - 1}{\gamma + 1} ee_3$$

$$ee_4 - ee_4(linear) = \frac{2ee_3(1 - ee_2^2)(\alpha - \gamma)(\gamma - \beta)(1 - a\beta)}{\delta - \varepsilon},$$

where:

$$\delta = a\beta(1 + \alpha + \beta + a\beta) + \gamma(1 + \alpha + \beta + 2a\beta + a^2\beta + a\beta^2 + a^2\beta^2) + \gamma^2(1 + \alpha + \beta + a\beta) + 3ee_3a\beta(1 + 2\gamma + \gamma^2)$$

$$\varepsilon = ee_3^2(\alpha(\alpha + \beta + a\beta) + \gamma(1 + \alpha + \beta + a^2\beta + a\beta^2 + a^2\beta^2) + \gamma^2(1 + \alpha + \beta))$$

As $1 \geq ee_2 \geq 0$ and the other parameters are positive: $\delta > \varepsilon$, and therefore, the denominator of (19) is positive.

As $1 \geq ee_2 \geq 0$, the term $2ee_2(1 - ee_2^2)$ of the numerator of (19) is positive.

As $\beta > \gamma > \alpha$, the term $(\alpha - \gamma)(\gamma - \beta)$ of the numerator of (19) is positive.

Therefore, the sign of the equation (19) depends on the value of $(1 - a\beta)$:
• If $\alpha \beta > 1$, the sign of (19) is negative and there is $(-)$-NLE (Figure S1).
• If $\alpha \beta = 1$, (19) is zero and the system has a linear behaviour (see point 1 in page S-3 and Figure S1).
• If $\alpha \beta < 1$, the sign of (19) is positive and there is $(+)$-NLE (Figure S1).

![Diagram of the outcomes at each kinetic scenario and the resulting NLEs in each case](image)

**Figure S1.** Diagram of the outcomes at each kinetic scenario and the resulting NLEs in each case when a) $\beta = 100$ and $ee_{ep} = 60\%$. b) $\beta = 0.01$ and $ee_{ep} = 60\%$. c) $\beta = 100$ and $ee_{ep} = 0\%$. d) $\beta = 0.01$ and $ee_{ep} = 0\%$. 
3. Procedure used to obtain rate constants for the kinetic modelling of Scheme 2

To find the rate constants which produced a nonlinear effect comparable to the nonlinear effect reported in Ref. 2, we used the “solver” function in Microsoft Excel to find the values of $\alpha$, $\beta$ and $\gamma$. The values we found minimized the square of the differences between the value of the steady-state equation for $ee_4$ (formula (18)) and the experimental data (page S64 of Ref. 2; we considered that the result for 98% $ee_3$ reported by Jørgensen et al. was 100%, therefore the $ee_4^{ep}$ was 0.9 and $\gamma$ was 19 for all our modelling of this reaction).

$$ee_4 = \frac{ee_3\alpha\beta(3 + \alpha - \alpha\beta) + ee_3^3(\alpha - 1)(\beta - 1)(\alpha\beta - \gamma) - ee_3^3\gamma(\alpha + \beta + 3\alpha\beta - 1)}{\alpha\beta(ee_3^3(\alpha + \beta + \alpha\beta - 3) - (\alpha + 1)(\beta + 1)) - \gamma(1 + \alpha + \beta + \alpha\beta + ee_3^3(\alpha(3\beta - 1) - \beta - 1))}$$ (18)

For Case 1, we used the following constraint in our optimization:

$$\alpha < \gamma < \beta$$

For Case 2, we used the following constraint in our optimization:

$$\alpha > \gamma > \beta$$

We created the COPASI model representing the reaction network in Scheme 2. We assigned all the kinetic constants to global quantities defined as follows:

$$k_1 = k_1$$ (20)

$$k_2 = \frac{k_3}{\alpha}$$ (rearranged 7)

$$k_3 = k_3$$ (21)

$$k_4 = \frac{k_3}{\beta}$$ (rearranged 8)

$$k_{-1} = \frac{k_3k_4((1-ee_4^{ep})k_1 - k_2 - ee_4^{ep}k_2)}{k_2k_3((ee_4^{ep} - 1) + k_4 + ee_4^{ep}k_4)}$$ (from 10 and 14) (22)

$$k_{-2} = \frac{k_2k_{-1}}{k_5}$$ (6)

Since no numerical data nor reaction profiles were reported for the kinetic studies in Ref. 2, we had to estimate the progress of the reaction from the images of the stacked NMR spectra in pages S66-S68 in Ref 2. We used COPASI to do a “parameter estimation” of the kinetic constants that better fitted the estimated data.
4. Kinetic modelling of Scheme 2

Using the reaction scheme proposed in Scheme 2, we found two sets of rate constants which reproduced the nonlinear effect reported in Ref. 2. The first set of rate constants produce II(\textit{RR}) as the major intermediate (Case 1, Figure S2, Table S1) where the reaction is under the major-minor kinetic scenario. The other set of rate constants produce II(\textit{SS}) as the major intermediate (Case 2, Figure S2, Table S1) which put the reaction under the lock-and-key kinetic scenario. In both cases, the major enantiomer of product was $4(\textit{SSSS})$.

![Diagram of Scheme 2 reaction](image)

**Figure S2.** Nonlinear effect observed from the reaction presented in Scheme 2.

**Table S1.** Parameters used to model the reaction in Scheme 2 considering $[1]^0 = 0.125$ M, $[2]^0 = 0.250$ M and $[3]^0 = 0.025$ M.

| Rate Constant | Case 1 (major-minor) | Case 2 (lock and key) |
|---------------|----------------------|-----------------------|
| $k_1 / M^2 \text{ min}^{-1}$ | 3.1143 | 9.00033 |
| $k_{-1} / \text{ min}^{-1}$ | 3.98047 | 9.90365 |
| $k_2 / M^2 \text{ min}^{-1}$ | 5.37969 | 0.158749 |
| $k_{-2} / \text{ min}^{-1}$ | 6.87591 | 0.174682 |
| $k_3 / M \text{ min}^{-1}$ | 8.14525 | 4.83977 |
| $k_4 / M \text{ min}^{-1}$ | 0.143667 | 8.36029 |
| $\alpha$ | 0.57890 | 56.6952 |
| $\beta$ | 56.6952 | 0.5789 |
| ee | 0.9 | 0.9 |

Provided COPASI models: “Scheme 2 Major-minor (case 1).cps” and “Scheme 2 Lock and key (case 2).cps”

The nonlinear effects shown in Figure S2 is possible with any set of kinetic constants that maintain the values of $\alpha$, $\beta$, ee. To exemplify this fact, we have reproduced the same nonlinear effect with rate constants differing by a magnitude of 14 (Figure S3, Table S2).
Figure S3. Nonlinear effect observed from the reaction presented in Scheme 2 using kinetic constants of Case 3 and Case 4.

Table S2. Parameters used for the modelling of Figure S3 considering \([1]_o = 0.125\ M, [2]_o = 0.250\ M\) and \([3]_o = 0.025\ M\).

| Case 3 (major-minor) | Case 4 (lock and key) |
|----------------------|------------------------|
| \(k_1 / M^2\ min^{-1}\) | 3.42 \(5.535\) |
| \(k_{-1} / \min\) | 7.86784\(\times\)10^{13} \(9.20838\times\)10^{14} |
| \(k_2 / M^2\ min^{-1}\) | 5.90776 \(9.76273\times\)10^{-2} |
| \(k_{-2} / \min\) | 1.3591\times\)10^{14} \(1.62419\times\)10^{13} |
| \(k_3 / M\ min^{-1}\) | 1.61\times\)10^{14} \(4.5\times\)10^{-14} |
| \(k_4 / M\ min^{-1}\) | 2.83975\times\)10^{12} \(7.77336\times\)10^{14} |
| \(\alpha\) | 0.57890 \(56.6952\) |
| \(\beta\) | 56.6952 \(0.5789\) |
| \(\text{ee}_{\text{catalyst}}\) | 0.9 \(0.9\) |

Provided COPASI models: “Scheme 2 Major-minor (case 3).cps” and “Scheme 2 Lock and key (case 4).cps”

To reproduce the experiment conducted by Jørgensen et al., where the intermediate II was isolated and reacted under the same conditions as the [10+2] cycloaddition, we used the parameters presented for Case 1 (Figure S4).

Figure S4. Formation of 1 and 4 from a reaction initiated from II(RR) in Case 1 ([II(RR)]\(_o\) = 0.125 M and [3]\(_o\) = 0.025 M).
5. Kinetic modelling of the extended reaction with unproductive diastereomeric intermediates

When the reaction in Scheme 2 is extended to include the formation of both unproductive diastereomeric intermediates (II(SR), II(RS)), and the catalyst bound intermediates (e.g. Int(SS)\textsuperscript{3}) we can also produce a nonlinear effect for both the kinetic scenarios in Case 1 and 2 (Figure S5, Table S3).

**Figure S5.** Nonlinear effect observed in the extended reaction.

**Table S3.** Parameters used for the modelling of Figure S5 considering $[1]_0 = 0.125$ M, $[2]_0 = 0.250$ M and $[3]_0 = 0.025$ M.

|                | Case 1 (major-minor) | Case 2 (lock-and-key) |
|----------------|----------------------|-----------------------|
| $k_1$ / M\textsuperscript{2} min\textsuperscript{-1} | 3.97749              | 8.55524               |
| $k_{-1}$ / min\textsuperscript{-1}               | 40.1836              | 1.92127 \times 10\textsuperscript{6} |
| $k_2$ / M\textsuperscript{2} min\textsuperscript{-1} | 20292.7              | 1.14530 \times 10\textsuperscript{-1} |
| $k_{-2}$ / min\textsuperscript{-1}               | 210                  | 8.16313 \times 10\textsuperscript{-3} |
| $k_3$ / M\textsuperscript{2} min\textsuperscript{-1} | 5.37749              | 5.85524               |
| $k_{-3}$ / min\textsuperscript{-1}               | 4000.18              | 1.92127 \times 10\textsuperscript{6} |
| $k_4$ / M\textsuperscript{2} min\textsuperscript{-1} | 14.5296              | 1.14530 \times 10\textsuperscript{-2} |
| $k_{-4}$ / min\textsuperscript{-1}               | 8.19613 \times 10\textsuperscript{6} | 8.19613 \times 10\textsuperscript{-2} |
| $k_5$ / min\textsuperscript{-1}                 | 1.82477 \times 10\textsuperscript{7} | 2.09886 \times 10\textsuperscript{7} |
| $k_{-5}$ / M\textsuperscript{-1}                | 6.26530 \times 10\textsuperscript{6} | 37.3379               |
| $k_6$ / min\textsuperscript{-1}                 | 2.1 \times 10\textsuperscript{-2} | 4.87739 \times 10\textsuperscript{-9} |
| $k_{-6}$ / M\textsuperscript{-1}                | 7.03902              | 2.72282 \times 10\textsuperscript{10} |
| $k_7$ / min\textsuperscript{-1}                 | 2.09886 \times 10\textsuperscript{7} | 1.89886 \times 10\textsuperscript{7} |
| $k_{-7}$ / M\textsuperscript{-1}                | 100054               | 37.3379               |
| $k_8$ / min\textsuperscript{-1}                 | 2.1                  | 4.87739 \times 10\textsuperscript{-9} |
| $k_{-8}$ / M\textsuperscript{-1}                | 1.32026 \times 10\textsuperscript{-5} | 4.39741 \times 10\textsuperscript{8} |
| $k_9$ / min\textsuperscript{-1}                 | 60.9146              | 1.10427               |
| $k_{10}$ / M\textsuperscript{-1}                | 7.26293 \times 10\textsuperscript{-1} | 1.32329               |

Provided COPASI models: “All diastereomers (case 1).cps” and “All diastereomers (case 2).cps”
6. Kinetic modelling of Scheme 2 with a completely enantiospecific catalyst in the final step

Even with a catalyst completely enantiospecific in the second step, we can produce a nonlinear effect, but only under the major-minor kinetic scenario where II(\textit{RR}) is the major intermediate and 4(\textit{SSSS}) is the major product (Figure S6, Table S4).

![Diagram](image)

\textbf{Figure S6.} Nonlinear effect observed when formation of 4 from intermediate II is completely enantiospecific.

\textbf{Table S4.} Parameters used for the modelling of Figure S6 considering \([1]_0 = 0.125 \text{ M} \) and \([2]_0 = 0.250 \text{ M} \).

| Parameter | Value |
|-----------|-------|
| \(k_1 / \text{M}^2 \text{ min}^{-1}\) | 4.36707 |
| \(k_{-1} / \text{min}^{-1}\) | 9.08032 |
| \(k_2 / \text{M}^2 \text{ min}^{-1}\) | 26.6285 |
| \(k_{-2} / \text{min}^{-1}\) | 55.3678 |
| \(k_3 / \text{min}^{-1}\) | 26.6285 |
| \(\alpha\) | 0.1631 |
| \(\text{ee}^\text{catalyst}\) | 1.0 |

Provided COPASI models: “Scheme 2 Enantiospecific second step.cps”

7. Kinetic modelling of Scheme 2 with an uncatalyzed final step

Even with an uncatalyzed second step, we can produce a nonlinear effect, but only under the lock-and-key kinetic scenario where II(\textit{SS}) is the major intermediate and 4(\textit{SSSS}) is the major product (Figure S7, Table S5).

![Diagram](image)

\textbf{Figure S7.} Nonlinear effect observed when formation of 4 from II is uncatalyzed.
Table S5. Parameters used for the modelling of Figure S7 considering $[1]_0 = 0.125$ M and $[2]_0 = 0.250$ M.

| Parameter   | Value     |
|-------------|-----------|
| $k_1 / M^2 \text{ min}^{-1}$ | 9.00123   |
| $k_{-1} / \text{ min}^{-1}$  | 18.6217   |
| $k_2 / M^2 \text{ min}^{-1}$ | 0.149642  |
| $k_{-2} / \text{ min}^{-1}$  | 0.309579  |
| $k_3 / \text{ min}^{-1}$     | 0.203631  |
| $\alpha$      | 60.1517   |
| $\beta$       | 1         |
| $\varepsilon$ | 0.9       |

Provided COPASI models: “Scheme 2 Uncatalyzed second step.cps”

8. Measurement of the order in catalyst for Scheme 2

To measure the order in catalyst for the reaction network shown in Scheme 2 we used time normalised analysis\(^3\) on reaction profiles generated in COPASI. We used the reaction conditions used in the experimental kinetic studies reported in the supporting information of Ref. 2 (page S65). Using these conditions, we measured an order of 1 in catalyst (Figure S8).

Figure S8. Order in catalyst is 1 for the reaction presented in Scheme 2.
We also derived the order in catalyst expected from the reaction pathway shown in Scheme 2:

Rate of formation of 4:

\[ r_4 = (k_3[3^+] + k_4[3^-])[[II(SS)] + (k_5[3^+] + k_6[3^-])[[II(RR)] \]  

(2)

Steady-state approximation for II(SS):

\[ (k_1[3^+] + k_2[3^-])[1][2] - (k_{-1}[3^+] + k_{-2}[3^-] + k_3[3^+] + k_4[3^-])[[II(SS)] \approx 0 \]  

(4)

Steady-state approximation for II(RR):

\[ (k_3[3^+] + k_4[3^-])[1][2] - (k_{-1}[3^+] + k_{-2}[3^-] + k_5[3^+] + k_6[3^-])[[II(RR)] \approx 0 \]  

(5)

From equations (2), (4), and (5) we derive the rate of formation of 4 in terms of 1 and 2:

\[ r_4 = [1][2][\frac{(k_1[3^+] + k_2[3^-])(k_3[3^+] + k_4[3^-])}{[3^+](k_{-1} + k_1) + [3^-](k_{-2} + k_1)} + \frac{(k_3[3^+] + k_4[3^-])(k_5[3^+] + k_6[3^-])}{[3^+](k_{-1} + k_2) + [3^-](k_{-2} + k_2)} \]  

(23)

Mass Balance of 3:

\[ [3] = [3^+] + [3^-] \]  

(24)

Enantiomeric ratio of catalyst 3:

\[ e_{r3} = \frac{[3^+]}{[3^-]} \]  

(9)

From equations (9), (24), and (23):

\[ r_4 = a[3]; \text{ where } a = \frac{[1][2][k_1+k_2 sve_k_a + k_3 + k_4 sve_a] + k_5 sve_k_a (k_1 + k_2) + k_6 sve_k_a (k_1 + k_2) + k_3 sve_k_a (k_1 + k_2) + k_4 sve_k_a (k_1 + k_2) + k_1 (k_3 + sve_k_a - enk_a) + sve_k_a}{(k_{-1} + sve_k_a + k_1) + (k_{-2} + sve_k_a + k_2)} \]  

(25)

9. Procedure for the modelling of Figure 5

For both Case 1 and 2, we plotted the ratio of intermediates \([II(RR)]/[II(SS)]\) at the end of each simulated reaction profiles ("Scheme 2 Major-minor (case 1)" and "Scheme 2 Lock and key (case 2)") against the \(ee\) of the catalyst \((ee)\).
10. Kinetic analysis of the mechanism shown in Ref. 2.

We represented the mechanism proposed in Ref. 2 (Figure 5) in Scheme S3. For our kinetic analysis of Scheme S3, we derived the equation for the ee of the product (ee₄) considering the possible formation of all the catalytic species containing two units of the same enantiomer of the catalyst. Following the description of the system in Ref. 2, we have imposed the equilibrium between all the intermediates referred as IV in Ref. 2. We represented the stereoisomeric intermediates IVₛₛ, IVₛᵣ, and IVᵣᵣ (from Ref. 2) as SS₃ dès₃, RR₃ dès₃ and SR₃ dès₃.

We used the following definitions and considered that IV is fully equilibrated in our derivation of the ee of the product (ee₄):

Enantiomeric excess of product 4:

\[
\text{ee}_4 = \frac{[4(\\text{SSSS})] - [4(\\text{RRRR})]}{[4(\\text{SSSS})] + [4(\\text{RRRR})]} \tag{10}
\]

Rate of formation of 4(SSSS):

\[
r_{4(\\text{SSSS})} = k_1[SS - 3^s3^s] + k_2[SS - 3^d3^d] \tag{26}
\]

Rate of formation of 4(RRRR):

\[
r_{4(\\text{RRRR})} = k_1[RR - 3^d3^d] + k_2[RR - 3^d3^s] \tag{27}
\]

Equilibrium of formation of SS₃ dès₃:

\[
K_1 = \frac{[SS - 3^s3^s]_{eq}}{[II(\\text{SS})]_{eq}(3^s)^2} \tag{28}
\]

Equilibrium of formation of SS₃ dès₃:

\[
K_2 = \frac{[SS - 3^d3^d]_{eq}}{[II(\\text{SS})]_{eq}(3^d)^2} \tag{29}
\]

Equilibrium of formation of RR₃ dès₃:

\[
K_1 = \frac{[RR - 3^d3^d]_{eq}}{[II(\\text{RR})]_{eq}(3^d)^2} \tag{30}
\]
Equilibrium of formation of \( RR - 3^3 S \):
\[
K_1 = \frac{[RR - 3^3 S]_{eq}}{[II(RR)]_{eq}[3^3 S]^2} \tag{31}
\]

Equilibrium of formation of catalytic intermediates leading to diastereomeric products \( SR - 3^3 S \):
\[
K_3 = \frac{[SR - 3^3 S]_{eq}}{[II(SR)]_{eq}[3^3 S]^2} \tag{32}
\]

Equilibrium of formation of catalytic intermediates leading to diastereomeric products \( RS - 3^3 S \):
\[
K_3 = \frac{[RS - 3^3 S]_{eq}}{[II(RS)]_{eq}[3^3 S]^2} \tag{33}
\]

Mass balance for the catalyst 3:
\[
[3]_r = [3^3]_r + [3^6]_r \tag{34}
\]

Mass balance for the catalyst 3^6:
\[
[3^6]_r = [3^3]_r + 2 [SS - 3^3 S]_{eq} + 2 [RR - 3^3 S]_{eq} + 2 [SR - 3^3 S]_{eq} \tag{35}
\]

Mass balance for the catalyst 3^6:
\[
[3^6]_r = [3^6]_r + 2 [SS - 3^6 S]_{eq} + 2 [RR - 3^6 S]_{eq} + 2 [RS - 3^6 S]_{eq} \tag{36}
\]

Enantiomeric excess of catalyst 3:
\[
\varepsilon = \frac{[3^3]_r - [3^6]_r}{[3^3]_r + [3^6]_r} \tag{37}
\]

II(SS) and II(RR) are enantiomers, therefore: \([II(SS)]_{eq} = [II(RR)]_{eq}\) \tag{38}

II(SR) and II(RS) are enantiomers, therefore: \([II(RS)]_{eq} = [II(SR)]_{eq}\) \tag{39}

From equations (10) and (26-31):
\[
\varepsilon = \frac{k_1[SS - 3^3 S] + k_2[SS - 3^6 S] - k_1[RR - 3^3 S] - k_2[RR - 3^6 S]}{k_1[SS - 3^3 S] + k_2[SS - 3^6 S] + k_1[RR - 3^3 S] + k_2[RR - 3^6 S]}
\]

\[
\varepsilon = \frac{k_1K_1[III(SS)]_{eq}[3^3 S]^2 + k_2K_2[III(SS)]_{eq}[3^6 S]^2 - k_1K_1[III(RR)]_{eq}[3^3 S]^2 - k_2K_2[III(RR)]_{eq}[3^6 S]^2}{k_1K_1[III(SS)]_{eq}[3^3 S]^2 + k_2K_2[III(SS)]_{eq}[3^6 S]^2 + k_1K_1[III(RR)]_{eq}[3^3 S]^2 + k_2K_2[III(RR)]_{eq}[3^6 S]^2}
\]

\[
\varepsilon = k_1K_1[3^3 S]^2 + k_2K_2[3^6 S]^2 - k_1K_1[3^3 S]^2 - k_2K_2[3^6 S]^2
\]

\[
\varepsilon = \frac{k_1K_1[3^3 S]^2 + k_2K_2[3^6 S]^2}{k_1K_1 + k_2K_2}
\]

\[
\varepsilon = \frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2}
\]

From equation (41) we derive the \( ee \) when using enantiomerically pure catalyst 3^3:
\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^3]^2}{[3^3]^2 + [3^6]^2}
\]

\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^6]^2}{[3^3]^2 + [3^6]^2}
\]

\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^3]^2}{[3^3]^2 + [3^6]^2}
\]

\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^3]^2 - [3^6]^2}{[3^3]^2 + [3^6]^2}
\]

\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^3]^2 - [3^6]^2}{[3^3]^2 + [3^6]^2}
\]

\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^3]^2 - [3^6]^2}{[3^3]^2 + [3^6]^2}
\]

\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^3]^2 - [3^6]^2}{[3^3]^2 + [3^6]^2}
\]

\[
\frac{k_1K_1 - k_2K_2}{k_1K_1 + k_2K_2} = \frac{[3^3]^2 - [3^6]^2}{[3^3]^2 + [3^6]^2}
\]
From equations (28), (31), (32) and (35):
\[ (2 K_1 [II(SS)]_{eq} + 2 K_2 [II(RR)]_{eq} + 2 K_3 [II(SR)]_{eq}) [3^2] + [3^2]_{T} = 0 \]
\[ [3^2] = \frac{2 [3]^T}{1 + \sqrt{1 + 4 [2 K_1 [II(SS)]_{eq} + 2 K_2 [II(RR)]_{eq} + 2 K_3 [II(SR)]_{eq}]} [3^2]_{T} \]  
(44)

From equations (29), (30), (33) and (36):
\[ (2 K_1 [II(SS)]_{eq} + 2 K_2 [II(RR)]_{eq} + 2 K_3 [III(RS)]_{eq}) [3^2] + [3^2]_{T} = 0 \]
\[ [3^2] = \frac{2 [3]^T}{1 + \sqrt{1 + 4 [2 K_1 [II(SS)]_{eq} + 2 K_2 [II(RR)]_{eq} + 2 K_3 [III(RS)]_{eq}]} [3^2]_{T} \]  
(45)

From equations (34) and (37):
\[ [3^2]_{T} = \frac{(1 + ee_3) [3]^T}{2} \]  
(46)
\[ [3^2]_{T} = \frac{(1 - ee_3) [3]^T}{2} \]  
(47)

From equations (38), (44) and (46):
\[ [3^2] = \frac{(1 + ee_3) [3]^T}{1 + \sqrt{1 + 2 a [3]^T} (1 + ee_3)} \] where \( a = 2 (K_1 + K_2) [II(SS)]_{eq} + 2 K_3 [II(RR)]_{eq} \)  
(48)

From equations (38), (39), (45) and (47):
\[ [3^2] = \frac{(1 - ee_3) [3]^T}{1 + \sqrt{1 + 2 a [3]^T} (1 - ee_3)} \] where \( a = 2 (K_1 + K_2) [II(SS)]_{eq} + 2 K_3 [II(RR)]_{eq} \)  
(49)

From equations (43), (48) and (49):
\[ ee_4 = \frac{(1 + ee_3)^2 (1 + \sqrt{1 + 2 a [3]^T} (1 - ee_3))^2 - (1 - ee_3)^2 (1 + \sqrt{1 + 2 a [3]^T} (1 + ee_3))^2}{(1 + ee_3)^2 (1 + \sqrt{1 + 2 a [3]^T} (1 - ee_3))^2 + (1 - ee_3)^2 (1 + \sqrt{1 + 2 a [3]^T} (1 + ee_3))^2} ee_4^{ep} \]
where \( a = 2 (K_1 + K_2) [II(SS)]_{eq} + 2 K_3 [II(RR)]_{eq} \)  
(50)

From equations (48) and (49) the fraction of catalyst as a monomer is:
\[ f_{mono} = \frac{[3^2] + [3^4]}{[3]^T} = \frac{1}{2} a [3]^T (1 + ee_3) + \sqrt{1 + 2 a [3]^T (1 - ee_3)} - 2 \]  
where \( a = 2 (K_1 + K_2) [II(SS)]_{eq} + 2 K_3 [II(RR)]_{eq} \)  
(51)

From equations (50) and (51), in the limiting case when \( b \) trends to zero:
\[ b = 2 (K_1 + K_2) [II(SS)]_{eq} + 2 K_3 [II(RR)]_{eq} [3]^T \]
\[ \lim_{b \to 0} ee_4 = \lim_{b \to 0} \frac{(1 + ee_3)^2 (1 + \sqrt{1 + b (1 - ee_3)})^2 - (1 - ee_3)^2 (1 + \sqrt{1 + b (1 + ee_3)})^2}{(1 + ee_3)^2 (1 + \sqrt{1 + b (1 - ee_3)})^2 + (1 - ee_3)^2 (1 + \sqrt{1 + b (1 + ee_3)})^2} ee_4^{ep} = \frac{2 ee_4}{1 + ee_3^2} ee_4^{ep} \]
\[ \lim_{b \to 0} f_{mono} = \lim_{b \to 0} \frac{1}{b} (1 + ee_3) + \sqrt{1 + b (1 - ee_3)} - 2 = 1 \]

From equations (50) and (51), in the limiting case when \( b \) trends to infinity:
\[ b = 2 (K_1 + K_2) [II(SS)]_{eq} + 2 K_3 [II(RR)]_{eq} [3]^T \]
\[ \lim_{b \to \infty} ee_4 = \lim_{b \to \infty} \frac{(1 + ee_3)^2 (1 + \sqrt{1 + b (1 - ee_3)})^2 - (1 - ee_3)^2 (1 + \sqrt{1 + b (1 + ee_3)})^2}{(1 + ee_3)^2 (1 + \sqrt{1 + b (1 - ee_3)})^2 + (1 - ee_3)^2 (1 + \sqrt{1 + b (1 + ee_3)})^2} ee_4^{ep} = ee_3 ee_4^{ep} \]
\[ \lim_{b \to \infty} f_{mono} = \lim_{b \to \infty} \frac{1}{b} (1 + ee_3) + \sqrt{1 + b (1 - ee_3)} - 2 = 0 \]
11. References

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