Extended Curriculum Vitae

Summary

I. CV

Yannick Geiger
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33 years old
French, German

ORCID: 0000-0003-2280-7107
ResearcherID: AAX-4059-2020

Education

2016 - 2019 **PhD in Chemistry,** Institut de Physique et Chimie des Matériaux de Strasbourg (IPCMS), University of Strasbourg (France). Under supervision of Dr. Stéphane Bellemin-Laponnaz.
"Excellent" for the performance in oral, written, discussion and for the scientific level.

2014 - 2016 **M. Sc.**, Faculty of Chemistry, University of Strasbourg (France).
Molecular & Supramolecular Chemistry, grade 15.9/20, ranked 3/26.
Includes 3 months of internship with Dr. Aidan McDonald at Trinity College Dublin, Ireland.

2011 - 2014 **B. Sc.**, Faculty of Chemistry, University of Strasbourg (France).
Chemistry "international profile", grade 15.2/20, ranked 2/70.
Including one semester at Laval University, Québec (QC), Canada.

2010 **Abitur** (German A-levels), Liebigschule, Frankfurt am Main (Germany).
1.0/6, ranked 2/65. German A-levels, specialities mathematics and biology.

Professional experience

Starting 1/12/2024 **Assistant Professor** (tenure-track, *Chaire de Professeur Junior*), Chemistry of Complex Matter (UMR 7140)/Faculty of Chemistry, University of Strasbourg (France).

2024 11 months **Post-doctoral fellow,** Institut de Science et d'Ingénierie Supramoléculaires (ISIS), University of Strasbourg (France), with Prof. Joseph Moran.
Work on prebiotic reaction networks.

2021 - 2023 3 years **Post-doctoral fellow,** Stratingh Institute for Chemistry, University of Groningen (Netherlands), with Prof. Sijbren Otto.
Study of the transition of chemistry to biology: structural analysis and influence of chirality in self-replicating supramolecular assemblies.

2019 - 2020 12 months **Post-doctoral fellow (continuation of PhD),** Institut de Physique et Chimie des Matériaux de Strasbourg (IPCMS), University of Strasbourg (France), with Dr. Stéphane Bellemin-Laponnaz.
Study of non-linear effects in asymmetric catalysis, sum-frequency generation in non-linear optics.

2013 - 2016 2-5 months **Research Internships (Master & Bachelor):**
DMO – IPCMS (Strasbourg), Dr. Stéphane Bellemin-Laponnaz.
Organic/Inorganic synthesis & analysis, recyclable asymmetric catalysis; 5 months

BIC – Trinity College Dublin (Ireland), Prof. Aidan McDonald.
Organic/Inorganic synthesis & analysis, spectroscopic studies (UV-vis, MS, EPR); 3 months
CLAC & LASYROC – Institut de Chimie de Strasbourg, Dr. S. Dagorne & Pr. J.-M. Weibel.
Organic/Inorganic synthesis & analysis, catalysis, polymerisation; 2+2 months.

2010 - 2011
9 months

Civic service, *StadtWaldHaus,* Francfort-sur-le-Main (Allemagne).
Guided visits for children about forest flora & fauna, ecology and biodiversity.

Awards & Grants

2020

Post-doctoral grant, oLife programme (website), Horizon 2020 Marie Skłodowska-Curie Action cofund (European Union)
Three years post-doc funding with Prof. Sijbren Otto (Groningen, Netherlands).

2020

PhD award "Henri Kagan" 2020, French Chemical Society, Organic Chemistry Division (SCF, DCO). *Link to the webpage of the DCO.*

2019

Post-doctoral grant, Labex NIE, 25 000€.
Partial funding of the post-doc at IPCMS (Strasbourg, France).

2016

PhD grant, French Ministry of Higher Education & Research, 90 000€ over 3 years.

2023 & 2017

Scholarships, attendance fee allowances for conference participation.
- SCF 2023 Congress, 26-28 July 2023, Nantes (France). *320€ from the French Chemical Society.*
- Summer School – Catalysis and Organometallic Synthesis, 24-28 July 2017, Würzburg (Germany). *300€ from the organizers.*

2015 & 2013

International mobility grants for stays in Québec and Dublin: Erasmus Internship *(European Commission)*; Boussole Grant, 2x *(Alsace Region)*; Unistra Grant *(University of Strasbourg)*.

Engagements & Responsibilities

2018-2022

Congress & Events organization
- Main organizer of **Interdisciplinary Origins of Life 2024 (IOoL24)** in Strasbourg, conference for early-career researchers. *Raising funds, preparation, communication.*
- Lorentz Workshop "Out-of-equilibrium Systems, Emergence, and Life", seminar over 3 days for the setup of future research agendas and frameworks. *Participation, report writing.*
- oLife lectures & on-site days, lecture days and museum excursion for post-docs.
- oLife Annual Meeting 2022, international conference (80 participants).
Preparation, communication, invitation of speakers, gathering & selecting abstracts, evening activities, contact for invited speakers and participants.
- PhD students' congress 2018, Doctoral School for Physics and Physical Chemistry, University of Strasbourg. *Moderation of panel discussion, preparation, oral communications selection, reception of an invited speaker (Prof. Philippe Buffat, EPFL, Lausanne, Switzerland).*

2015 - 2017

Student representative, Council of the Faculty of Chemistry, University of Strasbourg.
Taking part in meetings, collection and report of students' opinions on the faculty's teaching

offer, participation in the development of the 2018-2023 curriculum.

2011 - 2014 Active member of **ALCANES** (chemistry student's association in Strasbourg), including **Vice-president in charge of past papers** for the 2012-2013 academic year, Faculty of Chemistry, University of Strasbourg.
Bartending in the Faculty's cafeteria, organisation of events (welcome week for new students, memorial events, social evenings, annual chemistry football tournament); Collection & distribution of past exams, participation in regular board meetings.

Teaching & Supervision

2016-2023 **Teaching assistant**, *University of Groningen:* lecture "Chirality & Life" for Honours Bachelor Programme. *University of Strasbourg:* lecture on non-linear effects, inorganic chemistry (practicals & tutorial courses), chemistry basics (tutorial courses), training for job applications (CV, ML, job interviews), mentoring students in professional internships. *Total of 225 h.*

2018 - 2019 **Student supervision**, IPCMS, University of Strasbourg (group of Dr. Bellemin-Laponnaz).
Jordan Parmentier (Master student): 3 months; Gaston Muller, Laurie Balaguero (Bachelor students): 2 months each. Teaching organic/inorganic synthesis, asymmetric catalysis, NMR & GC analysis, internship report writing.

2015 **Student mentoring**, Faculty of Chemistry, University of Strasbourg.
Support course in organic chemistry to ca. 25 Bachelor students; organised by ALCANES.

Skills

Organic & Organometallic chemistry: synthesis, purification and identification of organic and organometallic compounds (complexes & metallopolymers of Ni, Cu, Zn), under inert atmosphere (Schlenck line and glovebox) in cryostat under liquid nitrogen.

Homogeneous catalysis: catalysed polymerisation, enantioselective catalysis, supramolecular catalysis.

Analytical instrumentation: NMR (1D, 2D, DOSY), IR (includes monitoring by ReactIR), MS (ESI-TOF, MALDI-TOF), UV-Vis, CD, EPR, DLS, freezing point osmometry, GC & HPLC with chiral stationary phase, separation of complex mixtures in RP-UPLC(-MS), treatment and analysis of electronic microscopy micrographs (TEM).

Analytical methodology: Hammet & Eyring plots, Kamlet-Taft treatment, metallopolymer titration in UV-vis, external calibration curves in DOSY NMR, spectrum deconvolution in UV-Vis and quantitative MS, non-linear effects in asymmetric catalysis (NLE), kinetic analysis via VTNA.

Data treatment & modelling: mathematical modelling of catalytic systems (NLE, Eyring plots); simulation of rate profiles by ordinary differential equations (ODE) curve fitting, treatment & integration of spectra and chromatograms (Matlab, Origin and Berkeley Madonna software).

Non-linear optics: sum-frequency generation on films, theoretical & experimental.

Chemistry & Office software: databases (SciFinder, Reaxys, CCDC); drawing and handling of molecules in 2D and 3D (ChemDraw, Chem3D, Mercury, Avogadro); Zotero, Microsoft Word, Excel and Powerpoint.

Languages: fluid in German, French, English; some Dutch (A2 level in the Common European Famework of Reference).

Other skills: teamwork, project management, organisation, writing, communication, mentoring, didactics.

Other interests

Athletics (sprint, long jump, discus throw; local competitions), climbing, cycling & hiking, cinema, cooking.
Member of **Décibulles** (organisation of a yearly music festival; trash collection & toilet cleaning).

II. Peer review activity, publications and conference communications

Peer review activity

Scientific manuscript evaluation

- *Origins of Life and Evolution of the Biosphere*, 1x **2022**, Springer-Nature,
- *Molecules*, 2x **2023**, MDPI,
- *International Journal of Molecular Sciences*, 2x **2024**, MDPI.

- With Joseph Moran:
  Chemical Communications 1x **2024**, RSC,
  Angewandte Chemie International Edition 1x **2024**, Wiley-VCH.

Grant proposal evaluation

- *National Science Centre, Poland (NCN)*, **2022**.

Publications

Blokhuis, A.; Geiger, Y.; Otto, S.*
When aggregation becomes the norm: interpreting experiments beyond their molecules
Manuscript in preparation.

Geiger, Y.*; Otto, S.*
Escaping product inhibition: the key to exponential self-replication
Manuscript in preparation.

12) Eleveld, M. J.; Geiger, Y.[+]; Wu, J.[+]; Kiani, A.; Schaeffer, G.; Otto, S.*
Competitive Exclusion among Self-Replicating Molecules Curtails the Tendency of Chemistry to Diversify
Nat. Chem. **2024***, ahead of print.* DOI: 10.1038/s41557-024-01664-0. Read-only link: https://rdcu.be/d1S5C
Highlighted in:

- phys.org

11) Thierry, T.[+]; Geiger, Y.[+]; Bellemin-Laponnaz S.*
Divergence of catalytic systems in the zinc-catalysed alkylation of benzaldehyde mediated by chiral proline-

based ligands
Nat. Synth. **2024**, *3*, 615. DOI: 10.1038/s44160-024-00491-y; free read-only link: https://rdcu.be/dAAg7
Highlighted in:

- INC website (National Institute of Chemistry, CNRS)

10) Thierry, T.; Frey, J.; Geiger, Y.; Bellemin-Laponnaz, S.*
Les effets non linéaires en catalyse asymétrique.
Act. Chim. **2024***, 491,* 40*. Tutorial review on non-linear effects for a broad scientific audience. Preprint on HAL: hal-04218082.*

9) Yang, S.[+]; Geiger, Y.[+], Geerts, M.; Eleveld, M. J.; Kiani, A.; Otto, S.*
Enantioselective Self-Replicators
J. Am. Chem. Soc. **2023**, *145,* 16889. DOI: 10.1021/jacs.3c05472

8) Thierry, T.; Geiger, Y.; Bellemin-Laponnaz, S.*
Observation of Hyperpositive Non-Linear Effect in Asymmetric Organozinc Alkylation in Presence of N-Pyrrolidinyl Norephedrine
Molecules **2022**, *12*, 3780. DOI: 10.3390/molecules27123780

7) Geiger, Y.; Bellemin-Laponnaz, S.*
Non-Linear Effects in Asymmetric Catalysis: Impact of Catalyst Precipitation
ChemCatChem **2022**, *14*, e202200165. DOI: 10.1002/cctc.202200165

6) Geiger, Y.*
One Soai reaction, two mechanisms?
Chem. Soc. Rev. **2022**, *51*, 1206. DOI: 10.1039/D1CS01038G

5) Geiger, Y.; Achard, T.; Maisse-François, A.; Bellemin-Laponnaz, S.*
Absence of non-linear effects in presence of aggregates in asymmetric catalysis
Eur. J. Org. Chem. (special issue) **2021**, *2021*, 2916. DOI: 10.1002/ejoc.202100183

- **Cover artwork** selected for EurJOC issue 21.
- Upon invitation as part of the Kagan 2020 PhD prize.

4) Geiger, Y.; Achard, T.; Maisse-François, A.; Bellemin-Laponnaz, S.*
Hyperpositive non-linear effects: enantiodivergence and modelling.
Chem. Sci. **2020**, *46*, 12453. DOI: 10.1039/D0SC04724D

- *Chemical Science* **Pick of the week** & **Hot Article**, highlighted on Twitter (1,2) & Facebook (1,2),
- Highlighted in *Nature Reviews Chemistry* **2020**, *4*, 635. DOI: 10.1038/s41570-020-00236-3

3) Geiger, Y.; Achard, T.; Maisse-François, A.; Bellemin-Laponnaz, S.*
Observation of hyperpositive non-linear effect in catalytic asymmetric organozinc additions to aldehydes.
Chirality (special issue) **2020***, 32*, 1250. DOI: 10.1002/chir.23271

2) Geiger, Y.; Achard, T.; Maisse-François, A.; Bellemin-Laponnaz, S.*
Hyperpositive non-linear effects in asymmetric catalysis.
Nat. Cat. **2020**, *3*, 422. DOI: 10.1038/s41929-020-0441-1
Highlighted in:

- Nature Chemistry Facebook page,
- Chemistry World,
- University of Strasbourg website,
- INC website (National Institute of Chemistry, CNRS).

1) Bellemin-Laponnaz, S.*; Achard, T.; Bissessar, D.; Geiger, Y.; Maisse-François, A.
Synthesis and Application of Dynamic Self-Supported Enantioselective Catalysts.
Coord. Chem. Rev. **2017**, *332*, 38. DOI: 10.1016/j.ccr.2016.10.005

[+]Both authors contributed equally.

Conference communications

Plenary lecture (30 min)

Towards *de novo* life

- **International Symposium on Living Systems Materialogy**, 05-06 August 2023, Tokyo (Japan), *50 participants*. Upon invitation, in replacement for Sijbren Otto who was unavailable for the talk.

Oral communications (15-25 min):

Competitive exclusion in self-replicating fibres

- **Journée SCF Alsace**, 08 March 2024, Strasbourg (France), *150 participants.*

Systems Mechanisms - enantioselection and competitive exclusion in self-replicators

- **Origins of Life Donostia Meeting 2023**, 02-04 October 2023, Donostia-San Sebastián (Spain), *95 participants*.

Towards designed asymmetric autocatalysts

- **Chirality 2023**, 24-27 July 2023, Rome (Italy), *400 participants*.

Escaping product inhibition: the key to exponential self-replication

- **SCF 2023 Congress**, 26-28 June 2023, Nantes (France), *400 participants*.
- **Origins Center Conference 2023**, 12-13 April 2023, Groningen (Netherlands), *80 participants*.

Chiral selective self-replicators

- **oLife Annual Meeting 2022**, 02-04 November 2022, Groningen (Netherlands), *80 participants*.
- **oLife Annual Meeting 2021**, 11-12 November 2021, Groningen (Netherlands), *50 participants*.

Hyperpositive non-linear effects in asymmetric catalysis

- **Autumn meeting of the Organic Chemistry Division (DCO) 2021**, French Chemical Society, 01 December 2021, Paris, *80 participants.* Upon invitation as part of the Henri Kagan 2020 PhD award.
- **Barrande-Vltava French-Czech Chemistry Meetings 2019**, 2-3 September 2019, Prague (Czech Republic), *50 participants*.
- **Chirality 2019**, 14-17 July 2019, Bordeaux (France), *>250 participants*.

Poster presentation:

Competitive exclusion in self-replicating fibres (+ 5 min flash presentation)

- **Supr@Paris 2024**, 15-17 May 2024, Paris (France), *260 participants.*

Chiral selective self-replicators

- **Chirality 2023**, 24-27 July 2023, Rome (Italy), *300 participants*.
- **SCF 2023 Congress**, 26-28 June 2023, Nantes (France), *400 participants*.
- **Molecular Origins of Life**, 16-17 June 2022, Munich (Germany), *170 participants*.
- **FMS Annual Meeting**, 13 May 2022, Zwolle (Netherlands), *200 participants*.

Hyperpositive non-linear effects in asymmetric catalysis

- **Coordination Chemistry Meeting of the French Chemical Society**, 23-24 January 2020, Marseille (France), *80 participants*.
- **LabEx NIE Meeting**, 13 July 2019, Strasbourg (France), *50 participants*.
- **Solvay Workshop "Chiral symmetry breaking at the molecular level"**, 28-30 November 2018, Brussels (Belgium), *100 participants*.
- **SCF Grand Est Congress**, 11-12 May 2017, Mulhouse (France), *>250 participants*.

Beyond chirality – pushing non-linear effects to the limits

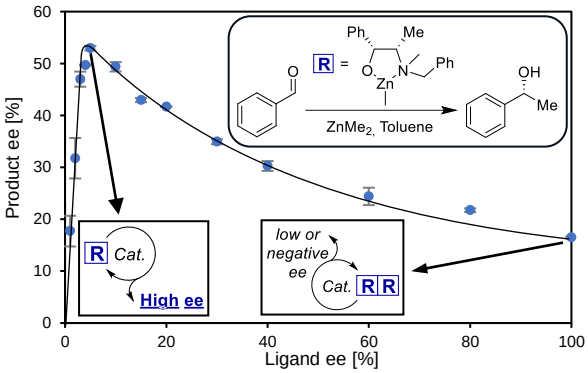
- **Summer School – Catalysis and Organometallic Synthesis**, 24-28 July 2017, Würzburg (Germany), *60 participants*.
- **Symposium "Chirality, Chemistry and Supramolecular Catalysis"**, 2-3 October 2017, Strasbourg (France), *80 participants*.

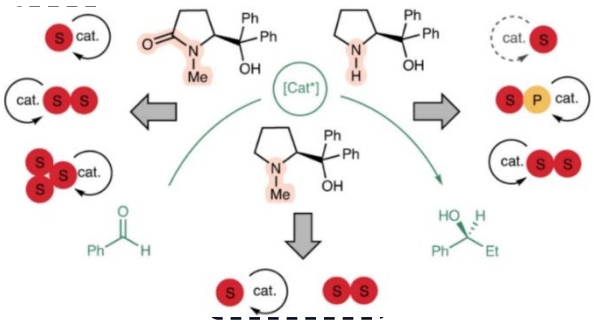
III. Research resumé

I am a physical organic chemist focused on the emergence of phenomena and behaviours caused by molecular aggregation: how to rationalise these and how to use them as tools to understand chemical systems. This encompasses asymmetric (auto)catalysis (non-linear phenomena, asymmetric amplification), supramolecular self-assemblies (emergence of self-replicators, exponential growth, nucleation phenomena), chirality-induced desymmetrization of processes, pseudophase separation of small molecules and how it affects composition and dynamics in reaction networks (Formose reaction, reaction networks of prebiotic relevance).

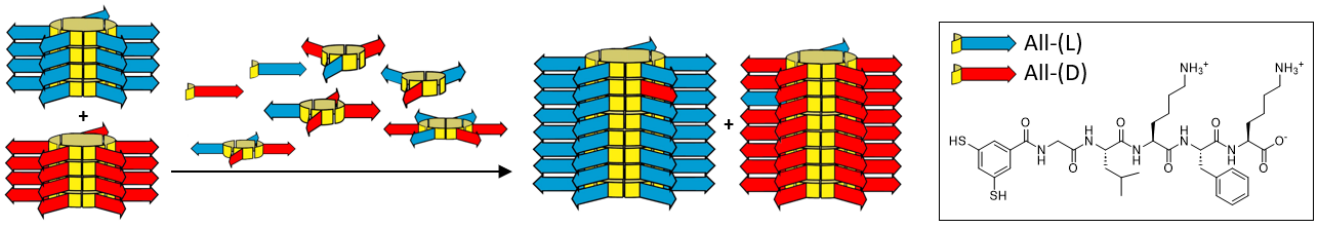
The systems chemistry approach of my work is at the edge between organic and physical chemistry, with a strong emphasis on mechanistic investigations and structure-activity relationships, using instrumental (1D & 2D NMR, IR, UV-vis, GC & HPLC, MS, DLS, Freezing Point Osmometry) and theoretical tools (kinetic analysis & simulations by ordinary differential equations, mathematical modelling).

During my PhD in Strasbourg, my research activities were focused on the study of complex catalytic systems, notably the addition of dialkylzincs to aromatic aldehydes catalysed by chiral aminoalcohols. The discovery of a hyperpositive non-linear effect (NLE; i.e. a scalemic catalyst giving a product with a higher enantiomeric excess than the enantiopure catalyst, cf. figure on the right) led to the conclusion that the catalytic aminoalcohol-alkylzinc complex aggregates and that these aggregates are also catalytically active - with an enantioselectivity that is opposite to that of the monomeric complex, as evidenced by an enantiodivergent NLE (product chirality sign switches upon variation of catalyst ee). This conclusion was supported by catalyst loading studies, kinetics and ^{1}H & DOSY NMR studies; mathematical modelling allowed to reproduce the NLE curves. Further studies were conducted on a system with no NLE even though there is catalyst aggregation and on the impact of catalyst precipitation on NLE curves (theoretical study). In a more recent study, we applied three proline-derived ligands to the same reaction (cf. figure on the left). Although the ligands bear only small structural differences, they were found to generate three totally different catalytic systems, in one case potentially including self-induction (modification of the catalyst by the reaction product) and in another having a catalytically active aggregation level higher than 2, resulting in at least three different catalytically active species generated in situ. This was supported by mathematical modelling of NLE curves and product ee vs. catalyst loading curves.





During my post-doc in Groningen I have worked on self-replicating supramolecular self-assemblies. They consist of peptide building blocks that form macrocycles with various ring sizes, then one of them spontaneously stacks to form fibres which grow exponentially by feeding on the other macrocycles. Self-replication is an essential part of the transition from chemistry to biology. One project was about the influence of the chirality of the peptide building blocks on the resulting fibre: some fibres can incorporate the two enantiomers randomly, while others incorporate only one with high fidelity (cf. figure below). Structural constraints induced by the sequence of the peptide used and by the resulting ring size were found to be at the origin of these phenomena.



Other work focused on understanding the behaviour of two different self-replicating fibres in competition for the same precursors. Kinetic and structural analyses showed that these interact and influence each other's uptake of precursors, leading to the extinction of one of them when subjected to an out-of-equilibrium regime (competitive exclusion). This came unexpected as a mere difference in growth rate would have been sufficient for competitive exclusion to take place, as the replicators on their own grow exponentially. In a separate study, the design principles necessary for self-replicators with exponential growth were assessed via simulations of kinetic profiles.

Related to both the PhD and post-doc was an in-depth analysis of mechanistic proposals for the Soai reaction, an autocatalytic addition of diisopropylzinc to pyrimidyl aldehydes capable of chiral symmetry breaking. An informed comparison showed that both (hotly debated) proposals could be valid and that there may be thus several variants of the Soai reaction.

IV. Extended summaries of past research

IV.1 Post-doc Groningen (self-replicating fibres)

The Otto group in Groningen works on self-replicating systems based on dynamic combinatorial libraries. The systems are made of simple building blocks consisting of an aromatic dithiol headgroup and a short peptide chain (typically 5 units long, cf. Figure 1). These oxidize in aqueous buffer to form cyclic oligomers (trimers, tetramers etc.) which constantly interconvert through disulfide exchange. Usually, one of these macrocycles is able to spontaneously stack to form fibres, which grow by feeding on smaller macrocycles and which hold together through π-π stacking and β-sheets. Mechanical stress (i. e. stirring) leads to fibre breakage and thus to more fibre ends, allowing for exponential growth. Whether these fibres emerge and which macrocycle size stacks depends mostly on the peptide sequence and length, but also the reaction conditions (temperature, buffer concentration, presence of additional salts).
This system is highly relevant for the *de novo* synthesis of life, since exponential self-replication is one of life's key components, but is in many aspects also a black box due to the difficulty to obtain structural information of the fibres. The following studies show how we used indirect methods (reference systems, relative kinetics, doping & food binding experiments, MD simulations and more) to get a better understanding of the fibres' dynamics, structures and inner workings.

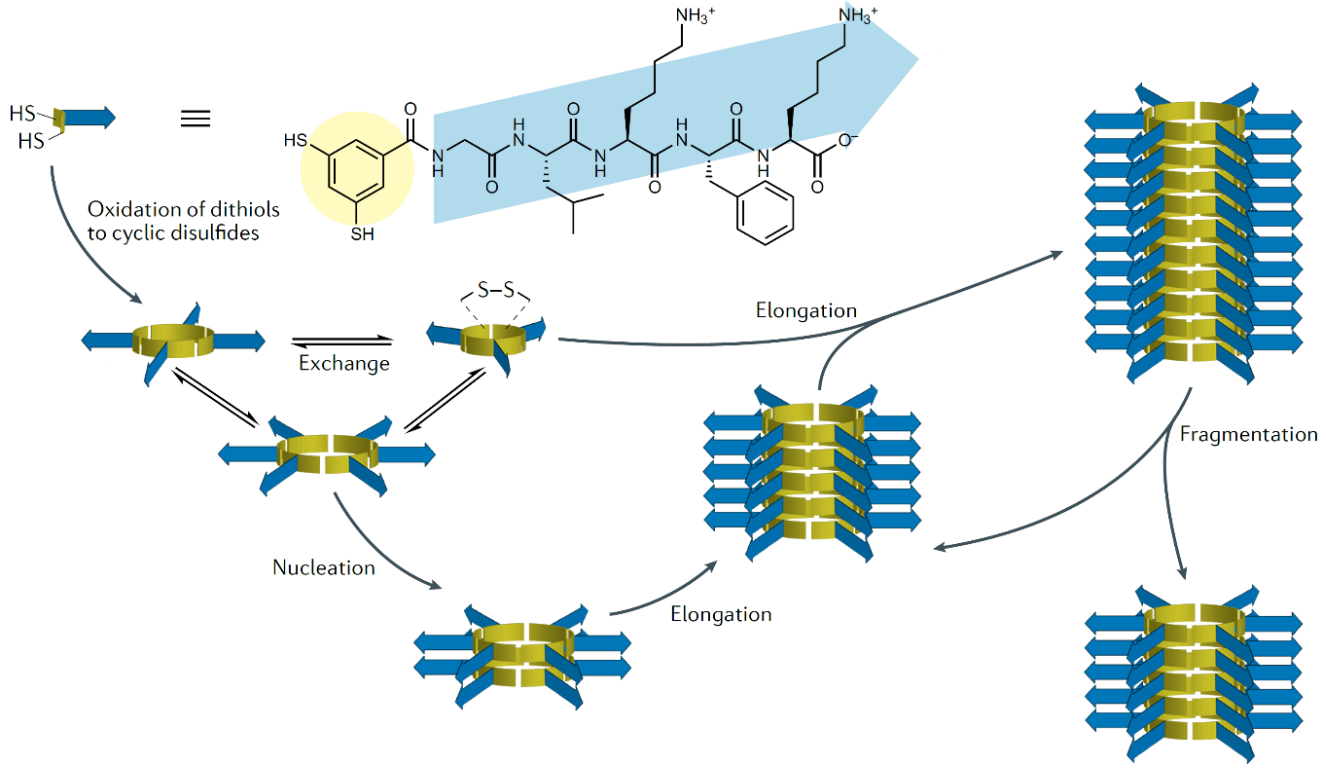


Figure 1. General scheme for the dynamic combinatorial libraries used in the Otto group in Groningen.

Yang, S.[+]; Geiger, Y.[+], Geerts, M. ; Eleveld, M. J.; Kiani, A.; Otto, S.
Enantioselective Selective Self-Replicators
J. Am. Chem. Soc. **2023**, *145,* 16889. DOI: 10.1021/jacs.3c05472

In this work, the influence of building block chirality on the emergence and composition of fibres was investigated. An earlier report shows that replicators made from hexamer macrocycles are chirally unspecific: they emerge & grow also from a racemic mixture of building blocks, giving mixed hexamers of statistical distribution. In contrast, we found pentamer macrocycles made of the same building block to be chiral selective: they don't emerge spontaneously from a racemic mixture and grow, upon seeding, only from same-chirality material – with an accumulated error of only 10% when seeded in racemic material (Figure 2).

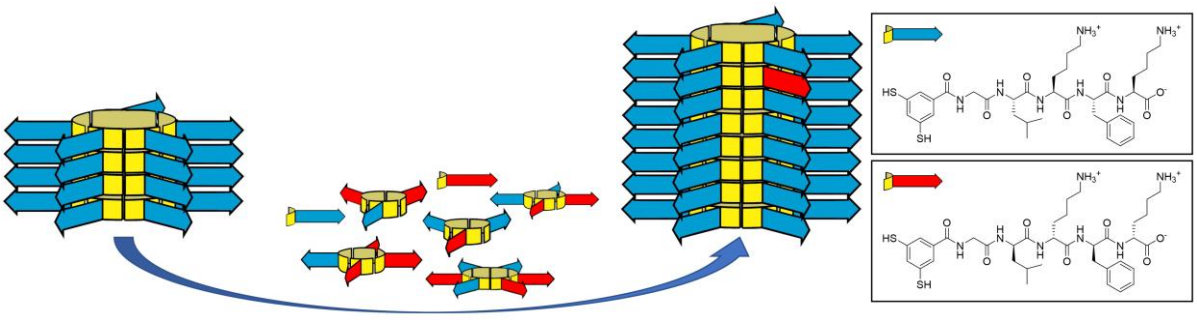


Figure 2. Scheme of enantiopure pentamer fibres that grow with high chiral selectivity (i. e. incorporating only few building blocks of the "wrong" chirality, here ca. 10%) from racemic material.

Two more pentamer replicators with different peptide sequences were also found to be chiral selective. The reason for hexamer and pentamer replicators being different on that matter was investigated via molecular dynamics calculations and comparison with reference systems: the pentamers, being odd-numbered, probably can adopt only a chirality-sensitive conformation ("Cartwheel") that relies on oriented salt bridges, while hexamers can also adopt a more forgiving structure ("Pairwise") which holds together through hydrophobic burial (Figure 3). This was confirmed by studying reference systems consisting of short building blocks (only one amino acid): one that must hold together mainly through salt bridges and thus can adopt only pairwise (and turned out to be chiral selective), and another that can hold together only through hydrophobic burial (and turned out not to be chiral selective).

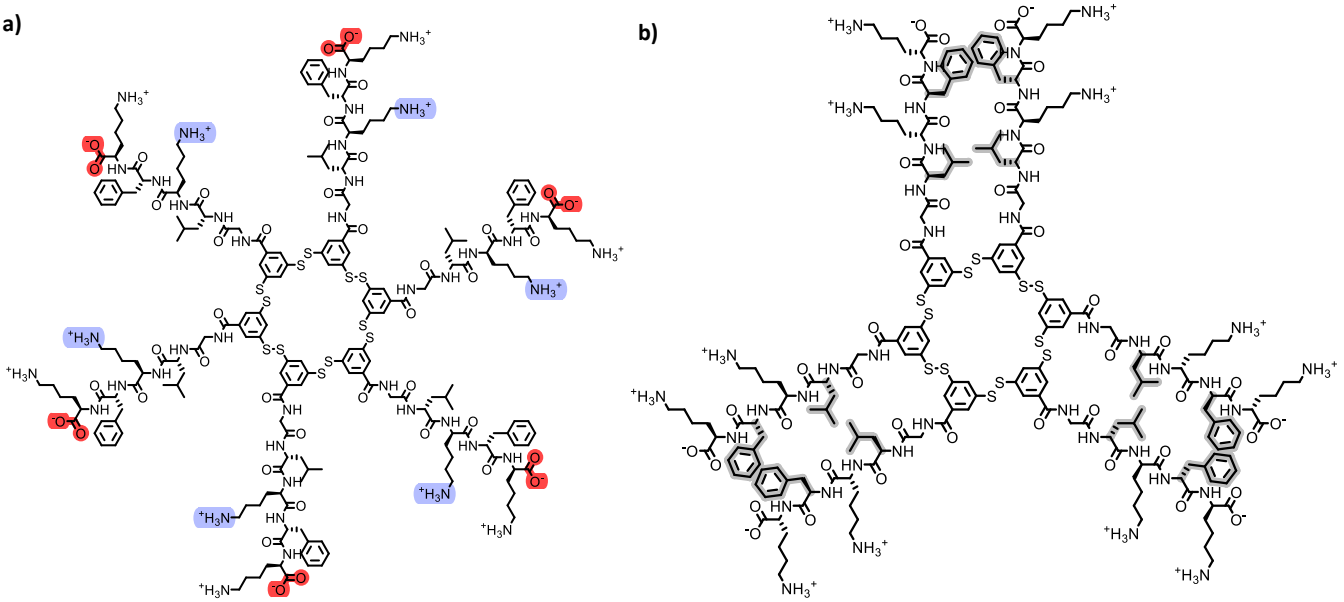


Figure 3. Schemes for different conformation hexamer macrocycles can adopt within fibres. a) Cartwheel conformation; the red and blue highlighted carboxylate and ammonium groups form salt bridges that are at the origin of the chiral specificity of that conformation. b) "Pairwise" conformation, here peptide strands pair up to maximise hydrophobic burial. No orientation-specific interactions are found here.

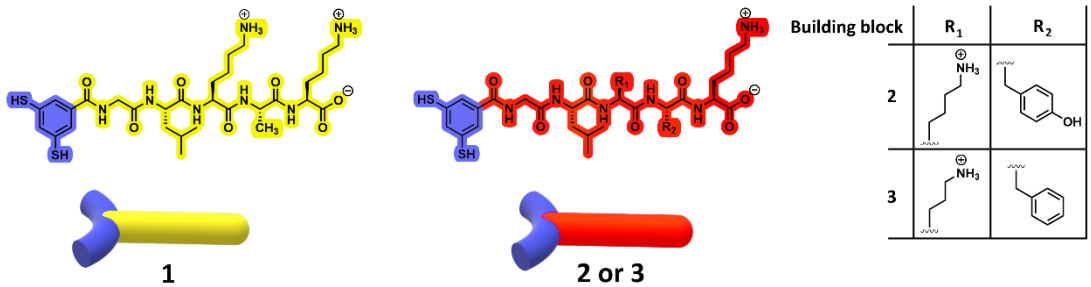
Contribution & impact: Shuo Yang initially found the first enantioselective pentamer replicator and performed preliminary experiments on opposite-handedness incorporation. I repeated and extended all experiments, made the link with pairwise & cartwheel conformations and studied the reference systems.
Enantioselectivity is necessary for the transition from a (close to) racemic world to a homochiral one, and thus is of relevance for the emergence of biological homochirality. Therefore, this study is of significant impact as there has been only a single study on chiral selectivity in replicators by the Ghadiri group. They used systems based on α-helical peptide with a lot of pre-incorporated chiral information: 32 chiral units in the replicator and 14/17 chiral units in the building blocks, achieving only parabolic growth. Our systems have exponential growth and the amount of chiral units was reduced to 20 and 4, respectively (pentamer replicator in Fig. 1) and even to 8 and 1, respectively (for one of the reference systems).

Eleveld, M. J.; Geiger, Y.[+]; Wu, J.[+]; Kiani, A.; Schaeffer, G.; Otto, S.
Competitive Exclusion among Self-Replicating Molecules Curtails the Tendency of Chemistry to Diversify
Nat. Chem. **2024***, ahead of print.* DOI: 10.1038/s41557-024-01664-0. Read-only link: https://rdcu.be/d1S5C

Self-replication being exponential is an important requirement for life since also because it allows for Darwinian evolution. It is a widely known phenomenon in biology that when two species compete for the same food source, the less competitive will die out over time; on the other hand, if they use different resources then both might coexist – one speaks then of environmental "niches". Theoretical studies have shown that holds for replicators in general, also purely chemical ones, as long as there is a mechanism for "death" – i. e. replicators can be destroyed or removed otherwise from the system.

In this study, our group reproduces these two scenarios using the group's self-replicating fibres. Two mixed systems, consisting of either building blocks **1** and **2** (system A) or **1** and **3** (system B) in a 1:1-ratio, give rise to mixed octamer and hexamer replicator fibres (Figure 4a). In system A, both replicators grow by incorporating the two building blocks without any preference. The replicators where subjected to serial transfer experiments: both octamer and hexamer were added into unassembled **1**+**2** "food" ("seeding") and were let to grow until full consumption; 10% were then transferred into fresh **1**+**2** material, effectively discarding 90% of the replicators (which is equivalent to death; Figure 4d). Over several of such repeats, the hexamer in system A completely disappears: it is outcompeted by the octamer (Figure 4e). In system B, the replicators have each a preference for one of the two building block: the octamer fibre incorporates more **1**, the hexamer prefers **3**. This leads to persistence of both replicators over serial transfer (Figure 4e).

a Structure of building blocks



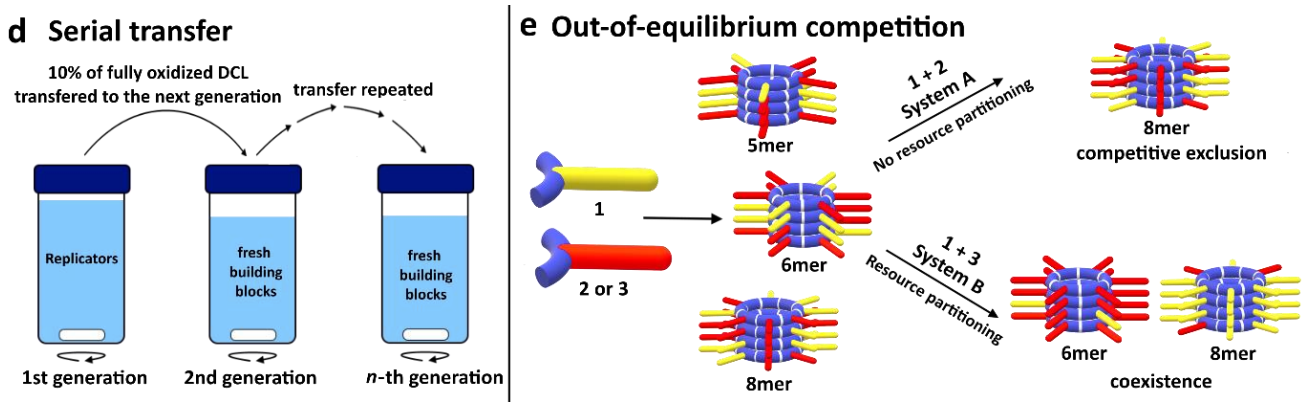


*Figure 4. a) Structure of the building blocks **1**, **2** and **3**. d) Scheme depicting the process of serial transfer, putting the system effectively out of thermodynamic equilibrium. e) The mixed **1+2** and **1+3** systems give rise to 5mer, 6mer and 8mer replicators, that either compete for the same resource and end up with the extinction of the 6mer (system A) or that partition the resources, which allows coexistence of both 6mer and 8mer replicators. 5mer replicators behave here like 6mer, which puts them in concurrence to the 6mer even in system B, where they die out.*

Furthermore, we investigated the interactional and structural reasons for the observed behaviours. In system B, centrifugation experiments showed that unassembled material bound to the fibre surface (where it diffuses along the fibre axis before being incorporated into the growing fibre) is enriched in **1** on octamers and in **3** on hexamers, thus directing which building blocks they incorporate, respectively. As for system A, kinetic experiments and analysis of fibre bundles in TEM showed that octamer and hexamer fibres aggregate in a way that their access to precursors is hampered and the **1**/**2** ratio of incorporated precursors is affected. This causes the hexamer to stop growing shortly after beginning of the reaction, while the octamer grows slowly but steadily and eventually accumulates over the hexamer. Food binding experiments suggest that the hexamer fibre binds more precursors than the octamer, especially the hydrophobic trimers, which may hint at a more hydrophobic surface. This tendency might lead to hexamers to bind more, and thus to become surrounded, by octamers and therefore being more deprived from food.

Contribution & impact: finding the right building block combinations and performing the serial transfers was performed by Marcel J. Eleveld. Juntian Wu and I were included to perform the mechanistic investigations; I performed experiments on system A and analysed & interpreted the overall mechanistic data.
This work is an important step in the complexification of chemical systems towards life-like features and behaviours. The mechanistic investigations have brought advancements in the understanding of the replicators' interaction with themselves and with their environment and explains other phenomena we have observed in our lab.

IV.2 Post-doc Groningen (phase separation)

Blokhuis, A.[+]*; Geiger, Y.[+]; Otto, S.*
When aggregation becomes the norm: interpreting experiments beyond their molecules
Manuscript in preparation.

Chemical theory and experimentalists usually assume molecules to be freely dissolved when put into solution; separate phases are invoked only when a substance is known or observed to form a solid precipitate or a separate liquid phase. Though, relying solely on optical feedback can be deceiving since even perfectly clear solutions can harbour separated phases. This is the case when solutes assemble into aggregates large enough to exhibit phase behaviour but small enough not to cause any turbidity. Due to the notorious difficulty to detect such "pseudophases", even by spectroscopy or other means, their presence in and impact on chemical systems is largely underestimated. This perspective article provides a comprehensive overview of (pseudo)phase

behaviour: how it arises from large aggregation, which properties it has, how it can be detected and how it impacts chemical systems, on the basis of theoretical and experimental examples.

One such example is taken from Otto group chemistry: prior to fibre emergence, the unassembled macrocycles (3mers, 4mers…) of the system were believed to be in solution, but their concentrations do not follow any equilibrium constant. This is because the equilibria involved are those of phases: when there is a change in overall concentration or oxidation state, the distribution of macrocycles adapts in a way to satisfy the phase compositions (each phase has a typical, fix distribution of constituents), not the equilibria of individual molecules.

A dynamic combinatorial library made of **B** consists, upon full oxidation, only of small macrocycles up to tetramers, but an increase in overall **B** concentration leads to sudden appearance of large macrocycles (LMCs) up to 51mers (Figure 5a). This is reminiscent of reaching a solubility limit or the critical micelle concentration with surfactants: the LMCs appear because a phase is formed in which they can exist. The relative concentrations of the LMCs do not change even if [$\mathbf{B}_{tot}$] is increased by almost a factor 10 (Figure 5b): this impossible for solution-phase equilibria (larger MCs would increase at the expense of smaller ones) but typical for phase behaviour. A large aggregate strives to maximise the interactions between its constituents, which is reached at a certain optimal composition; adding more material to the system only increases the number of aggregates with that same optimal ratio of constituents.

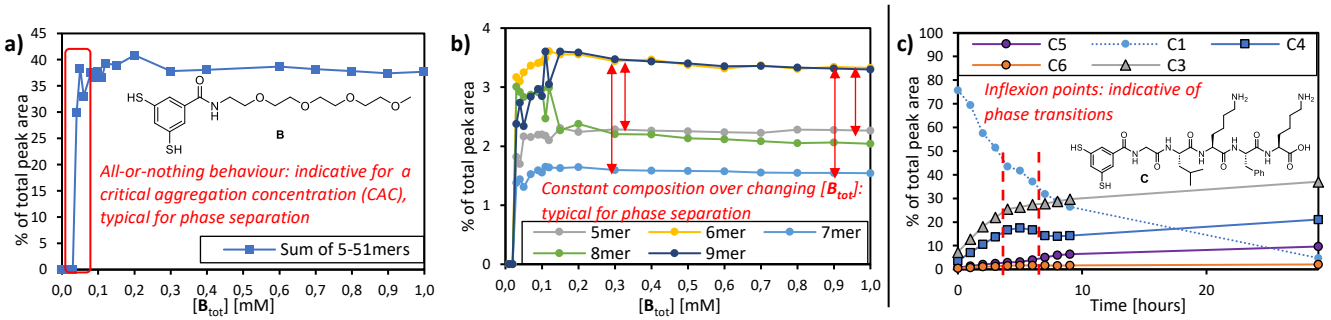


*Figure 5. Partial species distribution of dynamic combinatorial libraries (DCL) as shown in Figure 1. a) Percentage of the overall large macrocycles (LMCs, $\mathbf{B}_5$-$\mathbf{B}_{51}$) in a DCL made of various concentrations of **B**, b) detailed traces of LMCs $\mathbf{B}_5$-$\mathbf{B}_9$, c) kinetic trace of a DCL made of **C** getting oxidized over time (i. e. consumption of monomer $\mathbf{C}_1$, buildup of macrocycles $\mathbf{C}_3$-$\mathbf{C}_6$).*

The case of more than one pseudophase (i. e. aggregates with different constituent ratios coexist) can be recognized by discontinuities (red dashed lines, Figure 5c) when changing overall concentrations or, in this case, the oxidation state of the system. Phases interconvert over changing conditions: the discontinuities indicate states when a phase has been completely consumed by a second; further change leads to the appearance of a third one that grows at the expense of the second.

We also shed a light, on the basis of thermodynamic estimations, how common (pseudo)phase separation is expected to be. It needs a surprisingly little amount of interactions between molecules to bring the critical aggregation concentration (CAC, reminiscent of "CMC" used for micelles) to sub-mM ranges. Indeed, molecules as small as dipeptides or formaldehyde dimers/methanol adducts have been found to form large aggregates. This leads to the conclusion that pseudophase separation is likely to be a common thing, especially in water where the hydrophobic interaction is a powerful driving force to bring molecules together. We list several unsolved puzzles in chemistry, such as the Formose reaction, in which phase separation might be an overlooked factor.

Contribution & impact: The importance of phase separation in Otto group chemistry & in general was found by Alex Blokhuis, who wrote a first draft of the manuscript. I joined the authors to improve the text (structure, clarity, ease of understanding for a chemistry readership) and to add experimental examples by analysing published data from Otto group.

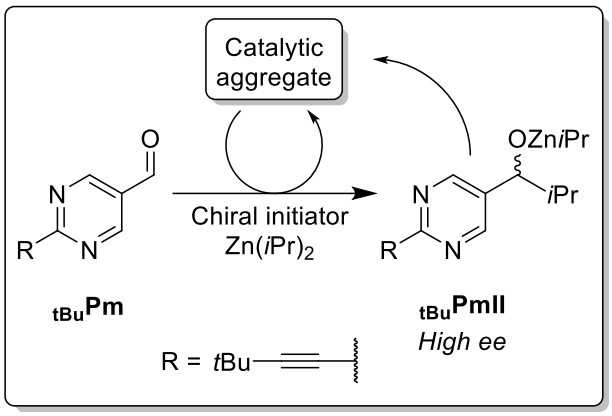
The insights shared and summarized in this article affect all domains of (presumed) solution-phase chemistry. The chemistry community being more aware of pseudophase separation is of great importance to get a better understanding of chemical systems, from simple synthetic reactions to complex reaction networks.

IV.3 Post-doc Groningen (theory of self-replication, asymmetric autocatalysis)

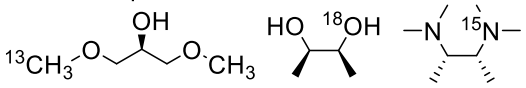
This part of my post-doctoral work is more conceptual, consists mostly of theoretical studies and interpretation of (literature) data and combines knowledge and concepts of both my post-doc and PhD topics. The first paper presented below uses knowledge about dialkylzinc chemistry gained from my PhD to properly interpret mechanistic data about the Soai reaction. The second uses insights from the first to address the issue of how to design exponential self-replicators

Geiger, Y.
One Soai reaction, two mechanisms?
Chem. Soc. Rev. **2022**, *51*, 1206. DOI: 10.1039/D1CS01038G

The autocatalytic Soai reaction is one of the biggest mysteries in the field of asymmetric catalysis: it consists in the addition of $Zn(iPr)_2$ to a pyrimidyl aldehyde yielding a chiral zinc akoxide, which in turn catalyses that reaction – i. e. its own production – in a highly enantioselective and chirality-amplifying way (Figure 6). Near to enantiopure product can be obtained starting from very low ee alkoxide that was added as an initiator; even unlikely chiral sources such as quartz crystals, circularly polarized light and chiral isotopomers can reliably direct the sign the overall final product will have. In absence of initiator, the reaction amplifies statistical fluctuations of the achiral background reaction: one obtains randomly the R- or S-enantiomer, sometimes even with an ee >80% - this is referred to as chiral symmetry breaking.



Chiral initiators (determine the sign of ***tBuPmII****):*
- Chiral organic compounds (alcohols, amines...)
- Cryptochiral hydrocarbon
- **tBuPmII** in ca. 0.00005% ee
- Enantiomorphic crystals (quartz, $NaClO_4$...)
- Enantiotopic crystal faces (gypsum)
- Circularly polarized light
- Chiral isotopomers:



Without chiral initiator:
- reaction yields randomly (*R*)- or (*S*)-**tBuPmII**

Figure 6. An overview of the Soai reaction (pyrimidine-based) and the different chiral initiators that have been used to drive to a non-random chiral outcome of the reaction.

These incredible performances have made the chemistry community puzzle over its mechanism: what is the active species, what makes it so enantioselective and how does it achieve chiral amplification? In recent years, two proposals have been made, based on extensive experimental work. The Denmark group claims a homochiral alkoxide tetramer to be the active species (Figure 7, left); the heterochiral (mixed) one does also form but would be kinetically incompetent. On the other hand, the Trapp group proposes a transient, mixed product-substrate dimer (hemiacetal) to be the active species (Figure 7, right): it is very slow to form and even thermodynamically unfavourable, but once it is made the autocatalytic cycle kicks in at a very fast rate. The amplification is achieved not by heterochiral aggregation but is based merely on statistics.

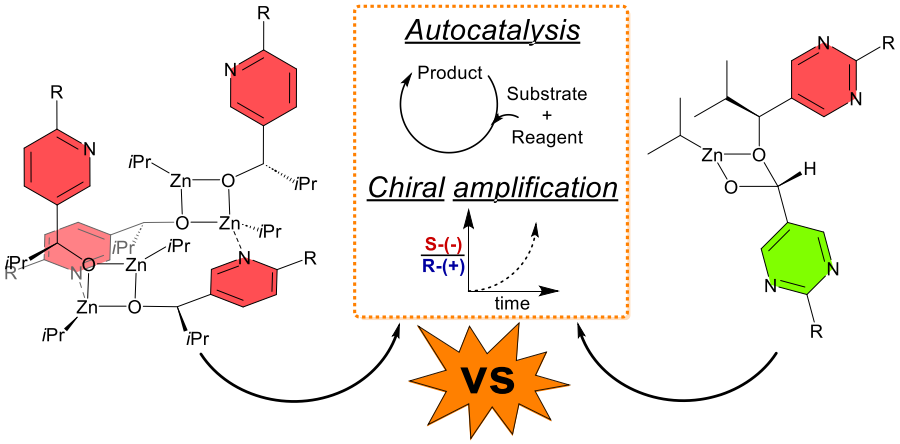


Figure 7. Possible catalytically active aggregates at the origin of the autocatalysis in the Soai reaction. Left: SMS-tetramer proposed by the Denmark group (pyridine-based), right: hemiacetal proposed by the Trapp group (pyrimidine-based).

These two scenarios are strikingly different and oppose each other, and there has been a fierce debate on which is the "true" mechanism for the Soai reaction. An in-dept analysis of the available data, backed up with my experience of the fluctional nature of dialkylzinc chemistry, led to the conclusion that *both* may be right – they possibly didn't study the same system. While the Trapp group worked with Soai's pyrimidine-based system (2 nitrogens in the aromatic ring), the Denmark group found pyridinyl substrates (only 1 nitrogen in the aromatic ring) to be also autocatalytic and chirality-amplifiying and worked with these, since they are easier to handle. A detailed discussion of previous literature data (X-ray diffraction, DOSY NMR, kinetic), how they (do not) fit with the studies' claims and of the electronic properties of pyridine and pyrimidine show that a lot speaks for both systems operating via different pathways.

Contribution & impact: the whole analysis was done by myself. The present Viewpoint Article first gives a concise summary of the two highly complex mechanistic studies, with the intend to make the subject accessible also to non-experts, and then discusses the studies in detail. That there are not one but two "Soai reactions" can, if confirmed by further work, lead to a deeper understanding of the principles that govern asymmetry-amplifying autocatalysis and help in the design of such (and other) complex systems.

Geiger, Y.; Otto, S.
Escaping product inhibition: the key to exponential self-replication
Manuscript in preparation.

The fact that the self-replicating fibres of Otto group exhibit exponential growth (i. e. with a kinetic order of 1 in self-replicator) is a very rare case in the field of self-replication, but is crucial to allow for Darwinian evolution. Sub-exponential replicators allow for the indefinite coexistence of replicators competing for the same food source, instead of the slowest one getting extinguished. Over the last three decades, many chemical systems were designed to self-replicate using a templating strategy, featuring e. g. self-complementary RNA strands, α-helical peptides or small organic molecules (denoted **T**, (Figure 8a). However, nearly all of them grow only sub-exponentially, with a kinetic order of 0.5-0.6 in self-replicator. They suffer from the templates inhibiting themselves at increasing concentrations (product inhibition). To date, no strategy has been proposed to overcome this issue.

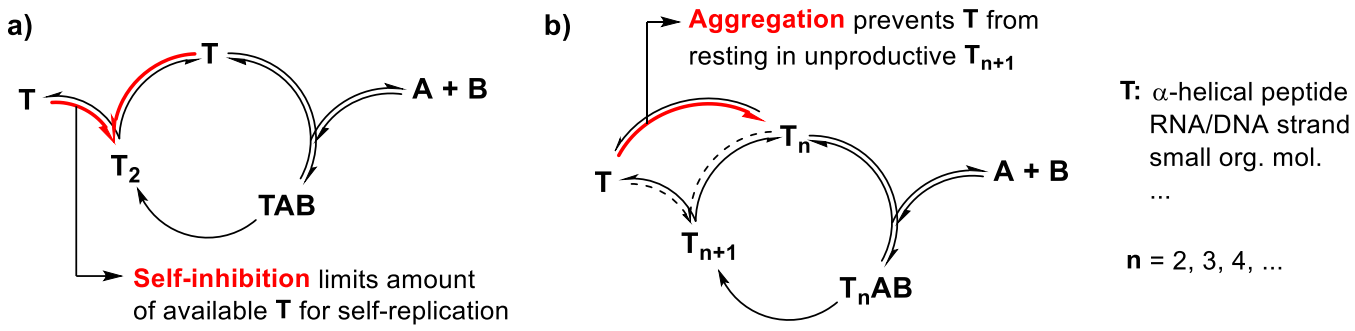


*Figure 8. General scheme for self-replication by a) simple template **T** and b) aggregated template **T_n**. The template binds to precursors **A** and **B** to form a ternary complex; ligation leads to the formation of a new **T** unit within **T_2** or **T_{n+1}**. Dissociation of that complex regenerates the template as well as a copy of it (a) or a subunit of it (b) that can further aggregate to finally form a new **T_n** unit.*

For this work, we analysed the few known (close to) exponential self-replicators that use a templating strategy, and also the autocatalytic Soai reaction which is in fact a self-replicating reaction, even though never mentioned as such. The analysis shows that aggregation might allow to overcome this issue (Figure 8b). The self-replicator being an aggregate **T_n** that promotes only the production of a subunit **T** (instead of copying itself as a whole) allows **T** to be siphoned off into the production of additional **T_n** instead of blocking itself, as long as the **T**⇌**T_n** aggregation constant is sufficiently high. Kinetic simulations using ordinary differential equations (ODEs) confirm this scenario: for n = 2 (i. e. the catalyst is dimeric), starting from a set of kinetic parameters where the system shows only quadratic growth (order in total **T** material of 0.5), increasing solely the K_2 dimerization constant gradually increases the kinetic order to 1 and leads thus to exponential growth. Over-exponential growth (order of >1) was also observed for cases with a low starting concentration of **T**, i. e. when monomeric **T** was only partially aggregated to **T_2**. Similar results were obtained for n = 3.

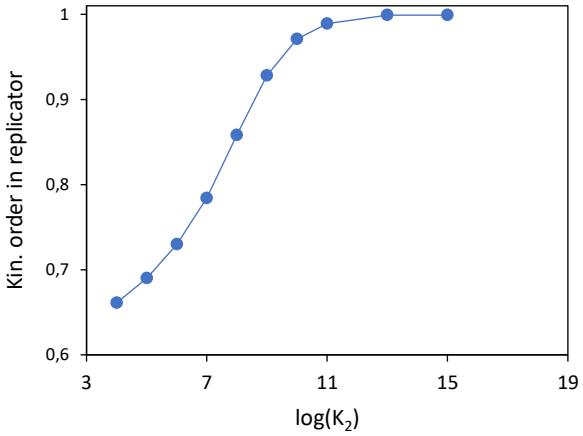


Figure 9. Kinetic order in self-replicator vs. K_n for n = 2. [A] & [B]: 0.01 mol; initial [T]: 1-10 mol%, K_{2+1}: $6.3 \cdot 10^7$; K_{AB}: $3.6 \cdot 10^5$.

Contribution & impact: I conceptualized this work, made the literature analysis and performed ODE modelling.

This work is of tremendous importance for the field of self-replication, which has mostly stalled except in our group since the possibilities offered by non-exponential replicators are limited. It opens perspectives for the design of exponential replicators (our group's system was found serendipitously): one should aim at self-replicating aggregates, not discrete molecules. This is easier said than done but with the advent of machine learning, there might be also new possibilities emerging in understanding and predicting aggregation.
The present study is a coin with two sides since it is inspired from two (seemingly different) fields and has an impact on both. The emphasis on kinetic order in self-replication is also crucial for the design of asymmetric autocatalysts other than the Soai reaction. The autocatalytic formation of only one out of two enantiomers from achiral precursors is a scenario related to two different replicators competing for the same food source (cf. following work): one of the two will get extinguished only if there is exponential growth. This must be considered in the design of asymmetric autocatalysts with high chiral amplification. This shows that both research communities of self-replication and asymmetric amplification benefit from being aware of each other, and should be rather merged than being clustered.

IV.4 Research during the PhD/post-doc in Strasbourg

The work at IPCMS in Strasbourg was mostly centred on mechanistic investigations in asymmetric catalysis, in the enantioselective addition of dialkylzinc to benzaldehydes catalysed by chiral aminoalcohols. The catalytic systems were studied by probing for non-linear effects (NLEs): non-linear correlations between product ee and ligand ee are usually indicators for catalyst aggregation, and lead to curious phenomena such as the product ee being higher than the ligand ee (chiral amplification).
This has an impact on the efficiency of catalysts – one possibly need not an enantiopure catalyst to obtain product with a maximal ee – but concerns also questions such as how did biological homochirality arise on earth. In the work presented in the following, NLEs have proven to be formidable mechanistic probes that unravel catalytic systems that are more complex than expected, especially when combined with simulations and kinetic analysis.

Geiger, Y.; Achard, T.; Maisse-François, A.; Bellemin-Laponnaz, S.
Hyperpositive non-linear effects in asymmetric catalysis.
Nat. Cat. **2020**, *3*, 422. DOI: 10.1038/s41929-020-0441-1

In this study a, chiral *N*-benzyl ephedrine (NBE) was applied in the enantioselective addition of $ZnMe_2$ and $ZnEt_2$ to benzaldehyde in toluene. This lead to the surprising discovery of a hyperpositive NLE: lowering the ligand ee does not lead to a decrease, but to an *increase* of product ee (47% with $ZnMe_2$, 5% with $ZnEt_2$).

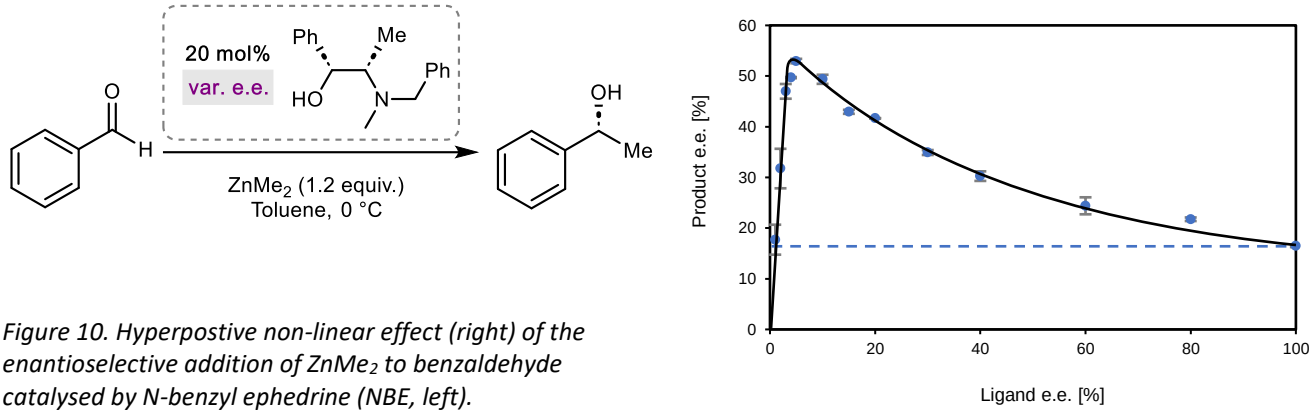


Figure 10. Hyperpostive non-linear effect (right) of the enantioselective addition of $ZnMe_2$ to benzaldehyde catalysed by N-benzyl ephedrine (NBE, left).

Mechanistic investigations revealed two factors responsible for that curious phenomenon: a racemic aggregate (1:1 R/S-ratio) of the catalyst being insoluble, and a homochiral dimer (only consisting of R; the minor S enantiomer being trapped in the precipitate) not only being formed but also being catalytically active; both the dimer and the monomeric catalyst yield product, but with a different enantioselectivity. Ligand ee lowering thus leads to a decrease of catalyst concentration (because of the racemate precipitation), which shifts the equilibrium from the homochiral aggregate to the more enantioselective monomer (Figure 11). This was confirmed by catalyst loading and temperature studies; kinetic investigations revealed a U-shaped curve in a kinetic order in catalyst *vs* catalyst loading plot, which is in line with the transition from one catalyst to another through an aggregation equilibrium. Autoinduction (i. e. the product binds to the catalyst to form a new catalytic species) was ruled out by looking at the product ee at a very early stage of the reaction (1-2% conversion) when the product is unlikely to have any effect: even then, lowering the catalyst loading leads to an increase in product ee similar to that of the finished reaction.

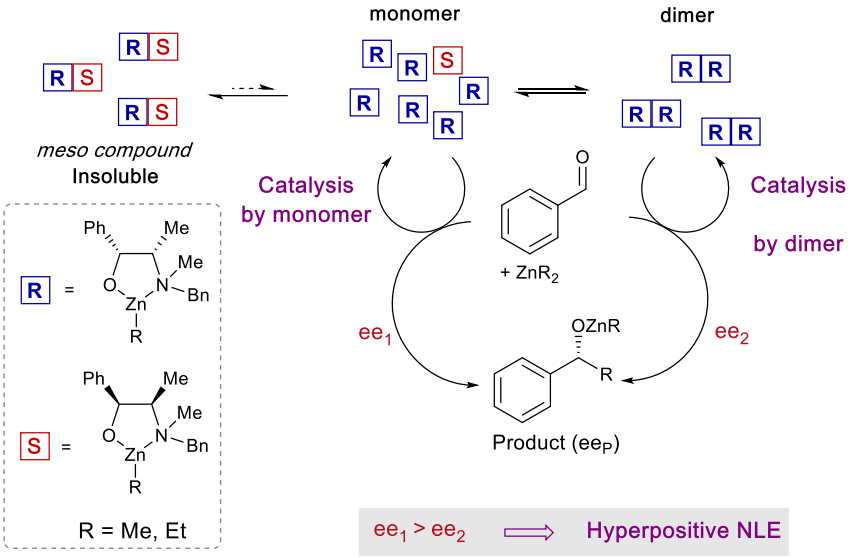


Figure 11. General scheme for the catalytic system at the origin of the hyperpositive non-linear effect.

Contribution & impact: the whole study was carried out by myself, under supervision by S. Bellemin-Laponnaz and practical mentorship & feedback by T. Achard & A. Maisse-François. The finding of a hyperpositive NLE is a landmark event as it has been theorized before (following a different mechanism than revealed here) but never observed experimentally; it is also one of the few conceptual advances in the field of NLEs since the early 2000's. Furthermore, it sheds new light on aminoalcohol-catalysed dialkylzinc additions: since catalysis through dimers was ruled out by Noyori for the DAIB ligand over several extensive studies, other aminoalcohols were largely supposed to follow the same mode of action without further questioning.

Geiger, Y.; Achard, T.; Maisse-François, A.; Bellemin-Laponnaz, S.
Hyperpositive non-linear effects: enantiodivergence and modelling.
Chem. Sci. **2020**, *46*, 12453. DOI: 10.1039/D0SC04724D

This work continues what was started in the study presented above (*Nat. Cat.* **2020**). This time, the ligand *N*-methyl ephedrine (NME) was applied in the addition of $ZnMe_2$ to benzaldehyde. In contrast to NBE, the complex resulting from non-enantiopure NME-ZnMe does not precipitate and therefore, the NLE differs: it is still (slightly) hyperpositive, but strongly displaced to lower product ees – to a point where the plot crosses the ligand ee-axis, when operating at the right temperature (Figure 12a). Enantiopure ligand gives product of up to 2% ee, but 50% ee ligand gives 2% ee of the other enantiomer product at room temperature (Figure 12b). Such enantiodivergent NLE shows that monomeric and homochiral dimeric catalysts not only yield product with different ee, but also of opposite sign (this may be true also for the NBE ligand). A literature survey showed that this applies to a variety of catalysts, which were prepared as either mono- or dimeric entities and applied independently in catalysis.

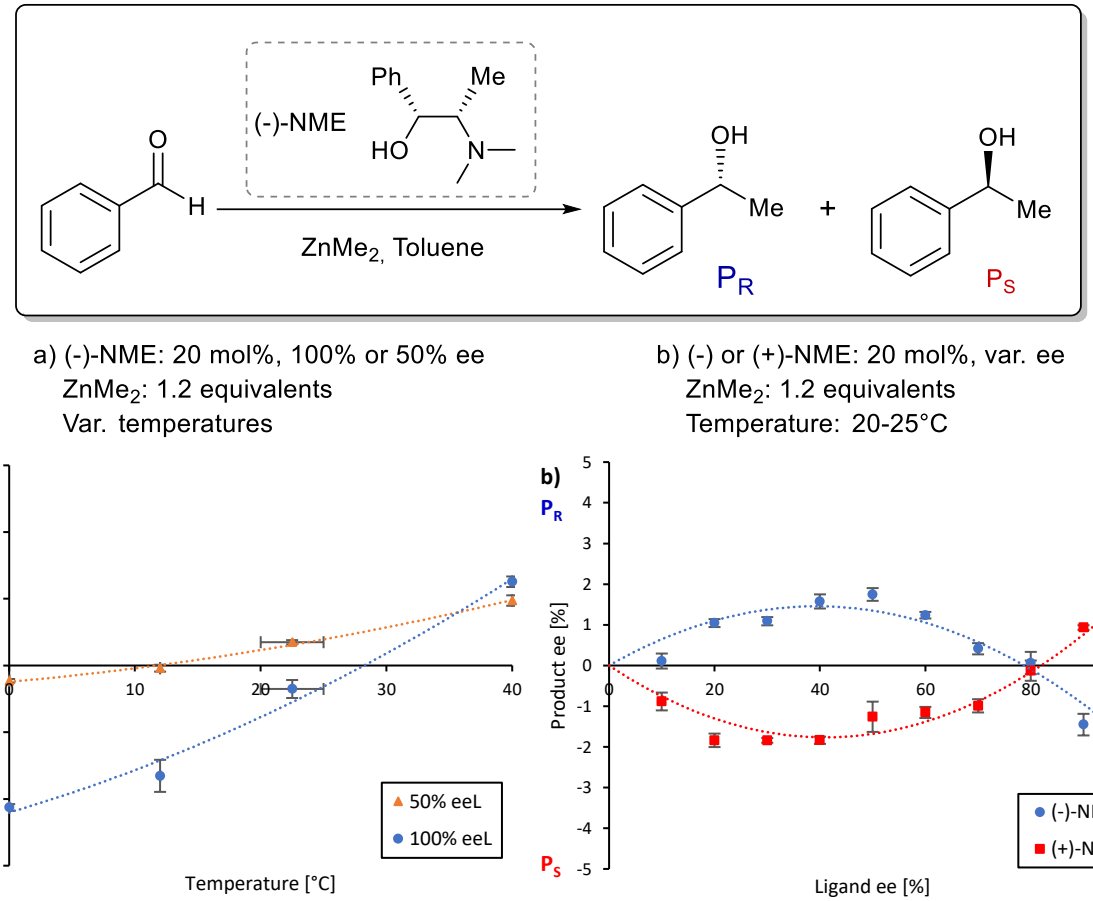


Figure 12. a) Product ee as a function of the reaction temperature (blue dots: 100% ligand ee; orange triangles: 50% ligand ee) and b) NLE at room temperature of (-)-NME (blue dots) and (+)-NME (red squares) of the NME-catalysed enantioselective addition of $ZnMe_2$ to benzaldehyde.

Furthermore, we introduced a theoretical aspect to this project by extending the mathematical models of Noyori, which allow to simulate NLE curves, to catalytically active dimers. A systematic study was caried out to probe the effects of the different parameters (dimerization constants, kinetic constants, enantioselectivities, total catalyst concentration) on NLE curves and observed kinetics constants (see Figure 13 for examples). Simulations confirmed the possibility of hyperpositive and enantiodivergent NLEs when both mono- and dimeric catalysts are kinetically competent and yield opposite product enantiomers, with curve shapes similar to the ones obtained experimentally; U-shaped kinetic order in catalyst *vs* catalyst plots could also be obtained.

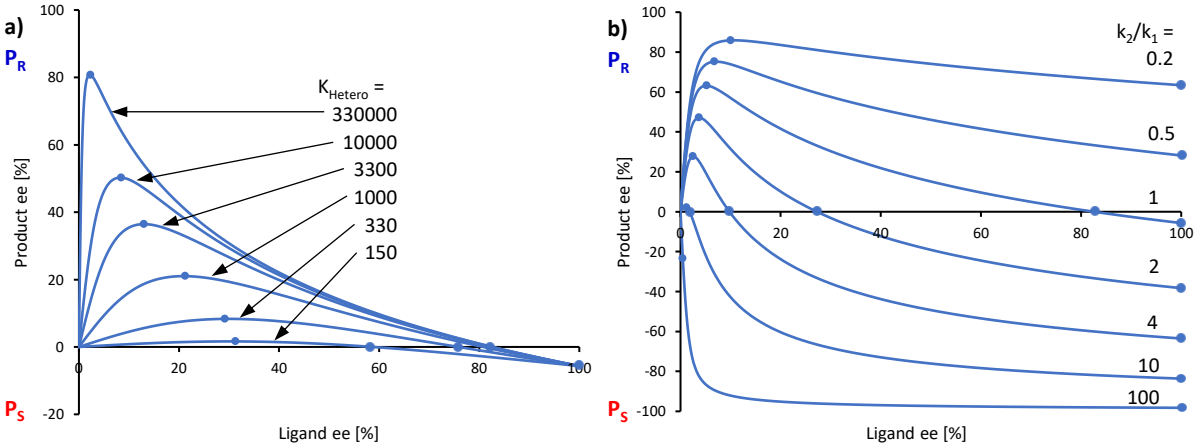


Figure 13. Examples of simulations of NLE curves of a system comprising catalytically active monomers and dimers. a) Variation of the heterochiral dimerization constant, b) variation of the ratio of the dimeric (k_2) to the monomeric (k_1) kinetic constants.

Contribution & impact: contribution is the same as in the entry above. This study confirms the claims from the previous work and adds a theoretical dimension to it; it is also, to the best of our knowledge, the first with evidence for two catalysts with opposite enantioselectivities in one pot.

Thierry, T.[+]; Geiger, Y.[+]; Bellemin-Laponnaz S.
Divergence of catalytic systems in the zinc-catalysed alkylation of benzaldehyde mediated by chiral proline-based ligands
Nat. Synth. **2024**, *3*, 615. DOI: 10.1038/s44160-024-00491-y; free read-only link: https://rdcu.be/dAAg7

In this work, our study of NLEs in aminoalcohol-mediated dialkylzinc additions was extended to proline derivatives. Three ligands that differ only through small chemical modifications were investigated for their reaction mechanisms in the addition of $ZnEt_2$ to benzaldehyde (Figure 14). **1** was found to follow a classical mechanistic scheme, with monomeric complexes catalysing and dimeric complexes being inactive; racemic precipitation causes a positive non-linear effect. This was evidenced by catalyst loading, DOSY NMR and kinetic studies.

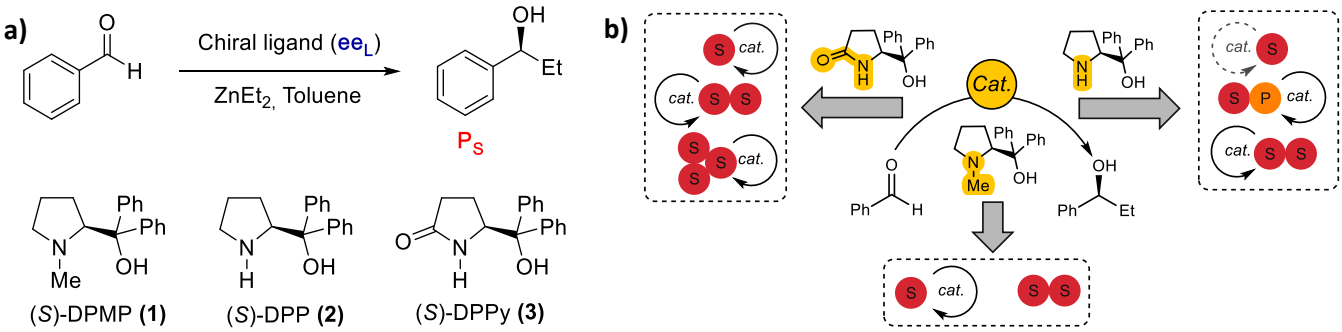


Figure 14. a) Addition of $ZnEt_2$ to benzaldehyde catalysed by three different proline-based aminoalcohols, b) overview of three different catalytic systems.

However, ligand **2** shows a strikingly different picture, even though not at first glance. At high catalyst loading its positive NLE is similar to that of the previous ligand (Figure 15a), but it shows now a strong product ee dependency on the catalyst loading (Figure 15b) and on the reaction time (Figure 15c). Reactions all start with a product ee >80%, but then the ee decreases over the course of the reaction – the lower the catalyst loading, the more drastic the ee downfall. We could attribute this behaviour to "auto-induction": the association of the product with the catalyst to form a new catalytically active species, with different enantioselectivity. The decrease in product ee over time was found to persist even when the catalyst remains partially precipitated during the reaction (saturation experiments), which rules out simple monomer-dimer equilibria as an explanation. Mathematical modelling allowed to qualitatively reproduce the curves from Figure 15c and suggested dimers and catalyst-product adducts to be the catalytically active species; monomers may be active to some degree.

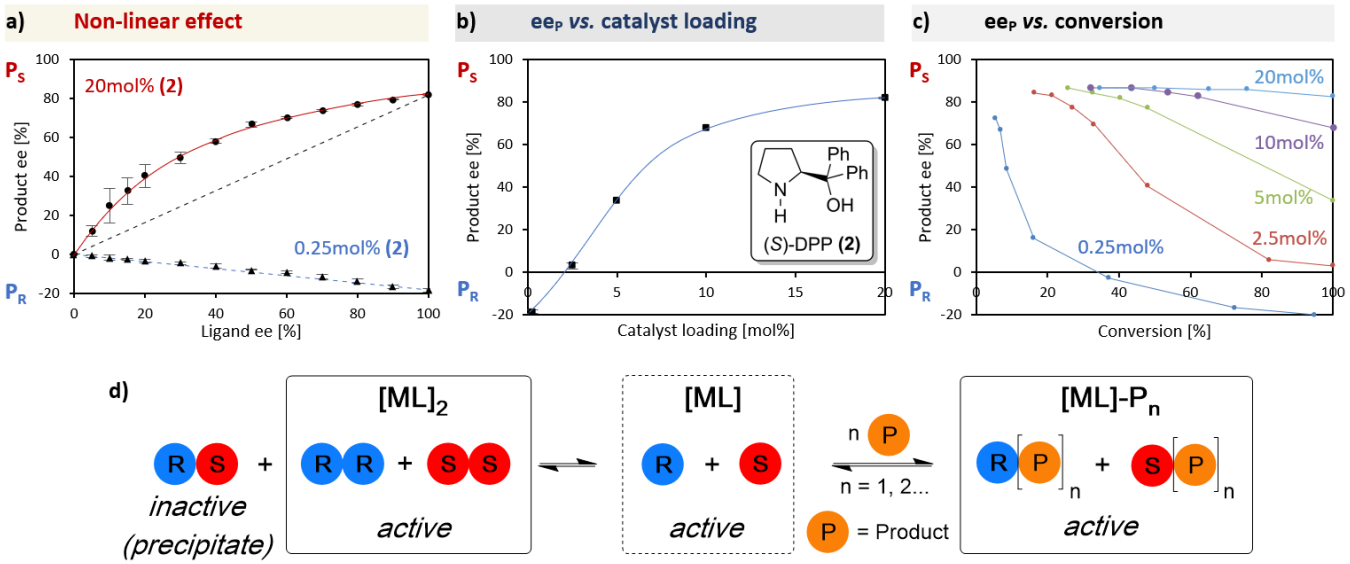


*Figure 15. a) DPP (**2**)-catalysed addition of $ZnEt_2$ to benzaldehyde: a) non-linear effect probing, b) product ee vs. catalyst loading using enantiopure DPP, c) product ee vs. conversion at different enantiopure DPP loadings, d) proposed catalytic system based on asymmetric induction.*

The third ligand, DPPy, shows again a different picture. It forms large aggregates with >2 nm radius (DPMP and DPP were not found to form larger objects than dimers) and shows a hyperpositive, enantiodivergent NLE of an unusual shape. That, and its behaviour in catalyst loading studies, cannot be explained by previous models; it contains at least three different species (of which one is of mixed chirality), which is possibly only if the aggregation state of the active species is higher than 2. This made us extend our mathematical model to trimeric aggregates; simulation of NLE and product ee *vs* catalyst loading curves including catalytically active trimers could reproduce the features observed experimentally with DPPy (Figure 16c-f), while a model comprising only monomeric and dimeric catalysts couldn't (Figure 16a+b).

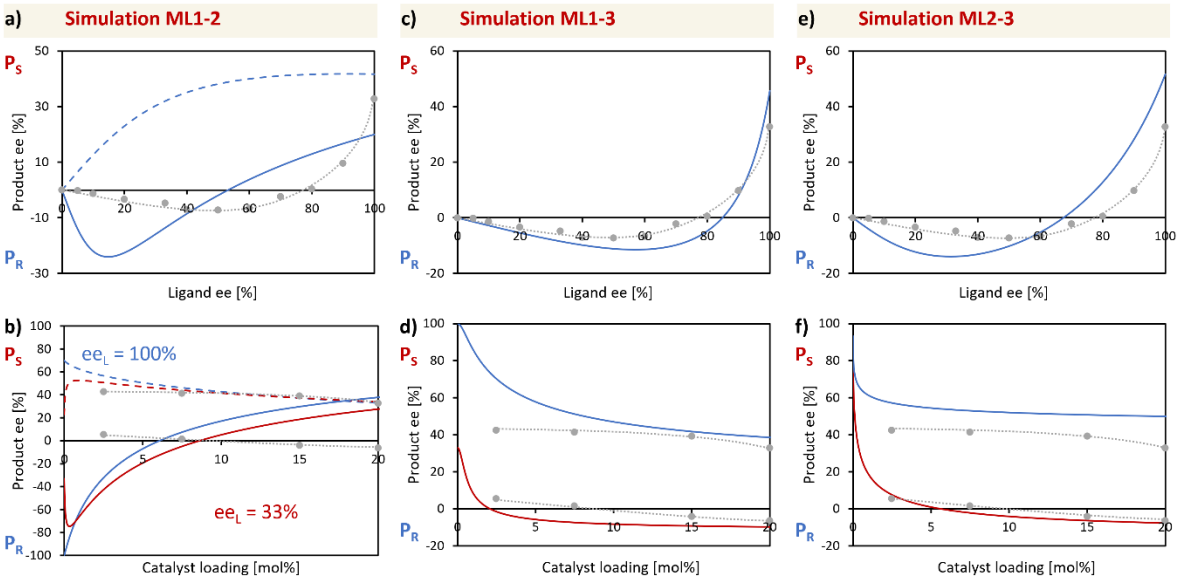


*Figure 16. Simulations of NLE (top) and product ee vs. cat. loading curves (bottom) following models with either monomers and dimers (a+b), monomers and trimers (c+d) or dimers and trimers (e+f) being present. Experimental data obtained with ligand **3** is added as grey filled circles/dotted lines. Blue lines: 100% ligand ee, red lines: 33% ligand ee. Simulations. In a) and b) the plain and dashed lines use two different sets of parameters.*

Contribution & impact: T. Thierry performed all experiments; I built the mathematical models, made simulations, participated in data treatment & interpretation and suggested experiments to perform (notably the kinetic studies).
This work shows how the systems-level behaviour of catalysts can dramatically change upon small chemical modifications, in a way that is difficult to predict. Especially the strong auto-induction seen with DPP is surprising since such behaviour could be excluded for the NBE ligand. Thus, it shows the limits of the "privileged chiral structure" paradigm: certain ligand frameworks may be well suited for high activity and enantioselectivity, but it does not allow to easily predict its systems-level behaviour which might work against the desired result. Furthermore, DPPy is the first example with strong evidence for an NLE caused by a catalyst with an aggregation level higher than 2, and with at least three different catalytic species being formed *in situ* from a single ligand.