

UNIVERSITE CATHOLIQUE DE LOUVAIN
INSTITUTE OF CONDENSED MATTER AND NANOSCIENCES
(IMCN)

Laboratory of Physical Chemistry

Prof. Tom Leyssens

**Controlling selectivity by crystal engineering on
aldolization and cycloaddition in the solid-state**

*Thèse présentée en vue de l'obtention du grade
de docteur en Sciences par*

Body Carole

Louvain-la-Neuve

Mai 2024

JURY MEMBERS

Prof. Y. Filinchuk
UCLouvain

Prof. J. Wouters
UNamur

Prof. E. Colacino
UMontpellier

Dr. K. Robeyns
UCLouvain

Prof. A. Delcorte (President)
UCLouvain

Prof. T. Leyssens (Supervisor)
UCLouvain

ACKNOWLEDGEMENTS

À l'issue de ces quatre années de thèse, c'est avec une certaine émotion que je me retrouve à écrire ces quelques lignes qui marquent la fin de la rédaction de ces quelques pages. À travers ces mots, je tiens à exprimer ma profonde gratitude à chacun de ceux qui m'ont accompagné tout du long.

Tout d'abord, je souhaite remercier mon promoteur de thèse le **Prof. Tom Leyssens**, pour son encadrement et son soutien durant ces années de recherche tant sur le plan professionnel que sur le plan personnel. Merci de m'avoir offert l'opportunité de me réorienter après 6 mois en industrie dans un poste qui ne me convenait pas vraiment, et à une époque où j'avais un grand besoin d'un changement de cadre.

Je tiens également à remercier **Dr. Xavier Buol** et **Dr. Michael Guillot**, mes premiers amis chercheurs, qui m'ont intégré dans l'équipe et épaulé au cours de mes premiers mois de recherche. Merci pour toutes les discussions instructives qui auront contribué à ma progression dans notre domaine de recherche. Je n'oublierai pas votre franc-parler, toujours bienveillant, qui m'aura fait avancer et évoluer et ce, dans plusieurs domaines.

Une bonne partie de cette thèse repose sur des analyses cristallographiques dans lesquelles le **Dr. Koen Robeyns** et le **Dr. Oleksii Shemchuk** m'ont été d'un grand service. Sans votre disponibilité et votre aide apportée tant sur la résolution des structures que sur l'utilisation des logiciels de visualisation des images cristallographiques, ce travail n'aurait pu voir le jour. Je tiens aussi à remercier **Laurent Collard** pour le développement des méthodes HPLC qui ont grandement contribué à cette thèse.

Durant la réalisation de cette thèse, j'ai eu l'occasion d'encadrer des étudiants qui réalisaient leur mémoire de fin d'études dans notre laboratoire. Cette expérience fut à chaque fois enrichissante, bien au-

delà du simple transfert de connaissances scientifiques. Merci à **Guillaume Wéry** et **Lisa Gubbels**, qui, en plus de leur contribution à ce projet par leur travail au laboratoire ont apporté beaucoup de joie de vivre et nourri l'équipe de leur motivation. Ce fût un plaisir de travailler avec vous, votre travail et votre intérêt sur la partie cycloaddition à l'état solide auront fortement aidé à l'avancement de ce projet.

Merci à **Chloé Matheys**, **Camila Caro Garrido** et **Joséphine de Meester**, qui ont toujours été présentes en cas de besoin. C'était avec un peu d'appréhension que je voyais cette nouvelle génération de chercheurs arriver au labo, mais finalement ce fut un réel plaisir d'avoir pu partager avec vous tous ces moments, que ce soit au laboratoire ou après les journées de boulot. Merci pour tous ces moments d'écoute et d'échanges sur les hauts et les bas qui sont passés sur ma route ces dernières années. Votre aide et votre soutien auront été important pour moi.

Je tiens à exprimer ma reconnaissance envers toutes les personnes du B1 qui ont participé de près ou de loin à mon projet de recherche, ou qui ont simplement apporté leur touche à l'ambiance du laboratoire. Que ce soit par des discussions, des conseils ou des encouragements, votre soutien a été précieux et a contribué à la réalisation de cette thèse.

Vive l'équipe STEL! **Vincent Delmez**, **Benoît Notredame**, **François Kerff**, **Simon De Kreijger**, merci pour tous ces fous rires, ces repas de midi au Dude, ces soirées au Brasse-Temps, ... Que d'instantanés mémorables que vous m'avez fait vivre depuis le début de mes études en chimie. Votre rencontre aura été des plus inoubliables. Ps : Rendez-vous tous les deuxièmes week-ends d'octobre.

Un grand merci également à mes parents pour leur soutien et leur compréhension tout au long de ce parcours. Merci pour toute l'aide apportée surtout sur le plan personnel. Votre présence presque tous les week-ends depuis plus d'un an pour la rénovation de notre maison

aura contribué à me donner la sérénité nécessaire à la rédaction de cette thèse, moment que j'appréhendais énormément, surtout avec ce chantier à mener en parallèle.

Merci également à toi, Louis, qui sera parrain une fois cette thèse défendue. La chimie est un peu loin de ton domaine de compétence, mais je n'oublie pas toute l'aide que tu as pu m'apporter au cours de mes études sur les matières plus mathématiques.

Finalement, merci à toi Fabrice pour ton soutien depuis le début de ces quatre années de recherche. Ton amour et tes mots d'encouragements ont été un point d'accroche et une source de motivation dans les moments où « plus rien n'allait ». Merci pour les discussions enrichissantes, ta mémoire d'éléphant et ta culture scientifique si large, qui ont nourri ma réflexion et m'auront fait voir mes projets sous d'autres angles.

Merci aussi à tous ceux que je n'ai pas cités ici, mais qui ont été autour de moi durant ces quatre années.

Carole

PS : Un merci tout particulier à toi Achille, qui a été un bébé des plus faciles, apportant joie et légèreté dans mes jours les plus chargés lors de la correction de ce manuscrit.

LIST OF ABBREVIATIONS

25DHBA	2,5-dihydroxybenzoic acid
2ETCA	2-ethoxy- <i>trans</i> -cinnamic acid
2MCCA	2-methoxy- <i>cis</i> -cinnamic acid
2MTCA	2-methoxy- <i>trans</i> -cinnamic acid
4MTCA	4-methoxy- <i>trans</i> -cinnamic acid
Å	Ångström (1Å = 0,1 nm)
Acet	Acetone
ACN	Acetonitrile
CC	Cocrystal
CCDC	Cambridge crystallographic data centre
CD3OD	Deuterated methanol
cHPLC	Chiral high-performance liquid chromatography
CIP	Cahn-Ingold-Prelog
CNT	Classical nucleation theory
COUM	Coumaric acid
CSD	Cambridge structural database
CSP	Chiral stationary phase
d	Distance
DCM	Dichloromethane
DMSO	Dimethylsulfoxide
DSC	Differential scanning calorimetry
de	Diastereomeric excess
ee	Enantiomeric excess
EMA	European medicines agency
EtOAc	Ethyl acetate
EtOH	Ethanol
FDA	Food and drug administration
FUMA	Fumaric acid
GC	Gas chromatography
GHS	Globally harmonized system
HIV-1	Human immunodeficiency viruses
HOMO	Highest occupied molecular orbital
H-P-E-S-W	Hajos-Parrish-Eder-Sauer-Wiechert
Hz	Hertz
IEC	Ion-exchange chromatography

ILAG	Ion and liquid assisted grinding
IUPAC	International Union of Pure and Applied Chemistry
J	Joule
K	Kelvin
LAG	Liquid assisted grinding
LC	Liquid chromatography
LCA	Life cycle assessment
LUMO	Lowest unoccupied molecular orbital
MeOH	Methanol
MZW	Metastable zone width
N/A	Non-applicable
NLEs	Non-linear effects
NMR	Nuclear magnetic resonance
PB	Planetary ball mill
POLAG	Polymer assisted grinding
rac	Racemic
rpm	Revolutions per minute
RT	Room temperature
SCXRD	Single crystal X-ray diffraction
SDS	Safety data sheets
SEC	Size-exclusion chromatography
SH	Shaker mill or vibratory mill
SUCA	Succinic acid
SY	Slurry
TA	<i>Temperature ambiente</i> (= Room temperature)
TCA	<i>Trans</i> -cinnamic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
UV	Ultraviolet
W	Watt
WC	Tungsten carbide
XRD	X-ray diffraction
XRPD	X-ray powder diffraction
ZrO ₂	Zirconium dioxide (zirconia)

ABSTRACT

The present thesis is at the crossroad between asymmetric organic synthesis and crystal engineering. Moreover, it aims at the development of low solvent consumption methods, thus it fits into the framework of green chemistry.

The use of crystal engineering principles, more precisely, the formation of cocrystals, allowed us to control the stereochemistry of two « carbon – carbon bond forming » organic reactions already studied elsewhere from the point of view of solvent-free synthesis: asymmetric aldolization reactions in the solid phase and photochemical [2+2] cycloaddition reactions in the solid phase. The stereochemistry of the products of these two reactions is mainly related to solid-state properties. It is by playing on these properties, via cocrystallization, that we have explored possibilities of controlling selectivity of these reactions.

Aldolization reactions are an important class of carbon – carbon bond formation reactions. As chemical and physical processes usually do not have stereochemical preferences, the classical synthesis of chiral molecules leads to racemic mixtures. However, an asymmetry can be imposed on the reaction by introducing a chiral catalyst. By interaction with the reactants, the chiral catalyst forms an asymmetry in the reaction environment. One of the enantiomers is preferentially formed and an enantiomeric excess is obtained, or even an enantiomerically pure compound in the best case. The use of natural amino acids such as proline, as chiral catalysts has become more and more common as they proved to be efficient organocatalysts in asymmetric aldol additions and are readily available. (These are referred to as organocatalyzed aldolizations). However, it is rare that an asymmetric reaction is completely selective. The product obtained is generally enantioenriched rather than enantiopure. The improvement of the enantiomeric excess (ee) requires knowledge of the factors and ideally an understanding of the mechanisms

determining the selectivity. Previous studies have shown non-linear relationships between catalyst and product ee, both in solution and in the solid phase. Based on the hypotheses that could explain this non-linearity in the solid phase, we have tried to increase the selectivity of an aldolization reaction catalyzed by proline, by playing on the solid form of this catalyst. This part of the project aims to direct the enantiomeric excess of organocatalyzed reactions in the solid-state. This was made possible with the use of a cocrystal between fumaric acid and proline as a catalyst in a solid-state aldolization reaction between tetrahydro-4H-thiopyran-4-one and 4-nitrobenzaldehyde.

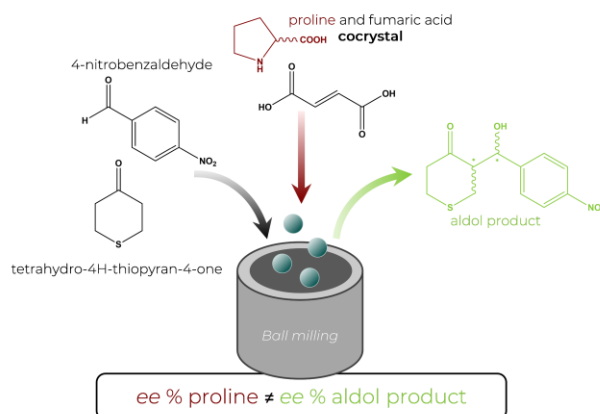


Figure 1 | Scheme of the aldolization reaction between tetrahydro-4H-thiopyran-4-one and 4-nitrobenzaldehyde in the solid-state, catalyzed by a cocrystal between proline and fumaric acid.

Photochemical [2 + 2] cycloadditions of alkenes in the crystalline state are synthetically very useful, as they generally produce only one stereoisomer predicted from the crystal structure of the alkene. This is called specificity because the reaction mechanism makes it impossible to form other enantiomers, thus making them inaccessible. To circumvent this problem, we have explored a method to control the orientation of the molecules within the crystal structure by cocrystallizing the cinnamic acid molecules. This part of the project aims at obtaining regioisomers otherwise difficult to produce for

solid-state photodimerization reactions. So far, one regioisomer of interest, β -truxinic acid, could be obtained in a thermodynamically controlled manner via cocrystallization between *trans*-cinnamic acid and 4,6-dichlororesorcinol. Up to now, the other regioisomers have not yet been obtained.

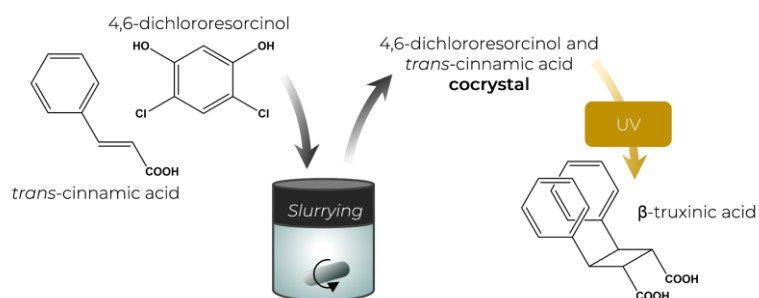


Figure 2 | Scheme of the formation of a cocrystal between *trans*-cinnamic acid and 4,6-dichlororesorcinol, followed by a [2+2] photochemical cycloaddition reaction of *trans*-cinnamic acid within this cocrystal.

RÉSUMÉ

La présente thèse se trouve au carrefour entre la synthèse organique asymétrique et l'ingénierie du cristal. Par ailleurs, elle vise au développement de méthodes peu consommatrices de solvants, de par ce fait elle rentre dans le cadre de la chimie verte.

L'utilisation de principes de l'ingénierie cristalline, plus précisément, la formation de cocristaux, nous a permis de contrôler la stéréochimie de deux réactions de synthèses organiques « de formation de liaisons carbone – carbone » déjà étudiées par ailleurs du point de vue de la synthèse sans solvant : les réactions d'aldolisation asymétriques en phase solide et les réactions de cycloaddition [2+2] photochimiques en phase solide. La stéréochimie des produits de ces deux réactions est principalement liée à des propriétés de l'état solide. C'est en jouant sur ces propriétés, via la cocrystallisation, que nous avons explorés différentes possibilités de contrôle sur la sélectivité de ces réactions.

Les réactions d'aldolisation sont une classe importante de réactions de formation de liaisons carbone – carbone. Les processus chimiques et physiques n'ayant d'ordinaire pas de préférences stéréochimiques, la synthèse classique de molécules chirale conduit à des mélanges racémiques. Cependant, une asymétrie peut être imposée à la réaction en y introduisant un catalyseur chiral. En interagissant avec les réactifs, le catalyseur chiral forme une dissymétrie dans l'environnement réactionnel. L'un des énantiomères se forme préférentiellement et l'on obtient un excès énantiomérique, voire un composé énantiomériquement pur dans le meilleur des cas. L'utilisation d'acides aminés naturels tel que la proline, comme catalyseurs chiraux est devenue de plus en plus courante car ils s'avèrent être des organocatalyseurs efficaces dans les additions asymétriques d'aldol et sont facilement disponibles. (On parle alors d'aldolisations organocatalysées). Il est cependant rare qu'une réaction asymétrique soit totalement sélective. Le produit obtenu est

généralement énantioenrichi et non énantipur. L'amélioration de l'excès énantiomérique (ee) nécessite une connaissance des facteurs et idéalement la compréhension des mécanismes déterminant la sélectivité. Des précédentes études ont mis en évidence des relations non-linéaires entre l'ee du catalyseur et des produits, tant en solution qu'en phase solide. Sur base des hypothèses pouvant expliquer cette non-linéarité assez interpellante en phase solide, nous avons tenté d'augmenter la sélectivité d'une réaction d'aldolisation catalysée par une proline, en jouant sur la forme solide de ce catalyseur. Cette partie du projet a pour but de diriger un excès énantiomérique de réactions organocatalysées à l'état solide. Ceci a été rendu possible avec l'utilisation comme catalyseur d'un cocrystal entre l'acide fumarique et la proline lors d'une réaction d'aldolisation à l'état solide entre le tétrahydro-4H-thiopyran-4-one et le 4-nitrobenzaldehyde.

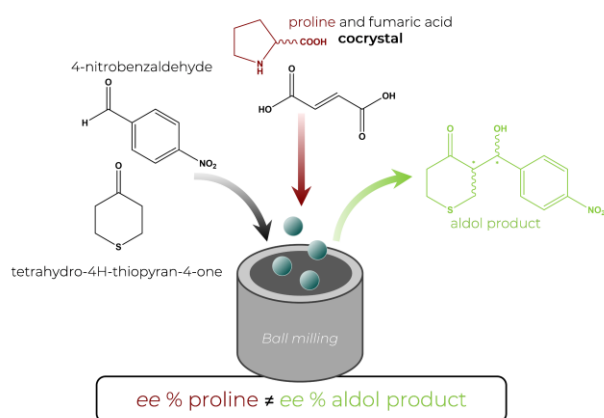


Figure 3 | Schéma de la réaction d'aldolisation entre le tétrahydro-4H-thiopyran-4-one et le 4-nitrobenzaldehyde à l'état solide et catalysée par un cocrystal entre la proline et l'acide fumarique.

Les cycloadditions [2 + 2] photochimiques d'alcènes à l'état cristallin sont synthétiquement très utiles, car elles ne produisent généralement qu'un seul stéréoisomère prédit à partir de la structure cristalline de l'alcène. On parlera ici de spécificité car le mécanisme réactionnel rend impossible la formation des autres énantiomères, les rendant donc inaccessibles. Pour contourner ce problème, nous

avons exploré une méthode permettant de contrôler l'orientation des molécules au sein de la structure cristalline en cocrystallisant les molécules d'acides cinnamiques. Cette partie du projet a pour but d'obtenir des régioisomères autrement difficiles à produire pour des réactions de photodimérisation à l'état solide. Jusqu'à maintenant, un seul régioisomère d'intérêt, l'acide β -truxinique, a pu être obtenu de manière thermodynamiquement contrôlée via la cocrystallisation entre l'acide *trans*-cinnamique et le 4,6-dichlororesorcinol. Malheureusement, aucun autre régioisomère n'a pu être atteint.

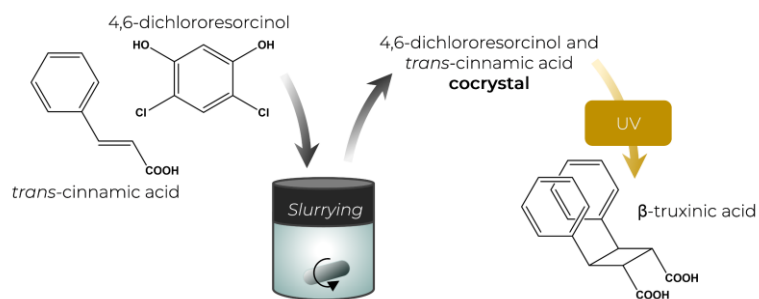


Figure 4 | Schéma de la formation d'un cocrystal entre l'acide *trans*-cinnamique et le 4,6-dichlororesorcinol suivi d'une réaction de cycloaddition photochimique [2+2] de l'acide *trans*-cinnamique au sein de ce cocrystal.

TABLE OF CONTENTS

Jury Members	iii
Acknowledgements	v
List of Abbreviations	ix
Abstract	xi
Résumé	xiv
Table of contents	xvii
 Preface and goals of this thesis	 1
 CHAPTER I: A REMINDER ON BASIC CONCEPTS	 11
1. Basic concepts about isomerism	11
1.1 Stereoisomer vs regioisomer	11
1.2 Chirality due to an asymmetric atom	12
1.3 Asymmetric multi-center stereoisomers	14
1.4 Chirality and its importance in everyday life	16
1.5 Separating enantiomers and chiral chromatography	18
1.6 Selectivity and specificity not always clear	20
2. Crystal engineering	22
2.1 Intermolecular interactions	22
2.2 States of matter – Phase transitions	26
2.3 Thermal analyses of phase transitions using DSC	30
2.4 Solid-state – Crystal – Crystal engineering	32
2.5 Crystallization process	34
2.6 Polymorphs	39
2.7 Cocrystals, salts and solvates: How to classify?	42
2.8 Amorphous phase	44
2.9 Symmetry of crystals	46
2.10 Characterizing crystals using X-Ray diffraction	53
3. Phase diagrams	62
3.1 Introduction to phase diagrams	62
3.2 Physical transformation of pure compounds	62
3.3 Binary phase diagram	63
3.4 Interpretation of binary phase diagrams	64
3.5 Binary phase diagram: solids forms and enantiomers	69
3.6 Ternary phase diagram	70
4. A deeper insight in mechanochemistry	74
4.1 A too restrictive definition	74
4.2 History of mechanochemistry	75
4.3 Mechanochemistry in a laboratory	76
4.4 Energy transfer in ball mill	79
4.5 What happens in a mechanochemical reaction ?	81
4.6 Really without solvent ?	86

CHAPTER II: ALDOLIZATION IN THE SOLID-STATE 91

1.	A brief review of organocatalyzed asymmetric aldol reaction	91
1.1	Timeline of the organocatalyzed asymmetric aldol reaction	91
1.2	Aldol addition reaction mechanism	92
1.3	Asymmetric aldol reaction catalyzed by proline	97
1.4	Challenge in asymmetric synthesis: Asymmetric amplification / depletion.	102
1.5	Can the solid-state also participate to asymmetric amplification?	104
1.6	Aldol reaction catalyzed by proline through mechanochemistry	108
2.	Goals and methodology	112
2.1	Crystal engineering to control aldol product enantioselectivity	112
2.2	Methodology	114
3.	Investigating the proline solid-state	117
3.1	Proline solid phase: hydrates and polymorphs	117
3.2	Proline cocrystals in the CSD	120
4.	Mechanochemical aldolization catalyzed by proline	137
4.1	Setting the mechanochemical conditions	137
4.2	Puzzling out a complicated cHPLC pattern working with 4-tert-butylcyclohexanone	140
4.3	Studying the impact of the proline ee working with 4-tert-butylcyclohexanone	150
4.4	Switching to tetrahydro-4H-thiopyran-4-one to reduce experimental variability	155
4.5	Results of aldolization with tetrahydro-4H-thiopyran-4-one using proline cocrystals	160
5.	Conclusion and perspectives	164

CHAPTER III: CYCLOADDITION IN THE SOLID-STATE 171

1.	A brief review of the [2+2] cycloaddition in the solid-state	171
1.1	Pericyclic reactions	171
1.2	Stereochemistry of cycloadditions	172
1.3	Permitted and prohibited reactions	174
1.4	Photochemical reactions of cinnamic acid in the solid-state	177
1.5	Control of dimerization	183
1.6	Control of dimerization with using a purely mechanochemical approach	184
2.	Goals and methodology	186
2.1	Crystal engineering to control the regioselectivity upon photodimerization	186
2.2	Methodology	188
3.	Results and discussion	192
3.1	Dimerization of parent compounds	192
3.2	Cocrystal screening	203
3.3	Analysis of the crystalline structures of the 14 confirmed cocrystals	206
3.4	Analysis of the reactivity of the 14 confirmed cocrystals	209
3.5	Analysis of the reactivity of the remaining suspected cocrystals	220
4.	Conclusion and perspectives	224

Conclusions	227
Appendices	229
1. Instruments	229
2. Supporting Information to Chapter II	231
3. Supporting Information to Chapter III	245
Bibliography	276

PREFACE AND GOALS OF THIS THESIS

The theme of sustainable development is becoming increasingly important. The climate change we are experiencing today is one of the major issues that should concern everyone. Our actions and activities influence the balance of the climatic, biological and physical systems. Everyone dreams of their own solution. « *The dreamer turns to space to try to grasp new materials. The reasonable person strives, each day, to consume a little less than the day before.* » [1] In recent years, scientists in the field of chemistry have been challenging themselves moving towards a greener chemistry, one that is more respectful of the environment and human health. Developed in the United States in the early 1990s, the concept of green chemistry covers the entire life cycle of a chemical product, from production to disposal. It provides a framework for preventing pollution from chemical activities. Over the last 25 years, numerous tools have been developed to measure and compare the ecological degree of chemical processes. [2] Developed in 1992, life cycle assessment (LCA) is a complex approach that takes into account several factors simultaneously, from product design to production, use and disposal. However, this holistic analysis is both data-intensive and time-consuming, as the various environmental impacts associated with all stages of a product's life cycle are considered. In 1998, 12 principles of green chemistry were defined by Anastas and Warner (Figure 5). [3] These principles involve the design and implementation of chemical processes to reduce the use and formation of harmful substances. Following these guidelines in your laboratory can help to reduce the environmental footprint. However, these principles only give a qualitative idea of the ecological character of chemical processes. Following these 12 principles does not allow us to compare, for example, a traditional manufacturing method with an alternative, which would be more environmentally friendly. The first two principles were supported by quantitative formulas. The “waste prevention” with the E factor ($= \text{waste (kg)} / 1 \text{ kg product}$) [4] and the “Atom

economy" which represents the percentage incorporation of reactants into the product in the ideal reaction. [5] For pharmaceutical compounds, the *E* factor is typically > 100 (< 0.1 for oil refining and < 1-5 for bulk chemicals). [6]



Figure 5 | The 12 principles of green chemistry described by Anastas et Warner in 1998, classified into three categories according to DOZN 2.0 model developed by Merck in 2022 for quantitative analysis. (Adapted from [7])

In 2022, Merck developed a quantitative green chemistry evaluator, DOZN 2.0, which scientists can base themselves upon to estimate the relative greenness of their products and processes. [7] DOZN 2.0 is based on readily available information like manufacturing information, globally harmonized system (GHS) and safety data sheets (SDS). This free web-based tool emphasizes three main categories which classifies the 12 principles: Improved resource used, energy efficiency and reduced human and environmental hazards. Some principles could belong to more than one group, but they have been classified where their benefit is greatest. A measurement is

given to each principle. The score for each group is calculated by taking the average of the different principles contained in the group. And the three scores are grouped together to give an overall score, normalized on a scale of 0 to 100, where 0 is the best.

Currently, studies are pushing towards applications in chemistry that reduce the use and generation of substances that are harmful to the environment, or at best eliminate them. This can be done by reducing the amount of solvent needed for organic synthesis. Organic solvents are often considered toxic or harmful, given the large volumes used in industry and the difficulties in containing volatile compounds. Mechanochemistry and other fields of solid-state reactivity show that reactions at the solid-state can offer such possibilities, and sometimes even offers potential for new pathways. [8] Of course, solid-state chemistry is not the answer to everything since it requires unique conditions to be usable. However, research in this field is growing, open new insights toward the green production and new solutions are discovered every day.

In organic synthesis, one of the main challenges relate the synthesis of regio- and stereoisomers. These can show different physicochemical properties, which can reflect e.g. through their biological effect. This is why it is important to be able to synthesize these molecules in a selective manner, ideally coming to a reaction in which a single stereo- or regioisomer is made.

In this thesis we couple these two concepts together, trying to control regio- and stereoisomerism with solid-state reactivity. To achieve such control, we focus on controlling the solid form of the catalyst or reactants used. We show the feasibility of using solid-state reactivity together with the concepts of crystal engineering for the control of stereo- and regiochemistry, through the study of two model reactions.

been developed to explain these variations to linearity. In the solid-state, non-linear effects can also be observed but are of a different nature than in solution. In the solid-state, the phase behavior of the components is important. When asymmetric organocatalyzed syntheses are performed in the solid-state (without solvent), the reaction seems to occur in a molten state (in equilibrium with a phase that would remain solid) which would then act as the reaction medium. The amount of chiral catalyst (ratio D vs L) present in this molten phase and thus available for the reaction, is then directly linked to its « solubility » in this specific reaction medium.

At the low ee of catalyst used, i.e. where the amount of L is too low to crystallize into L_s , the amount of L available increases gradually as more is added. At high ee, i.e. where the amount of D is too low to crystallize to DL_s , the amount of L available continues to increase. Implicating for these two areas, an increase in the ee of the aldol product. At medium ee, on the other hand, an interesting fact is observed, the ee of the aldol product remains constant over a whole range of catalyst ee. This is explained by the formation of a eutectic. At this specific range, no matter the ee of the overall catalyst is involved in the reaction, the ee of the catalyst in the molten reaction medium and thus available for the reaction, remains constant.

The goal of this part of the project is then to play on this equilibrium which exists between the catalyst and the melt phase. By cocrystallizing the catalyst with a coformer (cocrystallization agent), we should be able to move the eutectic and this preferably towards an increase of L in the melt phase. If more L becomes available in the melt phase for the reaction, then the enantiomeric excess of the aldol product should increase for a given overall catalyst ee. This would ultimately imply an increase in the selectivity of the reaction. Since it is not possible to know in advance whether the use of a catalyst cocrystal will increase or decrease the selectivity, different cocrystals will be tested. The coformers used to form the cocrystals with the

catalyst will be for simplification reasons achiral and should crystallize in the same ratios with both L- and DL-catalyst.

The system studied in this part is an aldol reaction catalyzed by proline, between a ketone (4-tert-butyl-cyclohexanone or tetrahydro-4H-thiopyran-4-one) and an aldehyde (4-nitrobenzaldehyde), all solid at room temperature. Cocrystallization agents tested are 2,5-dihydroxybenzoic acid, fumaric acid and succinic acid. (Figure 7)

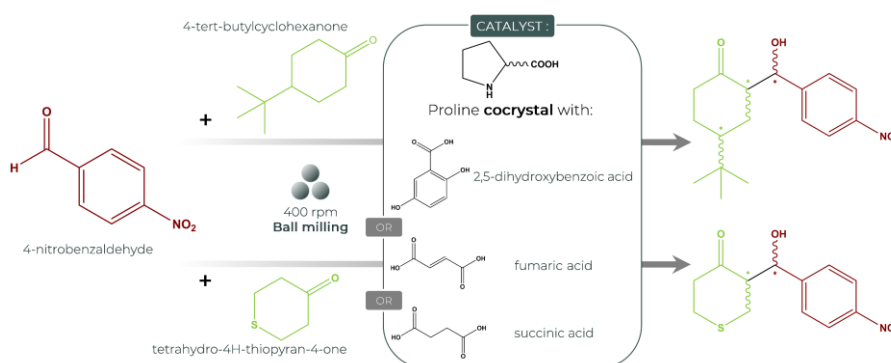


Figure 7 | General outline of reactions studied in chapter two.

In chapter 3, we will focus on a photochemical [2+2] cycloaddition reaction in the solid phase, for which we will try to obtain complete selectivity.

In solid-state photochemical [2+2] cycloaddition reactions, the arrangement of molecules within the solid impacts the regioselectivity of the reaction. The reaction between the double bonds can take place if mainly two criteria are met: the distance between them must be less than 4.2 Å and they must be aligned correctly. Certain reactions which slightly deviate from these two criteria can however sometimes take place due to a slight molecular movement within the crystal. Depending on the relative orientation of the groups on either side of the double bonds, different regioisomers of cyclobutane can be reached (Figure 8).

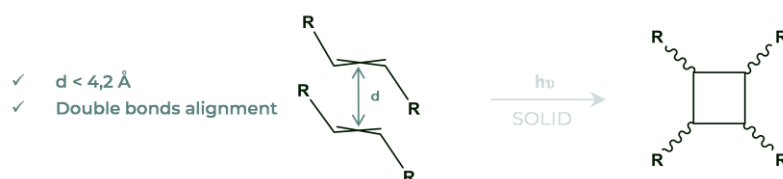


Figure 8 | Illustration of a solid-state photochemical [2+2] cycloaddition reaction fulfilling the reaction criteria. Depending on the position of the R groups, different regioisomers can be reached.

In this project, we will mainly focus on dimerization reactions of cinnamic acid derivatives (molecules comprising a double bond with on both sides an acid group and a phenyl group) which have already proven themselves in terms of reactivity in the solid-state. Cinnamic acids can by dimerization lead to truxillic and truxinic acids. These two acids are distinguished by the relative position of the acid and phenyl groups on the cyclobutane formed. Phenyls are found next to each other in truxinic acids while they are opposite to each other in truxillic acids (Figure 9). Some of these regioisomers can be achieved simply by irradiating the pure stable compound. To obtain other regioisomers, which are difficult to reach or never obtained before, it is interesting to develop methods based on solid-state principles.

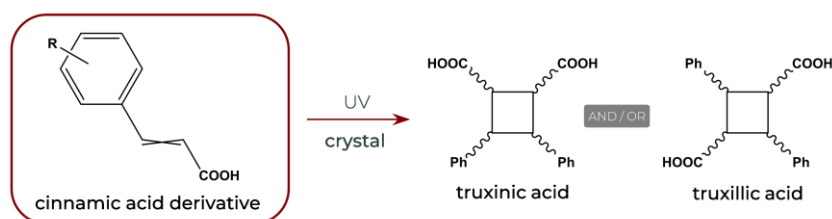


Figure 9 | Possible products of solid-state irradiation of cinnamic acid derivatives. Truxinic acid with phenyls next to each other and truxillic acid with phenyls opposite to each other.

The goal of this part of the project is therefore to play on the orientation of molecules within the solid using crystal engineering, more specifically by formation of cocrystals. By screening different cocrystallization agents with different cinnamic acids derivatives, we hope to be able to find new crystal structures in which the cinnamic acid molecules would be aligned in such a way as to lead after

irradiation to different regioisomers compared to those obtainable by the parent compounds (Figure 10).

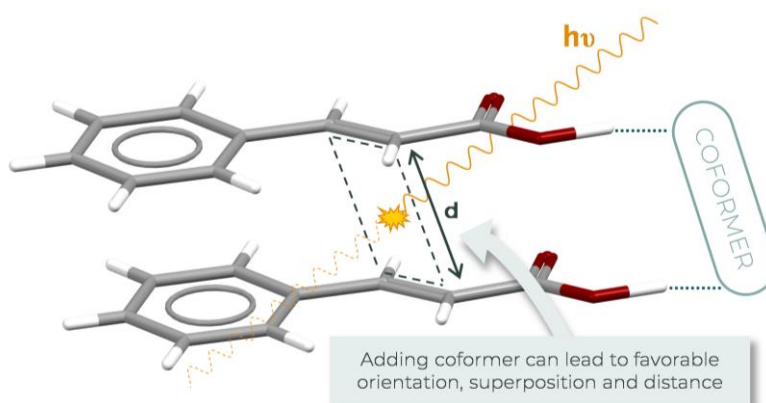


Figure 10 | example of controlling the orientation of cinnamic acid molecules (here *trans*-cinnamic acid) within the crystal, by adding a coformer. Upon irradiation, the reaction leads to a specific regioisomer (here β -truxinic acid)

Initially, the method developed in this project will go through solution, i.e. the formation of the cocrystal. The irradiation step will be done in the solid-state, at wavelengths ranging from 270 – 320 nm. But the cocrystal formation step could also be done using ball-milling, by mechanochemistry. The idea behind this would be to couple these two steps into one, by irradiating the compounds directly into the mill.

A total of 52 cocrystallization agents will be tested with different cinnamic acid derivatives: *trans*-cinnamic acid, 2-ethoxy-*trans*-cinnamic acid, 2-methoxy-*trans*-cinnamic acid, 2-methoxy-*cis*-cinnamic acid and 4-methoxy-*trans*-cinnamic acid (Figure 164).

In this thesis, we chose to discuss recent advances for each of these two topics at the onset of chapters II and III, rather than in a general introduction. We did, nevertheless, decide to add a small chapter (chapter I) giving basic theoretical reminders of the physicochemical principles and techniques necessary for the understanding of this project. These reminders are written for students who would like to enter the field.

CHAPTER I

A REMINDER ON BASIC CONCEPTS

A REMINDER ON BASIC CONCEPTS

1. Basic concepts about isomerism

1.1 Stereoisomer vs regioisomer

The concept of isomerism is used in organic chemistry to distinguish molecules having the same gross molecular formula but having different spatial (stereoisomerism) or structural (constitutional isomerism) arrangements. This classification is shown in Figure 11. The first type, **constitutional isomers**, are differentiated by different sequences of their atoms; they do not have the same structural formula and can be subdivided in functional isomers, or positional isomers. These latter are also called **regioisomers**. **Stereoisomers**, on the other hand, have the same structural formula (their atoms are linked to each other similarly) but they differentiate via the spatial organization of atoms. When this spatial arrangement is due to simple bond rotation, stereoisomerism is said to be conformational. When this spatial arrangement is due to the placement of substituents on e.g. an asymmetric atom (B, C, N, Si, P, S), known as a « stereogenic » atom, (or other ways seen in the next point), the stereochemistry is said to be configurational.

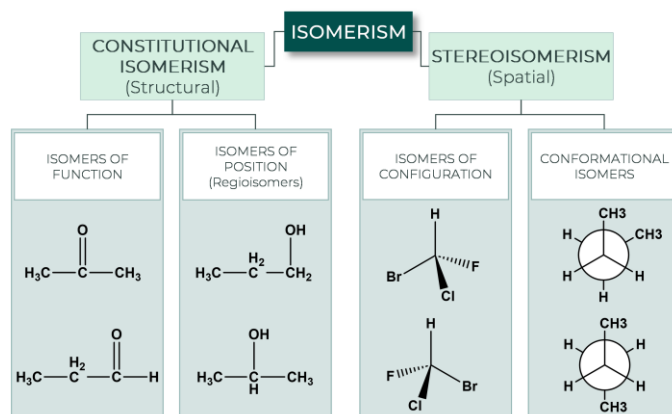


Figure 11 | Different types of isomerism.

1.2 Chirality due to an asymmetric atom

The notion of **chirality** has intrigued scientists for 174 years now. In 1848, Pasteur published his work « *Research on the relationships that may exist between the crystalline form, the chemical composition and the direction of rotary polarization.* », [9] which he carried out on tartaric acids (wine ferments), shown in Figure 12. This research led to the idea of molecular asymmetry, today called chirality. An object is chiral, when it is not superimposable on its mirror image. These two mirror images are called **enantiomers** for molecules (stereoisomer-like isomers) and enantiomorphs for macroscopic objects such as crystals. Pasteur showed that in the specific case of the double sodium-ammonium salt of tartaric acid, the two enantiomers could be separated by hand upon crystallization, merely by analyzing the form of the crystals.

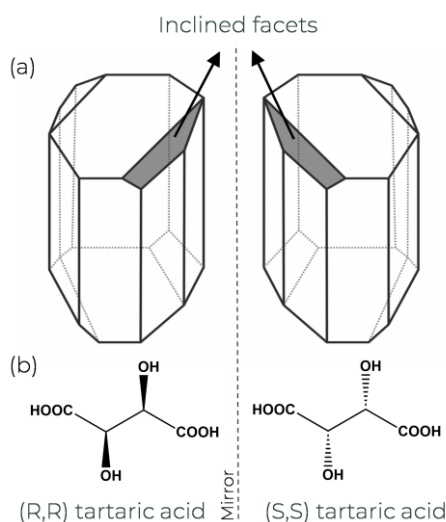


Figure 12 | (a) Hemihedral crystals of double sodium-ammonium tartrates. (b) Chemical structures of enantiomeric tartaric acid. (Adapted from [10])

Tartaric acid is a molecule showing the most well-known type of chirality, called central chirality. Chirality in this case, is due to asymmetric/stereogenic atoms called chiral centers. There are however other ways of inducing chirality. Binol, for example, shows an axial chirality, while ferrocene has a planar chirality, see Figure 13.

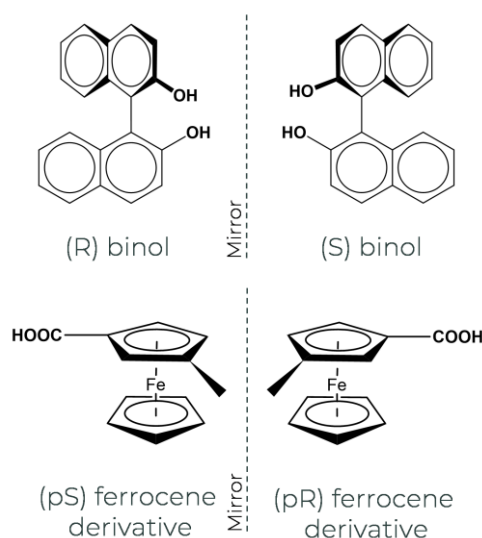


Figure 13 | Binol is characterized by axial chirality, while ferrocene shows planar chirality.

Enantiomers are true mirror images and as such have identical physical and chemical properties, with exception of those properties impacted by spatial arrangement. A typical example of this, is the difference in interaction with polarized light, illustrated in Figure 14. Polarized light is obtained by passing normal light (whose electric field oscillates in all directions) through a polarizer (which will cause the electric field to oscillate in a single plane). When polarized light passes through an achiral compound, its plane of polarization remains unchanged (**optically inactive** compound). On the other hand, when it crosses a chiral compound, its plane changes direction (**optically active** compound). An optically active compound is **dextrorotatory** if it rotates the plane of polarization clockwise and **levorotatory** if it rotates this plane anticlockwise. If a given enantiomer is dextrorotatory, the opposite enantiomer is levorotatory. [11]

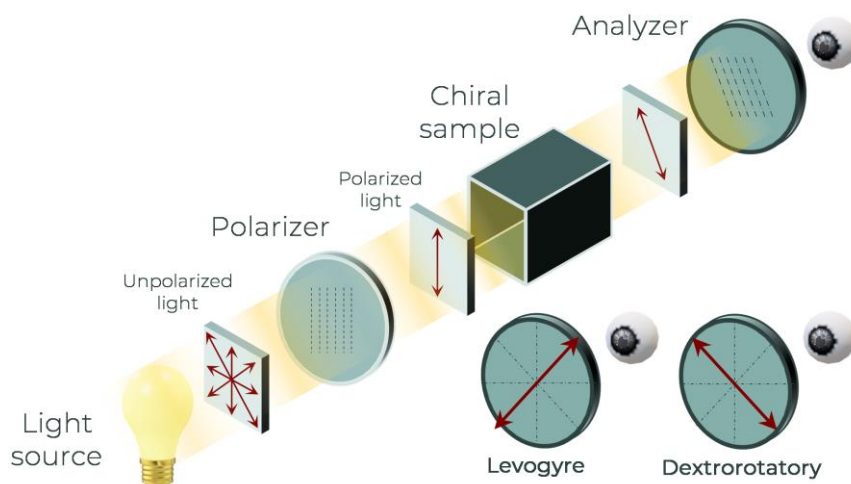


Figure 14 | Principle of creation of polarized light and its interaction with a chiral sample.

1.3 Asymmetric multi-center stereoisomers

When several asymmetric centers are present on a molecule, a multitude of stereoisomers can be formed depending on the configuration of each center. A compound can have a maximum of 2^n stereoisomers, where n is the number of asymmetric centers, provided that no center of inversion or plane of symmetry is present on the molecule.

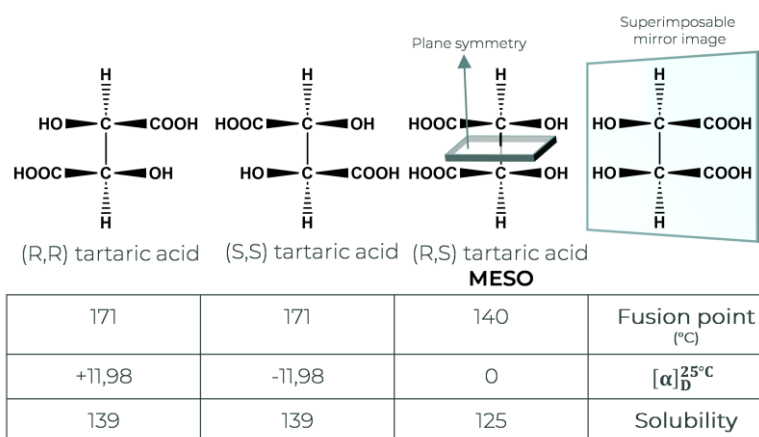


Figure 15 | Difference in some physical properties between two enantiomers and a diastereoisomer (solubility is in g / 100 g of H₂O at 15°C).

When multiple chiral centers are present, not all stereoisomers are enantiomerically linked to each other. If they are not enantiomers, the stereoisomers are called **diastereoisomers**. Diastereoisomers have different physical properties (melting point, boiling point, solubility, etc.) and different chemical properties (so they do not react at the same rate with an achiral reagent contrary to enantiomers) (Figure 15).

In case a mirror-plane occurs in the molecule, both mirror images of the compound superimpose. In this specific case, the compound is called a **meso**-compound and the compound should be considered non-chiral, see Figure 15. [12]

Different nomenclatures exist to determine the spatial arrangement. The **Cahn-Ingold-Prelog (CIP)** priority system makes it possible to establish a nomenclature to differentiate between stereoisomers. R/S nomenclature is used for asymmetric centers, most commonly sp^3 carbons. The E/Z nomenclature is used for diastereoisomers, most often having sp^2 carbons. The CIP system is not used for *cis-trans* nomenclature, which is governed by steric hindrance.

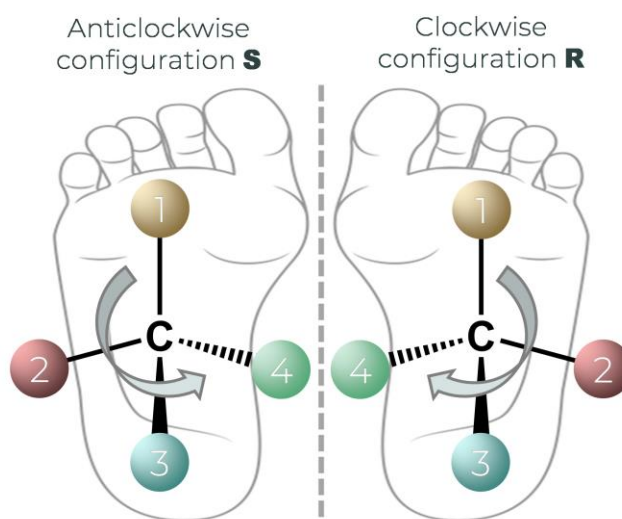


Figure 16 | Application of Cahn-Ingold-Prelog rules.

The order of priority of substituents indicates the rating R or S, as represented in Figure 16. For each substitute, the relative priority depends on the atomic number of the atoms (Z) directly linked to the asymmetric center; the higher it is, the higher its focus will be. If two substituents are centrally bonded with the same atom, then the atomic number of the next atom defines the precedence and so on. A lone pair of electrons is considered as an atom with atomic number 0. Double and triple bonds are regarded as two and three single bonds, respectively. The *cis* configuration takes precedence over *trans*.

In the presence of a mixture of two enantiomers, the term **racemic** is used if the quantities of R and S are equal. Conversely, the term non-racemic will be used when there is an excess of one enantiomer over the other. This **enantiomeric excess (ee %)** can be calculated using Equation 1 (n_R and n_S represent the molar fractions of each enantiomer. C_R and C_S represent the concentration of each enantiomer). The concentration of each enantiomer required, can be obtained for example by chromatography or chiral NMR or else by polarimetry. [13]

$$ee \% (R) = n_R - n_S = \frac{C_R - C_S}{C_R + C_S} \times 100 \quad (\text{Eq. 1})$$

1.4 Chirality and its importance in everyday life

Throughout observation of microorganism Pasteur noted that chirality and life seemed intimately related. He found that some microorganisms consume only a specific enantiomer of a chiral compound. [14]

A very surprising feature in of some biological processes is their ability to produce optically active molecules. In general, biosynthesis of a substance that has asymmetric centers almost always leads to the formation of a pure stereoisomer. Amino acids in protein e.g. all have the same configuration, which is also true for sugars. Why terrestrial life chose one handedness over another remains one of the enigmas

of the origins of life. Because of this single handedness of amino acids, two enantiomers of a given chiral substance can behave very different in a biological environment. These different interactions lead to differences in the biological activities of the two enantiomers, such as toxicity, immune response, etc. This explains why production of pure enantiomers aroused enormous interest in the agrochemical, perfume, aroma and especially pharmaceutical industries. [15]

Figure 17, shows a model which explains why enantiomers can show a different biological response. In this model, the three substituents A, B and C of the active enantiomer can interact with the three binding sites a, b and c of the receptor. In case of the inactive enantiomer there will always be a mismatch of at least one of the binding sites.

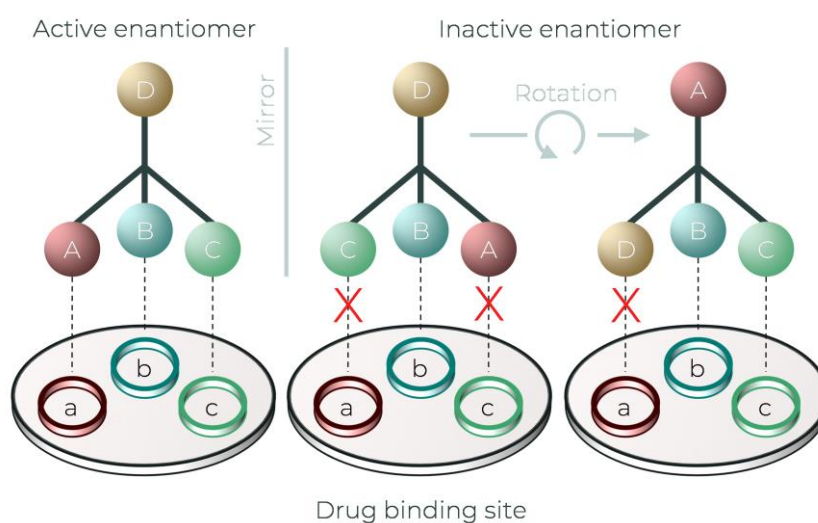


Figure 17 | Illustration of the Easson-Stedman hypothetical interaction between two enantiomers of a racemic drug with a receptor at the drug binding sites. (Adapted from [16])

The importance of chiral drug development should not be underestimated. Since the 1950s and specifically the disaster related to thalidomide, chirality has been very important in the development of biologically active compounds. [10] In 2006, 56% of drugs on the market were chiral and only 12% of them were commercialized under

an enantiopure form. [16] A pharmacological development strategy called “chiral switch” (which refers to the market replacement of a previously approved racemate by its enantiopure version) was important between 1994 and 2011. However, this strategy has been used less frequently during the last decade leaving more room for the market introduction of enantiopure chiral drugs. [17] This is mainly due to new FDA and EMA regulations which push to favor the development of new enantiopure compounds at the expense of the “chiral switch” strategy. [18] Figure 18 shows the number of achiral, racemic and enantiopure drugs approved annually by the FDA during the period 2010-2020.

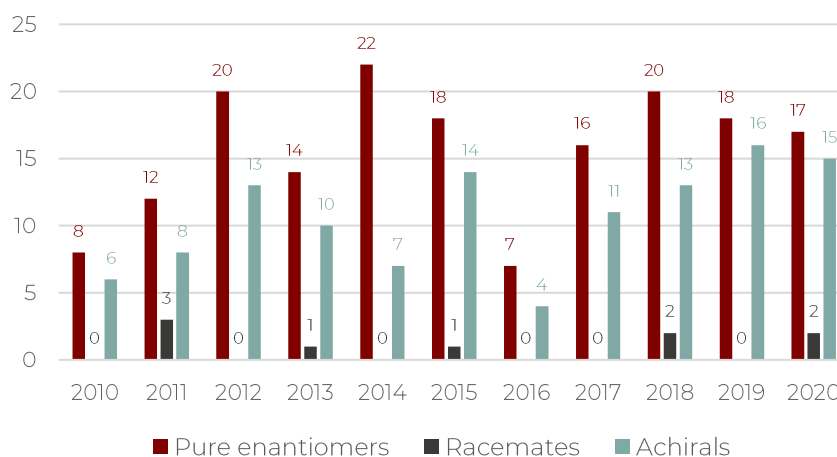


Figure 18 | Comparison on the number of yearly FDA approved drugs (pure enantiomers, racemates and achiral compounds) over the period 2010-2020. (Adapted from [18])

1.5 Separating enantiomers and chiral chromatography

The manual separation of enantiomers carried out by Pasteur cannot serve as a universal method, because only a small number of compounds form asymmetric crystals under certain specific conditions. Most of the time enantiomers crystallize together and form a single kind of symmetrical crystals. To quote Pasteur: « *Chance only favours the prepared mind.* »

Fortunately, enantiomers can now be easily separated using various chiral methods (chromatography, cocrystallization, etc.). Using a chiral medium can help separate enantiomers as they will behave differently in such an environment. Like a left foot that prefers a left shoe.

Chiral chromatography makes it possible to physically separate enantiomers. Like any **chromatographic method**, compounds are separated based on their distribution between a mobile and stationary phase. The **mobile phase, liquid** in liquid chromatography (LC) or gaseous in **gas** chromatography (GC), flows along the solid stationary phase. The mobile phase carries the various compounds through the stationary phase, which will be able to retain compounds more or less strongly on its surface. When a compound is adsorbed on the stationary phase, its speed is zero whereas it flows at the speed of the mobile phase the rest of the time. The elution speed is the average speed of a compound, itself determined by the fraction of the time spent by the compound in the mobile and stationary phases respectively. In this way, the affinity of the compounds for one phase or the other results in different elution speeds enabling the separation of compounds. At the limit where the compound would have no affinity for the stationary phase, the compound elutes at the rate of the mobile phase, in which it spends the entire time.

Different types of chromatography are distinguished according to the **nature of the phases** and the **physical or chemical interactions** they provide: Size-exclusion chromatography (SEC), ion-exchange chromatography (IEC), chiral stationary phase (CSP), inverse-phase, normal-phase, etc. These different types of phases can be arranged in a wide variety of geometries to cover the range of analytical and preparative applications: Thin-layer chromatography (TLC), high performance liquid chromatography (HPLC), flash chromatography, etc.

A typical **chromatograph** is described in Figure 19, the mobile phase solvents are contained in a reservoir. Pumps mix them and push

them through a column. An injector, often automatic, injects the samples through the column. Coupled with a detector (such as UV, Fluorescence, mass spectrometer, etc.), a two-dimensional representation, called a **chromatogram**, can be obtained after data processing. The two dimensions are signal intensity and time, showing different retention/elution time of compounds. The eluted compounds will be represented as peaks which allow a qualitative or quantitative analysis.

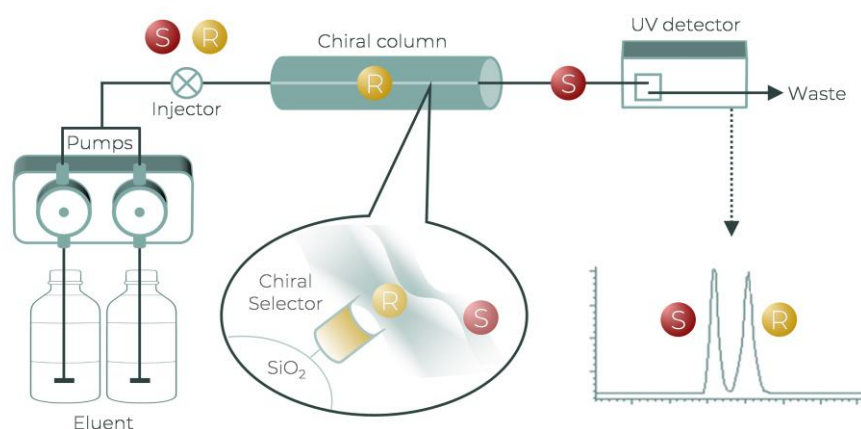


Figure 19 | Working principle of chiral HPLC

The most commonly used chiral chromatography is **high-pressure liquid chromatography** (HPLC) where a thin column contains the solid **chiral stationary phase** (CSP). Most of the time, these chiral stationary phases consist of a silica gel on which are grafted chiral molecules expressing specific interactions for each enantiomer.

1.6 Selectivity and specificity not always clear

Selectivity and specificity are two concepts that are often confused. In organic synthesis, they make it possible to describe and/or predict the structural and stereochemical relationships between reactants and products, as well as the yield.

While a selective reaction *selects* according to different factors (such as access to the reaction center, steric hindrance, ...) between several

possible products, a specific mechanism will *specify* the product formed by the reaction (depending on the reactants used).

Selectivity refers to the fact that for several products made possible by a reaction, only one predominates. The mechanism of the reaction favors the formation of one product over the others.

- A reaction is **regioselective** if it can lead to several position isomers and only one is the majority.
- A reaction is **stereoselective** if it can lead to several stereoisomers and only one is predominant. If the possible stereoisomers share a diastereoisomeric or enantiomeric relationship, the reaction can be said to be diastereoselective or enantioselective.

Specificity refers to the fact that the result of the product obtained by a reaction depends on the reactant involved. The mechanism of the reaction leads to a single product. [19]

- The term **regiospecificity** can be used for highly regioselective reactions.
- The term **stereospecificity** can be used for highly stereoselective reactions.

2. Crystal engineering

2.1 Intermolecular interactions

Intermolecular interactions (Figure 20) are essentially electrostatic in nature (created by electric charges). They induce attractions or repulsions between particles. [20]

Van der Waals interactions can be decomposed into three terms: Keesom forces (**dipole - dipole interactions**), Debye forces (**induced dipole - dipole interactions**) and London dispersion forces (**induced dipole - induced dipole interactions**).

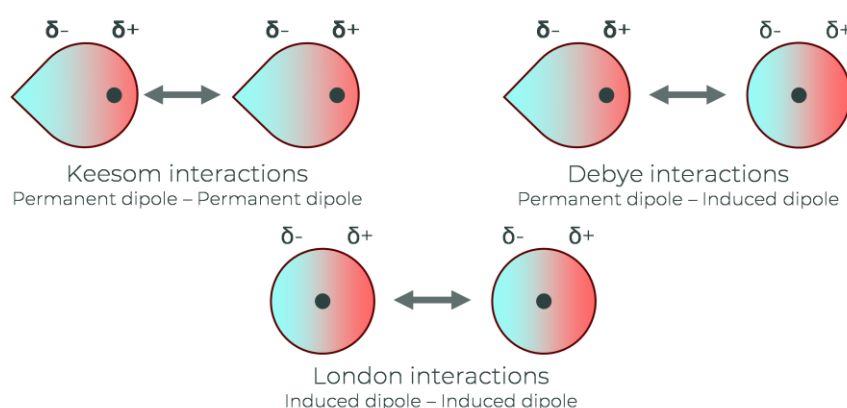


Figure 20 | Van der Waals interactions

A **permanent dipole** results in a polar particle having an asymmetric charge distribution. The centroids of its positive and negative charges do not coincide which generates a **dipole moment**. If a molecule is polarizable, its electronic cloud will be deformed under the effect of an electric field, resulting in the formation of an **induced dipole**. This electric field can for example be generated by a polar molecule or another induced dipole. London forces exist because there is a strong chance at any time the electron density of the particles will not be evenly distributed across the particle. This creates a dipole moment which can itself induce a dipole in another particle.

Hydrogen bonding is a permanent dipole - permanent dipole type interaction between a hydrogen atom bonded to an electronegative atom (F, O, N, Cl) and a non-bonding pair of another electronegative atom. The electrons of the covalent bond between the hydrogen and the electronegative atom will be attracted to the latter. The hydrogen will then be endowed with a positive partial charge which will itself be attracted by a negative partial charge (the non-binding doublet). This bond can be intra- or intermolecular. The bond energy of hydrogen bonds is about ten times greater than Van der Waals interactions. In addition, hydrogen bonds are directional bonds. This can be explained by the fact that they are only 90% electrostatic and possess a covalent bond character for about 10%. [21] Figure 21 shows a representation of hydrogen bond in ice.

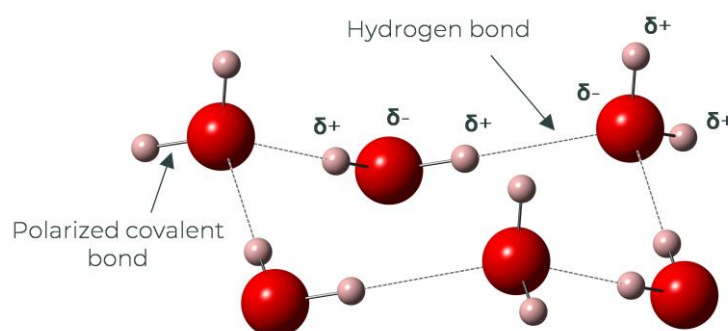


Figure 21 | Hydrogen bond in ice.

Halogen bond is, like the hydrogen bond, an interaction between an electron-deficient atom and an electron-rich entity, except that the electron-deficient atom with a positive partial charge is not a hydrogen atom, but a halogen such as Cl, I, Br or F (Figure 22). [22]



Figure 22 | E (donor) participates in the formation of the electrodeficient species (H or X). A (acceptor) is the rich electron entity.

$\pi - \pi$ stacking is an interaction between aromatic rings since they contain π electron clouds above and below their ring. The arrangement of aromatic rings can be done in three different ways: sandwich, parallel displaced stacking, or T-shaped (Figure 23).

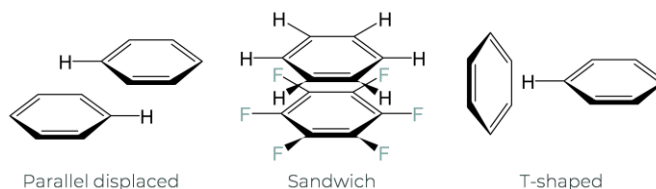


Figure 23 | Arrangement of aromatic rings with $\pi - \pi$ stacking.

Depending on the stack, the interactions can be repulsive or attractive. For example, the sandwich packing of benzene will be electrostatically stabilized by London interactions between the two electron clouds but will be destabilized due to repulsive quadrupole interactions. The staggered configuration reduces these repulsive interactions. The T-shaped configuration involves quadrupole attractive interactions (Figure 24).

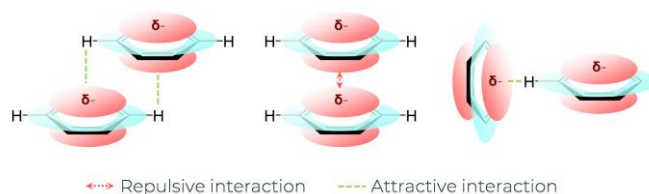


Figure 24 | Repulsive and attractive interactions for different arrangements of aromatic rings in a $\pi - \pi$ stacking.

The polarity of the aromatic ring can be reversed with electronegative substituents. In this case, sandwich stacking will be favored electrostatically.

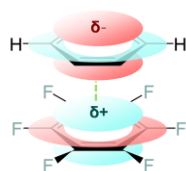


Figure 25 | Attractive interaction in a sandwich arrangement with reversed polarity.

Figure 26 represents the overall potential interaction for a two-particle system. Starting from two distant particles, and bringing them closer together, the potential decreases. At a particular stage, we can no longer bring the molecules together because we cannot superimpose them. The potential, therefore, passes through a minimum and rises sharply once the distance is too low. As the structure is fixed by the various intermolecular interactions, the potential of the system decreases, which releases energy. Energy must be supplied to a frozen system to overcome these interactions.

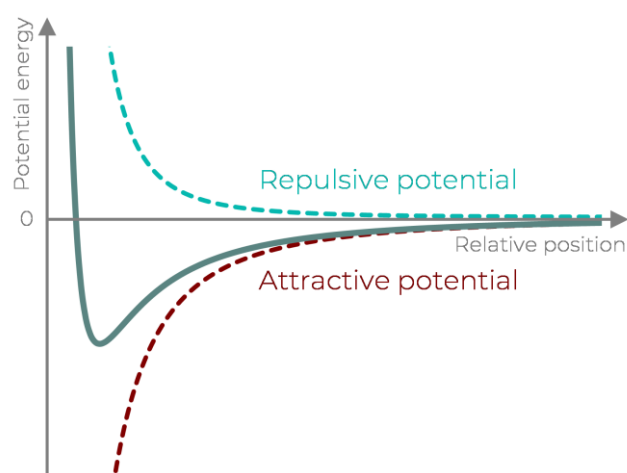


Figure 26 | Potential energy curve of two particles according to their relative position.

Table 1 shows the main intra- and intermolecular interactions as well as an approximation of their energy in kJ/mol. When an intramolecular bond forms between two atoms, this combination has less energy than the total energy of the two separate atoms. When this lower energy is due to the complete transfer of electrons, the interaction is said to be ionic. On the other hand, if this is due to a sharing of electrons, the interaction is said to be covalent. The metallic interaction can be represented as a sea of electrons in which a large number of cations are maintained.

Table 1 | Summary of the major intra- and intermolecular interactions.

	Kind of interaction	Interaction factor	Energy (KJ/mol)
Strong bond	Covalent bond	Orbital overlap	100 – 1000
	Ionic bond	Ions charge	400 – 1000
	Metallic bond	Delocalized electrons	75 – 1000
Weak bond	Hydrogen bond	Electronegativity (90%)	10 – 40
	Halogen bond	Electronegativity	10 – 200
	$\pi - \pi$ stacking	Electronegativity	8 – 12
	Van der Waals	Electronegativity	5 – 25

2.2 States of matter – Phase transitions

Matter can be found in different states (or phases). The main ones are the solid, liquid and gaseous states. In gaseous form, matter does not have its own volume or its own shape. The gas will occupy all the available volume (disregarding gravitation otherwise the stars would be diluted in space). Particles (atoms, molecules or ions) are bodies independent of each other. Apart from the instants of collision, they are relatively distant from each other. In liquid form, matter has its own volume but does not have its own shape. The liquid will take the shape of the container that holds it. The particles are held close to each other by intermolecular interactions but continue to move by rolling past each other. In solid form, matter has its own volume and shape. The particles are arranged to each other in a fixed configuration to a first approximation. The stability of the structure is due to the intermolecular interactions existing between its constituents. Depending on the energy of the particles, the intermolecular interactions will or will not be strong enough to keep the system in a solid or liquid state.

In a gas, the particles have a kinetic energy such that intermolecular interactions are inoperative. In a liquid, particles have less kinetic energy than in a gas. The intermolecular interactions are therefore strong enough to keep the particles close to each other, but their kinetic energy is still too great for these interactions to be able to keep

them fixed. In a solid, the kinetic energy of the particles is low enough for intermolecular interactions to dominate and freeze everything.

The temperature of a system is directly related to the **kinetic energy** E_{kin} of the particles that compose it. When energy is supplied to a system, it will generally increase the kinetic energy of the particles and therefore the temperature. However, once a certain threshold is reached, the addition of energy breaks the cohesion maintained until then by intermolecular interactions. In a solid, the particles detach from each other in a process called fusion. In a liquid, particles break free from each other, in a process called boiling. These state changes are accompanied by an increase in the **potential energy** E_{pot} of the system, without an increase in the temperature of the system, as shown in Figure 27. Indeed, some work (force x displacement) must be done to overcome interactions. Once all interactions are broken, the added energy will again be stored as kinetic energy and the temperature will rise again. Since the energy variation of the system is positive, melting and boiling are endothermic phase transitions, just like sublimation. Conversely, freezing, condensation and deposition release energy, the energy variation of the system is therefore negative, these phase transitions are therefore exothermic. As shown in Figure 28. The potential jumps shown can be explained via Figure 26. Indeed, during the transition from a gas to a liquid, or from a liquid to a solid, the system descends into the well of potential. Energy is then released, so the transition is indeed exothermic.

The sum of the kinetic (corresponding to the movements of the particles that constitute it) and potential (corresponding to the interactions between the particles that constitute it) energies of a system, i.e., the total energy, is called **internal energy** U . When a system passes from an initial state i , of internal energy U_i to a final state f , of internal energy U_f , this change of energy is noted ΔU .

$$U = E_{\text{kin}} + E_{\text{pot}} \quad (\text{Eq. 2})$$

$$\Delta U = U_f - U_i \quad (\text{Eq. 3})$$

The energy exchange of a system with its environment, which will therefore vary the kinetic and potential energies of the particles, can take place in the form of **heat transfer Q** or via **work W** . In general, this work is carried out as expansion work against constant external pressure.

$$\Delta U = Q + W = Q - P \Delta V \quad [J] \quad (\text{Eq. 4})$$

The quantity of energy exchanged in the form of heat is part to increase the internal energy and in part to push away the atmosphere, and is called **enthalpy ΔH** .

$$\Delta H = Q = \Delta U + P \Delta V \quad [J] \quad (\text{Eq. 5})$$

The quantity of energy exchanged in the form of heat during a change of state results from the modification (rupture or establishment) of intermolecular interactions. At constant temperature and pressure, this energy **Q** is called **enthalpy of transformation** (or latent heat) **ΔH** for a quantity of matter **n** .

$$\Delta H = \frac{Q}{n} \quad [J/mol] \quad (\text{Eq. 6})$$

The **(molar or mass) heat capacity at constant pressure C_p** , is the quantity of heat **Q** that must be transferred to a certain quantity of matter **n** to increase its temperature by a certain quantity. (**C_v** at constant volume).

$$C_p = \frac{dQ}{n dT} \quad [J/Kmol] \text{ ou } [J/Kg] \quad (\text{Eq. 7})$$

In Figure 27, the C_p is considered constant in each state. In reality, it increases with temperature, giving curves and not straight lines.

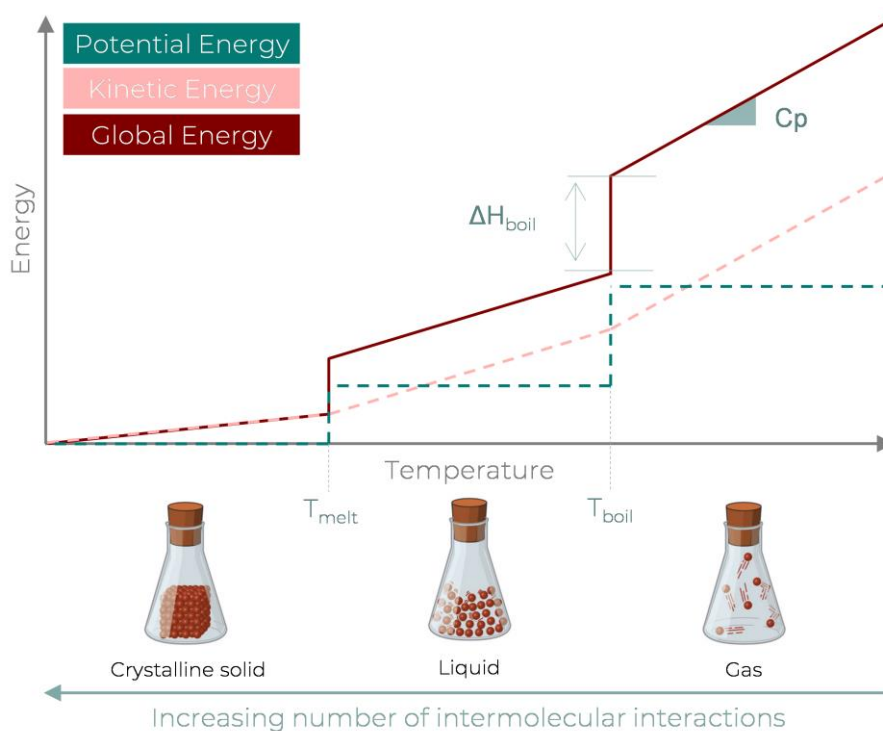


Figure 27 | Potential and kinetic energy in different states of matter when energy is added to the system. In each phase, this energy makes it possible to increase its kinetic energy and therefore its temperature. During each phase transition, intermolecular interactions are broken, resulting in an increase in potential energy. (Images of the Erlenmeyer flasks are reproduced from [23])

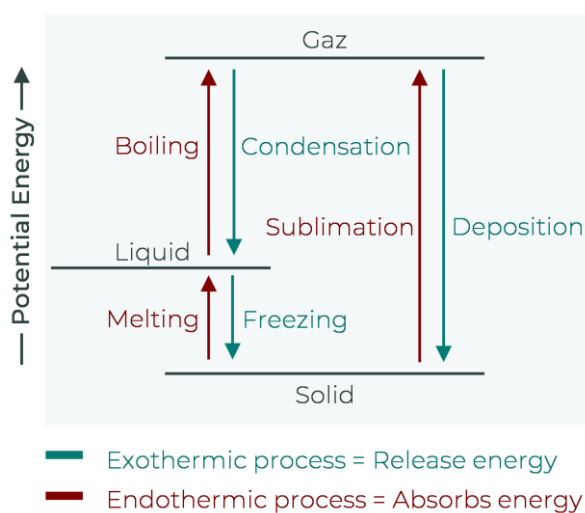


Figure 28 | Phase transitions.

The example of melting benzene can be used to visualize the correlation between enthalpy of change of state and intermolecular interactions. The enthalpy of fusion of benzene is around 10 kJ/mol and the energy of the $\pi - \pi$ interactions are around 8 to 12 kJ/mol. [24]

Transitions between different phases are due to changes in intermolecular interactions and do not affect intramolecular interactions. Intramolecular forces take place within the particle itself and hold it together, like covalent bonds. Intermolecular forces, on the other hand, take place between molecules and determine many properties. Generally intramolecular forces are much stronger than intermolecular forces. For example, it takes 17 kJ to change one mole of liquid HCl to gas, while it takes 430 kJ to break the covalent bonds between H and Cl. [23]

2.3 Thermal analyses of phase transitions using DSC

Since heat is usually released or absorbed during phase transitions, it is possible to observe them using thermal analyses, such as **differential scanning calorimetry** (DSC). The heat absorbed or released by a sample is measured when, by Joule effect (current which heats a resistance), the temperature of the sample and that of a reference are continuously increased, at constant pressure. This analysis is carried out under an inert atmosphere to avoid any reaction with the atmosphere of the furnace.

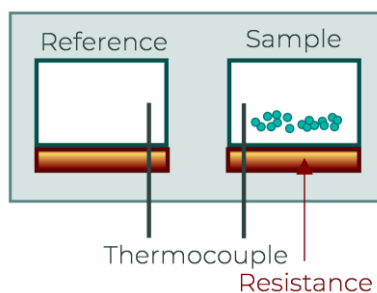


Figure 29 | Differential scanning calorimeter schematic diagram.

The DSC is composed of two small compartments each containing a resistance. By a current, the resistors heat up at a constant rate. The electrical power supplied is adjusted to maintain the same temperature in the two compartments throughout the analysis. To constantly increase the temperature of the reference, the power will be the same all the time. On the other hand, for the sample, it will depend on the physical or chemical transformations which will absorb or release energy. For a process that releases energy, the power will be decreased. Because this released energy will participate in an increase in temperature in the compartment. A graph representing the difference between the sample and the reference in terms of their response to the temperature increase is obtained.

If no physical or chemical process occurs from a temperature T_0 to a temperature T , then the quantity of heat supplied is equal to $Q_p = C_p \Delta T$. Again, it is assumed here that the heat capacity C_p is constant and does not vary with temperature.

On the other hand, if a physical or chemical process intervenes, then the quantity of heat supplied to reach the same temperature T is equal to $Q_p + Q_{p,ex}$.

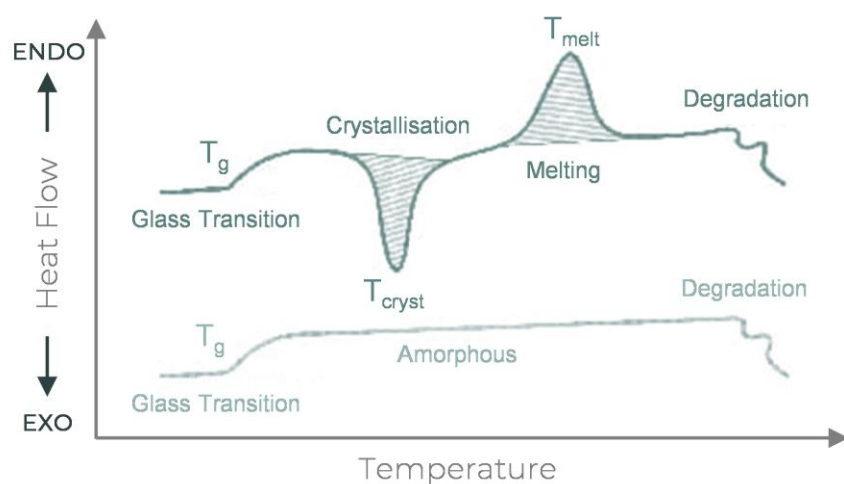


Figure 30 | Curve of differential scanning calorimetry. Heat flow (proportional to the electric power) as a function of temperature. (Adapted from [25])

2.4 Solid-state – Crystal – Crystal engineering

An ordered and periodic arrangement of particles in a solid characterizes it as **crystalline**, unlike **amorphous** solid forms in which the particles are disordered over medium and long distances. (At short distances, most compounds are ordered). This is illustrated in Figure 31 for SiO_2 .

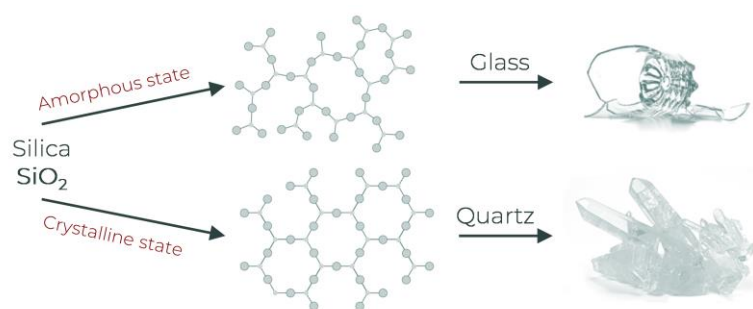


Figure 31 | Amorphous and crystalline state.

The different physicochemical properties of a crystalline solid and the resulting properties such as bioavailability are directly related to the intermolecular interactions existing between the particles that compose it. [26–28]

Table 2 | Physicochemical properties of solids.

Physical and thermodynamic properties	Density, thermal and electrical conductivity, hygroscopicity, melting points, free energy, chemical potential, heat capacity, vapor pressure, solubility, thermal stability
Spectroscopic properties	Electronic, vibrational and rotational, nuclear magnetic resonance
kinetic properties	Rate of dissolution, kinetics of solid-state reactions, kinetic stability
surface properties	Surface free energy, crystal habit, surface area, Particle Size Distribution
Mechanical properties	Hardness, compression, thermal expansion, packing efficiency
chemical properties	Chemical and photochemical reactivity, reactivity with excipients

Solid-state scientists use different strategies when trying to alter the properties of a compound by altering its crystal form; namely the formation of polymorphs, hydrates, solvates, salts and cocrystals, illustrated in Figure 32. The non-volatile molecule in a cocrystal is called a **coformer**. These different crystalline forms will be detailed in the following points. [29, 30]

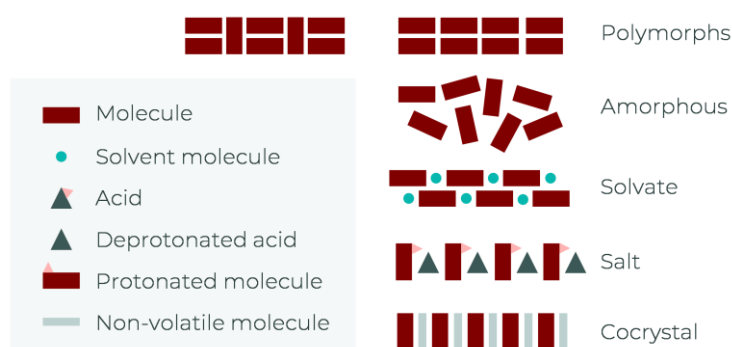


Figure 32 | Schematic depiction of various types of crystalline solid forms (polymorphs, solvate, salt and cocrystal) and amorphous solid. (Adapted from [31])

This interest in the origin and nature of intermolecular interactions and their use in the design and preparation of new crystal structures constitutes **crystal engineering**.

The earliest appearances of the term crystal engineering are most often associated with G. M. J. Schmidt. He was recognized for the correlation he made between the solid-state reactivity and the crystal structure of many photodimerizable compounds such as cinnamic acids. After which he will describe the futuristic period of research in the field of crystal structure prediction as « the phase of crystal engineering ». [32, 33] The definition, today used to define crystalline engineering, was given by Desiraju in 1989: « *Crystal engineering is the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in design of new solids with desired physical and chemical properties.* » [34]

Crystal engineering uses the rules of supramolecular chemistry. It is based on intermolecular interactions to build new solid forms. [35–37] The most used interactions in this field are the hydrogen and halogen bonds and less importantly, the π - π staking. These interactions define substructure patterns, called **supramolecular synthon**. [38] It is a practical concept aimed at understanding and designing molecular crystal structures. When the supramolecular synthon occurs between two identical functional groups, it is called homosynthon. When the supramolecular synthon occurs between two different functional groups, it is called heterosynthon, see Figure 33. The supramolecular synthon formation may be made for example, between molecules having hydrogen bond donors and hydrogen bond acceptors.

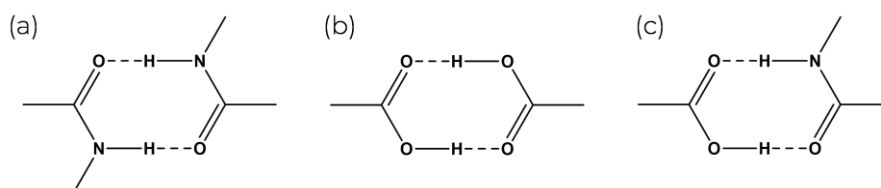


Figure 33 | (a) Amid-amid homosynthon (b) Acid-acid homosynthon (c) Acid-amid hetero-synthon.

2.5 Crystallization process

Obtaining solid forms with adequate physical and chemical properties is crucial. In general, crystallization is obtained by reducing the solubility of the compound in a solution, via cooling, evaporation, addition of an anti-solvent or a combination of these methods. Another method commonly used to cause crystallization is to carry out a chemical reaction; for example, an acid base reaction which forms a salt which precipitates. **Solubility curves** are commonly used to illustrate the relationship between solubility, temperature, and solvent type. Depending on the solvent used, the solubility curve will be different. If the solubility of a compound is high in a certain solvent, then a large amount of product can be crystallized per unit mass of solvent.

For the crystallization of a solid from a solution to take place, the concentration in solution must be higher than the solubility, the solution is said to be supersaturated. A solution can retain its supersaturation for a certain time, called the **induction time**, without the formation of a new solid phase over a whole concentration range. This range, called **metastable zone width (MZW)**, therefore describes the zone where nucleation is not yet spontaneous. [39] It lies between the spontaneous nucleation curves (kinetic event) and the solubility curve (thermodynamic event). As the supersaturation increases, the induction time decreases. The MZW depends on the degree of supersaturation imposed on the system by the rate of evaporation and cooling or the use of an antisolvent decreasing the overall solubility. It also depends on the stirring conditions.

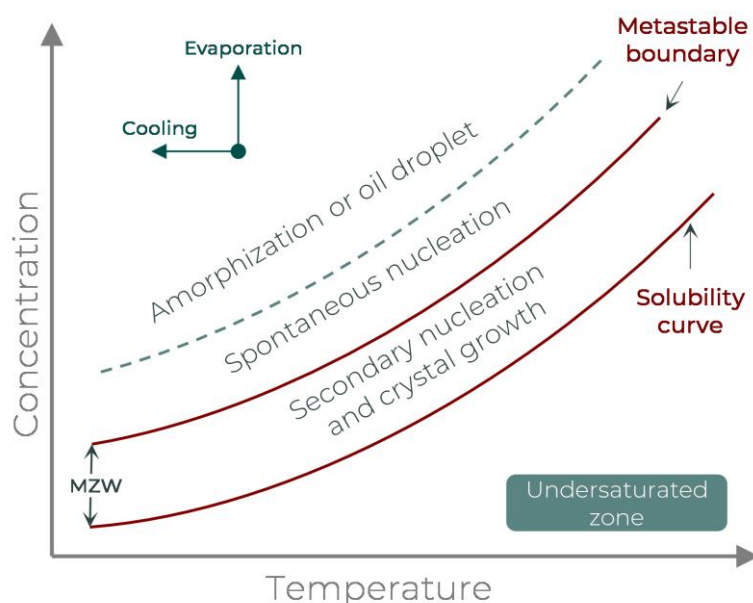


Figure 34 | Zones in a solution: this diagram is a hypothetical expanded map between supersaturation and various crystallization phenomena.

Depending on the importance of the degree of supersaturation, several phenomena can therefore occur, represented in Figure 34: [40]

- In the metastable zone, before the induction time, secondary nucleation (concept explained later) and crystal growth can take place.
- Once the metastable zone has been crossed, spontaneous or primary nucleation (concept explained later) can take place.
- Too much supersaturation can lead to amorphization or oil formation due to the viscosity of the solution.

By accurately identifying dissolution points (points on the solubility curve) and nucleation points (points on the metastable boundary curve) at different solute concentrations, it is possible to determine the metastable zone width.

A crystallization process takes place in two stages: nucleation and crystal growth. At the first stage, **nucleation**, a new phase is formed in the solution, new crystals appear. This step will determine the emerging crystalline phase. It is then obvious that it is necessary to seek the conditions of nucleation in which the nucleation of the desired crystalline form happens first compared to the others. During rapid nucleation, several crystals form almost simultaneously. The growth of these crystals depletes the medium in solute and the crystallization stops. In this case, the majority of the crystals reach approximately identical sizes. On the other hand, if the nucleation is slow, few crystals nucleate at the same time. The supersaturation in the solution then slowly decreases and new crystals nucleate. The crystals then have different sizes. The control of the nucleation therefore makes it possible to control mainly the size, the size distribution and the polymorphism of the crystals (concept which will be described later). In the second stage, **crystal growth**, particles gradually attach to nuclei to form larger crystals (Figure 35). [41]

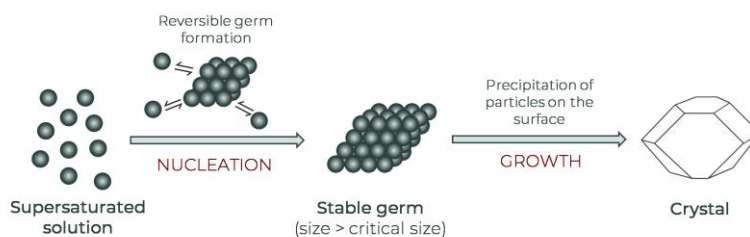


Figure 35 | Formation of a crystal by evaporation of a supersaturated solution – nucleation and growth phenomena.

This two-step separation is related to free energy; crystal growth is simply a kind of chemical reaction that takes place in free-energy descent, while nucleation can only occur by initially going free-energy ascent.

Theories explaining nucleation mechanisms are generally divided into two categories: classical nucleation theory and non-classical nucleation mechanisms.

Throughout the 20th century, **classical nucleation theory** (CNT) dominated. This theory makes it easy to understand the processes involved in crystallization. In this theory, the particles arrange themselves in subcritical seeds following the successive aggregation of the particles to finally form a critical seed, so as to minimize their free energy. To be a critical seed, that is to say a stable seed that can subsequently grow and become a crystal, it must reach a certain size. As long as this size is not reached, the subcritical, unstable germ can dissolve after its appearance (Figure 36).

The observations of the last 20 years have brought out several other theories, the so-called non-classical theories. One of the main ones is the **two-step nucleation** which envisages that the molecules of a saturated solution, first assemble into a sort of disordered dense phase from which a crystalline nucleus emerges. [42] These two theories are illustrated in Figure 37.

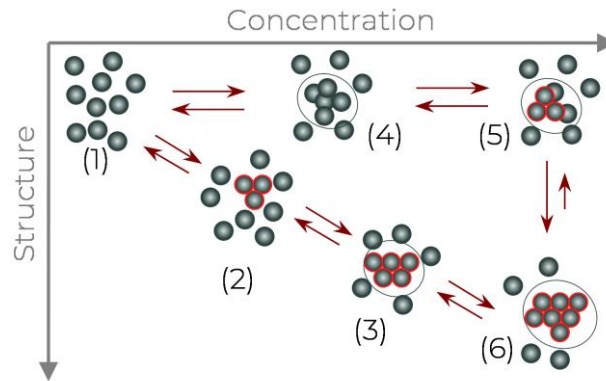


Figure 36 | In a homogeneous initial liquid (1), CNT suggests the formation of subcritical germs following the successive aggregation of particles (2) until reaching the critical germ (3). The subcritical and critical seeds directly have the structure of the crystal (6). In contrast, the two-step nucleation theory suggests a first step with the formation of a denser disordered phase (4). In the second step (5), the high density in this denser phase increases the rate of nucleation.

With regard to free energy, the classical theory of nucleation involves only one jump. The two-step theory involves two jumps. On Figure 37(b), the intermediate minimum corresponds to the dense liquid phase and the final minimum corresponds to the crystal resulting from the structuring of the intermediate phase. ΔG^*_1 is the kinetic barrier for the formation of a dense liquid phase, ΔG^*_2 , the kinetic barrier for the formation of a crystal nucleus in the dense liquid phase. [43]

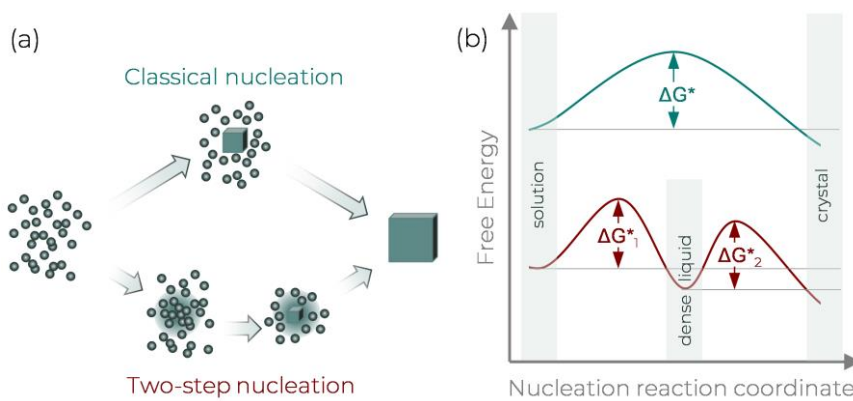


Figure 37 | (a) Schematic illustration of mechanism of nucleation of crystals. Classical nucleation and two-step nucleation. (b) The free energy ΔG along the two possible nucleation pathways: classical nucleation, top; two-step nucleation, bottom.

As shown in Figure 38, two main types of nucleation exist. **Primary nucleation**, where the first crystals appear spontaneously and **secondary nucleation**, where nucleation is induced by other crystals of the same compound that are already present. This nucleation technique is seeding. It can help to achieve the desired crystalline form. During a primary nucleation, if this nucleation is due to the presence of a foreign body (for example dust), then this nucleation is said to be **heterogeneous**. Unlike **homogeneous** nucleation where crystals appear in solution without any external help.

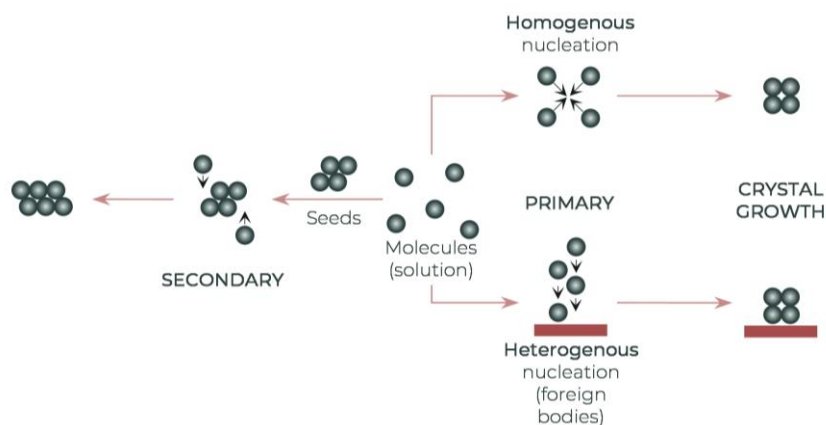


Figure 38 | Different sorts of nucleation.

2.6 Polymorphs

The presence on the same particle of several permanent and/or induced dipoles enriches the possibilities of interactions. The particles can then arrange themselves in various ways in a solid. Different crystal arrangements of the same chemical composition are called polymorphs (Figure 39). According to McCrone's definition: « *The polymorphism of any element or compound is its ability to crystallize as more than one distinct crystal species.* » [31] Since from one polymorph to another it is different intermolecular interactions that fix the structure, the polymorphs have different physicochemical properties. These differences disappear in the liquid or vapor phases. [44–48]

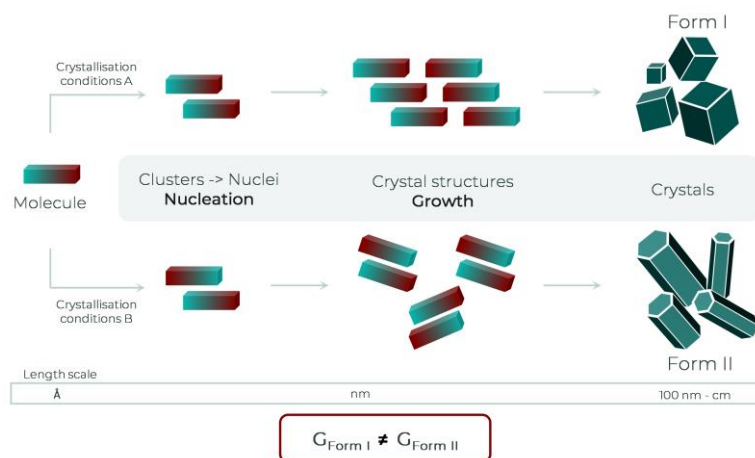


Figure 39 | Growth of two polymorphs.

According to the Gibbs energy as a function of temperature, a stable polymorph can be unstable at another temperature. [49] At a given pressure, 2 types of systems are encountered : monotropic and enantiotropic polymorphic systems, represented on Figure 40. In a monotropic system, there is only one stable form, no matter the temperature. In an enantiotropic system, there is a temperature, called the **transition temperature**. Below the melting point, one polymorph is stable and above this temperature, the other polymorph becomes the most stable. If the higher melting polymorph has lower heat of fusion, the polymorphs are enantiotropically related, otherwise monotropically.

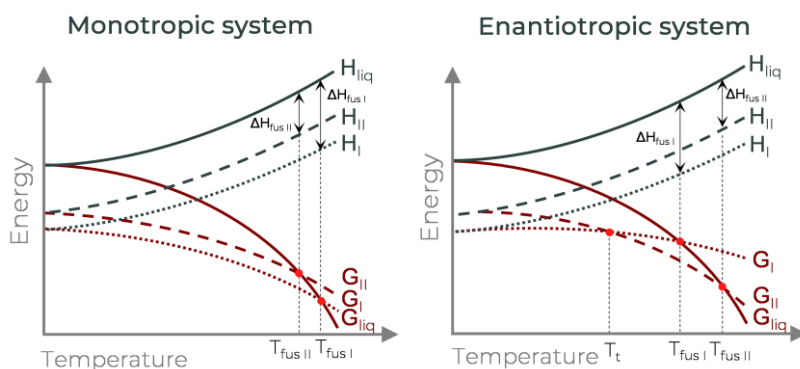


Figure 40 | Theoretical monotropic and enantiotropic energy diagrams of two polymorphs.

According to Figure 40, the enthalpy increases with the increment of temperature. The slope of the curvature can be expressed as C_p . Based on the third law of thermodynamics; the value of entropy term (TS) is positive. The Gibbs free energy decreases with the temperature, since the slope of curvature is equal to the negative value of the entropy. [50]

The nucleation kinetics and the (thermodynamic) stability of the polymorphs influence the first polymorphic form observed during crystallization and the polymorphic form which will be stable over time. [51] In general, during the crystallization of a compound, the system does not go directly to the most stable conformation (corresponding to the lowest free energy) but prefers to reach intermediate stages (called metastable) having the free energy closest to the initial state (Figure 41). The system will continue to evolve until equilibrium, towards the most stable polymorph. This is Ostwald's rule, it is not a universal law but a common tendency observed in nature. [52]

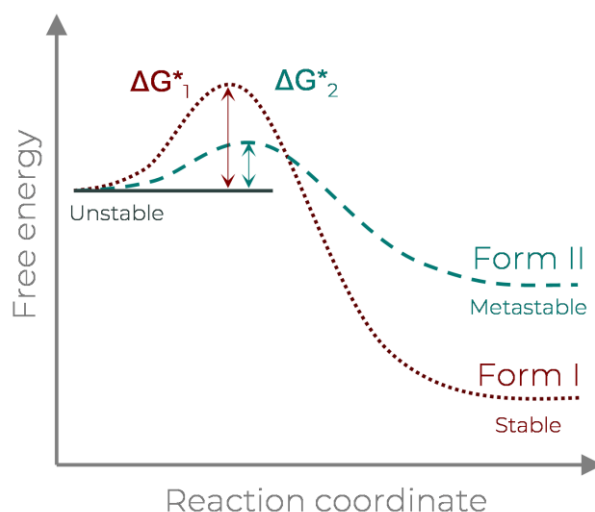


Figure 41 | The Ostwald's rule of stages in the case of one metastable polymorph and a stable polymorph.

A high-profile case of polymorphism was ritonavir, a drug used to treat HIV-1 infection and introduced in 1996. In 1998, a more stable, low-energy polymorph (Form II) appeared, causing slow dissolution of the marketed form and compromising the oral bioavailability of the drug. The solubility of the two ritonavir polymorphs was related to the structure of the solid form. Form II exhibits lower solubility and dissolution than form I, thanks to the presence of stronger hydrogen bonds and a better arrangement (all the strong hydrogen bond donors and acceptors have been satisfied). [53]

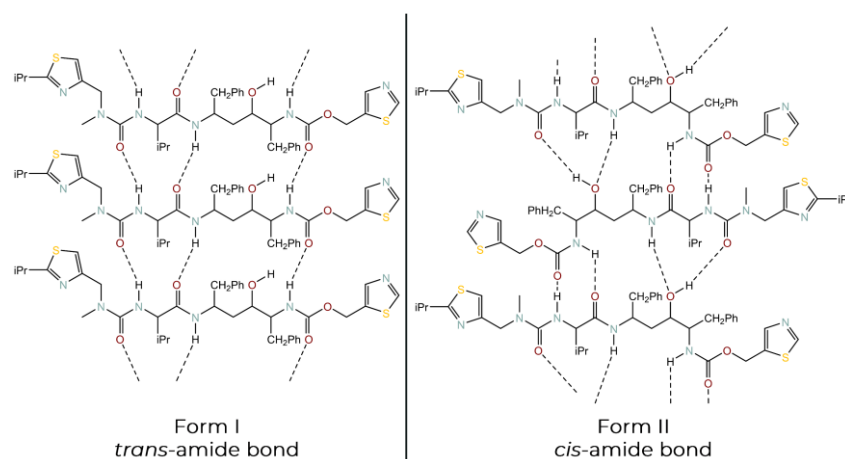


Figure 42 | Hydrogen bonds present in ritonavir form I and form II crystal structures. (Adapted from [54])

2.7 Cocrystals, salts and solvates: How to classify?

There is no universally accepted definition of cocrystals yet, either in the pharmaceutical industry or in the scientific literature.

The scientific community prefers the classification shown in Figure 43. Classes are not mutually exclusive and give seven subclasses. [55] For an unambiguous classification, multicomponent solid forms must fall into a single subclass.

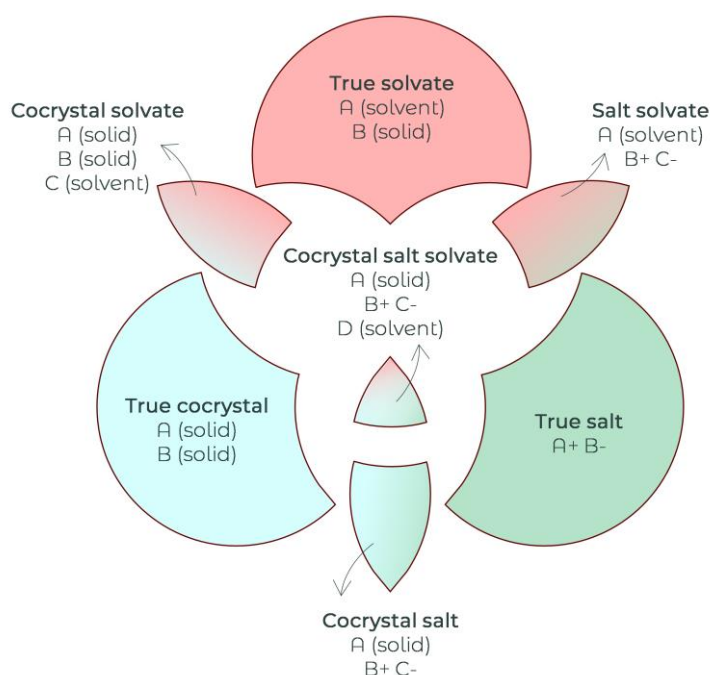


Figure 43 | Scientific classification of solid-states. (Adapted from [55])

Scientists define a **cocrystal** as follows: « Solids that are crystalline single phase materials composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ration which are neither solvates nor simple salts. » [56]

Salts and cocrystals can be distinguished by the location of the proton between an acid and a base. In a **salt** the hydrogen atom is transferred from the hydrogen donor (acid) to the acceptor (base). In cocrystals proton transfer is absent. It is the forces of the acid and the base, as well as the crystal environment, which will determine the extent of the proton transfer. For example, it has been shown that aminophylline hydrate and anhydrate exhibit different protonation states even though they are the same acid-base pair. [57] The location of the proton can be determined by X-ray or neutron diffraction experiments as well as spectroscopic data. [58] But this is not always the case. pK_a values can be indicators of salt or cocrystal formation. [59] As a general rule of thumb, salts form when there is a difference

greater than 3 units of pK_a between both species : ΔpK_a (pK_a (base) - pK_a (acid)) > 3. There will be formation of a cocrystal when ΔpK_a is inferior to 0. Between these two extremes, for acid-base complexes with similar pK_a values, proton transfer is not predictable, as the structure effects prevail. Often disordered structures occur, leading to the existence of a so-called salt-cocrystal continuum. Normally pK_a values describe equilibrium behavior in solution and are not intended to be applied to the solid-state. However, these values give useful indications. [60]

In a **solvate**, solvent molecules can be found in two different ways in a crystal structure. Either they are integrated into the crystal structure and form interactions with molecules of the compound, or they are found into spaces of the crystalline structure created between molecules of the compound. A main issue with solvates is that solvents can be volatile. After a while, a solvate can therefore be desolvated and amorphized or transform to a different crystalline state.

2.8 Amorphous phase

The amorphous phase is a solid phase exhibiting some short-range ordering, on the order of a few Angstroms, similar to that of a crystal, in contrast to the long-range organization of the crystalline state. [61, 62] In principle, the formation of an amorphous phase occurs when the rate of solidification is faster than the rate at which molecules can organize themselves into the crystal structure. [63] A pure amorphous phase is characterized by a **glass transition** T_g , kinetic parameter, which is the vitrification temperature of a liquid and may vary depending on the temperature scanning rate. This transition takes place without the release or absorption of heat. [64]

Glasses represent the majority of amorphous solids, they are comparable to tiny fragments of liquid, with a very high viscosity, which makes it possible to classify them among the solids. [65]

Various solidification paths of a liquid can occur, as shown in Figure 44:

- During sufficiently slow cooling, the compound follows the ADEF path. It is then a simple crystallization of the particles below the melting temperature (T_m).
- When cooling too quickly, the compound follows the DB line. The compound then remains in the liquid state, below its melting point. The viscosity increases rapidly and continuously, the compound does not crystallize and becomes a glassy solid.

Imagining that the compound remains liquid, line BG, it will cut the crystal line, line EF, at point H. The corresponding temperature is called the **Kauzmann temperature** T_K . [66] Below this temperature, the enthalpy of the subcooled liquid is lower than that of the crystalline solid. Which would mean that the liquid is more ordered than the solid. This fact, called Kauzmann's paradox, is impossible because a liquid cannot be more ordered than a crystalline solid. [67] However, this paradox is avoided in practice because the subcooled liquid always turns into a glassy solid before reaching T_K . [61, 68]

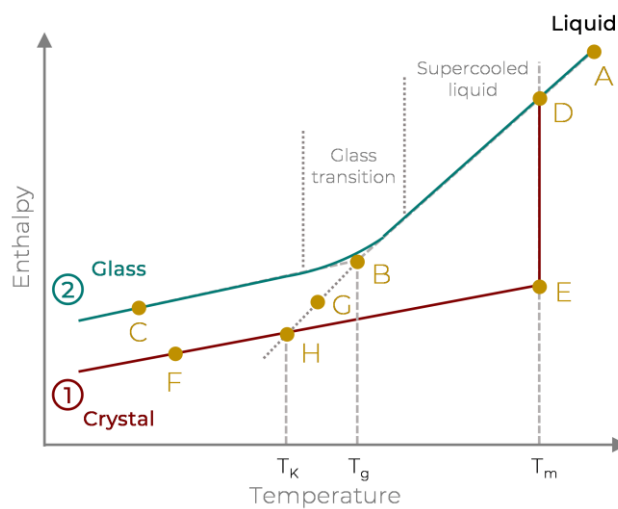


Figure 44 | Enthalpy variation from a liquid phase to a glass or a crystalline phase, as a function of temperature.

2.9 Symmetry of crystals

General considerations:

As previously described, a perfect crystalline form is characterized by an infinite periodic and ordered arrangement in three dimensions, of a repeating pattern of atoms, molecules or ions, called **structural units**. The position of each single pattern can be represented by a point, called **node** and forms a **spatial lattice** (tridimensional translation lattice), represented in Figure 45. The spatial lattice is therefore similar to an ordered three-dimensional and infinite set of points. The crystalline structure can then be obtained by associating the same structural unit with each node of the lattice.

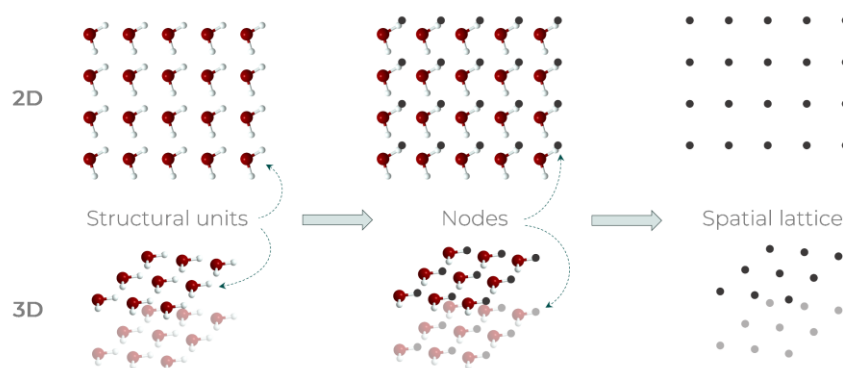


Figure 45 | Illustration of structural units forming a spatial lattice in 2 and 3 dimensions. The use of water molecule is just for illustration and is not the real arrangement of an ice crystal.

Connecting adjacent nodes forms parallelepipeds called **unit cells**, each of those parallelepipeds having the same content. The whole object can be built from the unit cell using only translation (Figure 46a). The lengths of the edges and the angles of a unit cell, called **unit cell parameters**, are denoted respectively a , b , c and α , β , γ (Figure 46b). It is important to note that there are several ways to define the unit cell for a lattice.

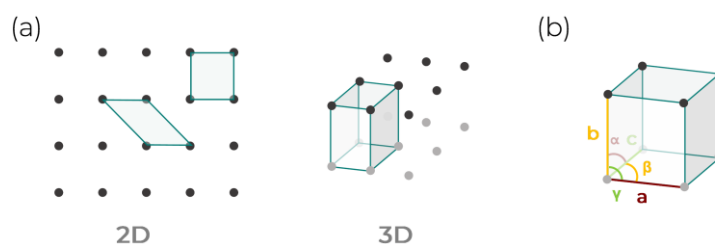


Figure 46 | (a) Example of unit cell in 2 and 3 dimensions. (b) unit cell parameters : lengths and edges.

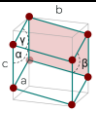
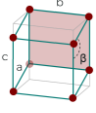
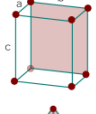
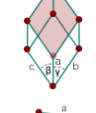
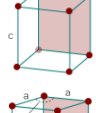
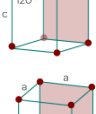
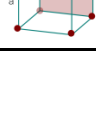
Classification of periodic objects :

Two approaches are possible to describe periodic objects. The first approach considers the lattice as a starting point, leading to 7 reticular systems and leading to 14 Bravais lattices, considering the lattice symmetry. The second considers the point symmetry that can be found in the crystal (considering its content), leading to 32 point symmetry groups. These 32 point symmetry groups can be classified in 7 crystal systems, characterized by the presence of minimal symmetry elements. For a complete classification of periodic objects (into 230 space groups as we will see further), it is necessary to combine those approaches.

Classification according to the lattice

In three-dimensional geometry, there are 7 types of parallelepipeds (corresponding to 7 **reticular systems**), which allow to tile a periodic object, listed in Table 3. Any periodic lattice can be described with at least one of those systems. In a reticular system, all the crystals that share the same symmetry point group of the lattice are grouped together. In some cases, the way the unit cell is chosen will change the category of the geometry. By convention, the unit cell corresponding to the system with the highest symmetry is chosen. (see Figure 47).

Table 3 | Seven unit cell geometries.

Unit cell geometry	Type of unit cell	Lattice symmetry
Triclinic	 $a \neq b \neq c$ $\alpha \neq \beta \neq \gamma \neq 90^\circ$	$\bar{1}$
Monoclinic	 $a \neq b \neq c$ $\alpha = \gamma = 90^\circ$ $\beta \neq 90^\circ$	$2/m$
Orthorhombic	 $a \neq b \neq c$ $\alpha = \beta = \gamma = 90^\circ$	mmm
Rhombohedral	 $a = b = c$ $\alpha = \beta = \gamma \neq 90^\circ$	$\bar{3}m$
Tetragonal	 $a = b \neq c$ $\alpha = \beta = \gamma = 90^\circ$	$4/mmm$
Hexagonal	 $a = b \neq c$ $\alpha = \beta = 90^\circ$ $\gamma = 120^\circ$	$6/mmm$
Cubic	 $a = b = c$ $\alpha = \beta = \gamma = 90^\circ$	$m\bar{3}m$

To go further in the classification based on the lattice, we must now introduce the concept of centering. The **primitive unit cell** that we have considered in all the examples above is the smallest possible unit cell, with nodes only at its vertices. As the 8 nodes are each shared between 8 neighboring cells, there is a total of 1 node per unit cell. However, there are cases where the full symmetry of the lattice does not appear in the primitive unit cell, hence the use of a **conventional unit cell** which highlights the full symmetry of the lattice (see Figure 47). Besides the nodes at its vertices, the conventional unit cell may include nodes at its center or on its faces.

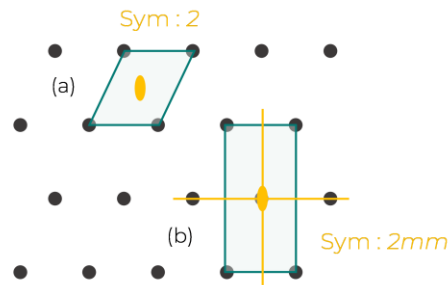
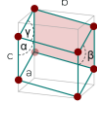
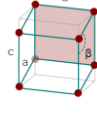
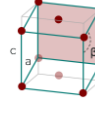
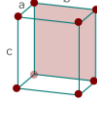
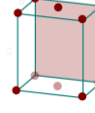
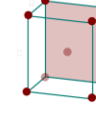
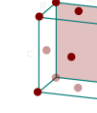
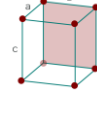
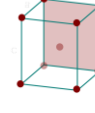
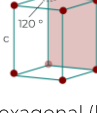
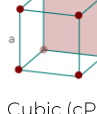
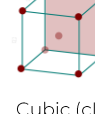


Figure 47 | Example of primitive and conventional unit cell in 2D. (a) primitive unit cell with low symmetry – only one 2-fold axis. (b) centered unit cell with high symmetry – 2-fold axis with 2 mirror planes.

Primitive unit cells (P) have nodes only at the vertices. The centered elementary unit cells (I) also have a node in their center. Face-centered unit cells (F) have nodes in the center of each of their six faces. Unit cells with two centered faces (S) have nodes at the center of two opposite faces. An additional centering mode (rhombohedral centering) will not be described herein.

By using centering, the 7 unit cell geometries extend into 14 **Bravais lattices** allowing the classification of all three-dimensional periodic lattices (Table 4).

Table 4 | Seven unit cell geometries and fourteen Bravais lattices.

Unit cell geometry	Bravais lattices			
Triclinic $a \neq b \neq c$ $\alpha \neq \beta \neq \gamma \neq 90^\circ$	 Triclinic (aP)			
Monoclinic $a \neq b \neq c$ $\alpha = \gamma = 90^\circ$ $\beta \neq 90^\circ$	  Monoclinic (mP) Monoclinic (mS)			
Orthorhombic $a \neq b \neq c$ $\alpha = \beta = \gamma = 90^\circ$	    Orthorhombic (oP) Orthorhombic (oC) Orthorhombic (oI) Orthorhombic (oF)			
Rhombohedral $a = b = c$ $\alpha = \beta = \gamma \neq 90^\circ$	 Rhombohedral (hR)			
Tetragonal $a = b \neq c$ $\alpha = \beta = \gamma = 90^\circ$	  Tetragonal (tP) Tetragonal (tI)			
Hexagonal $a = b \neq c$ $\alpha = \beta = 90^\circ$ $\gamma = 120^\circ$	 Hexagonal (hP)			
Cubic $a = b = c$ $\alpha = \beta = \gamma = 90^\circ$	   Cubic (cP) Cubic (cI) Cubic (cF)			

Classification according to morphological symmetry (group theory)

Within a finite object, several elements of point symmetry can be found, passing through its center. Those elements can be reduced to rotation and roto-inversion axes. All elements constitute what is called a point symmetry group. It is easy to visualize that there is an infinite number of point symmetry groups, as they can be built around 2-fold, 3-fold, ..., ∞ -fold rotation axes.

Switching from finite objects to periodical objects imposes restrictions on the symmetry operations. It can be shown that 5-fold axes and above 6-fold axes are not compatible with the periodic nature of the object. This reduces the number of possible **point symmetry groups** to 32.

Combining the lattice approach and the point symmetry approach

In crystallography these 32 point symmetry groups are classified in 7 **crystal systems** characterized by the presence of minimal symmetry elements: triclinic (one 1-fold axis), monoclinic (one 2-fold axis or one mirror plane), orthorhombic (three 2-fold axes or two mirror planes with one 2-fold axis), tetragonal (one 4-fold axis), trigonal (one 3-fold axis), hexagonal (one 6-fold axis), cubic (four 3-fold axes and three 2-fold axes).

The correspondence between lattice symmetry (reticular system) and crystal morphology symmetry (crystalline systems) is only partial (See Table 5). The correspondence is complete for the triclinic, monoclinic, orthorhombic, tetragonal and cubic systems. However, crystals in the trigonal crystal system can have either a hexagonal or a rhombohedral lattice.

Table 5 | Relation between crystal systems, Bravais lattice and point symmetry groups.

Bravais lattices	Crystal systems	Point symmetry groups
aP	Triclinic	$1, \bar{1}$
mP, mS	Monoclinic	$m, 2, 2/m$
oP, oS, oF, oI	Orthorhombic	$mm2, 222, mmm$
tP, tI	Tetragonal	$4, \bar{4}, 4mm, \bar{4}2m, \frac{4}{m}, 422, 4/mmm$
hR	Trigonal	$3, \bar{3}, 3m, 32, \bar{3}m$
hP	Trigonal	$3, \bar{3}, 3m, 32, \bar{3}m$
hP	Hexagonal	$6, \bar{6}, 6mm, \bar{6}2m, 6/m, 622, 6/mmm$
cP, cF, cI	Cubic	$23, m\bar{3}, 432, \bar{4}3m, m\bar{3}m$

Combining the 32 point symmetry groups with the 14 Bravais lattices would theoretically lead to 448 possibilities. Out of those combinations, some are impossible (the point symmetry must keep the translation lattice invariant), and some are redundant. Only 230 different possibilities can be distinguished. Those are called **space groups**.

Reconstruct a crystal from its minimal description :

The **asymmetric unit** is the smallest part of the crystal from which it is possible to completely generate the content of the unit cell by applying the different operations of symmetry (Figure 48) and of the full crystal by translation.

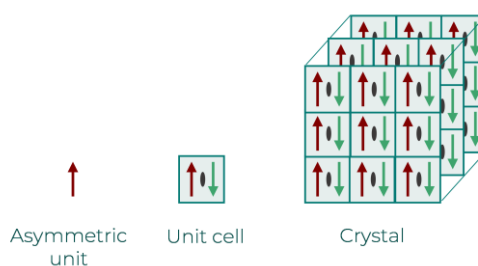


Figure 48 | The crystal assembly from the asymmetric unit to the crystal. Here the unit cell comprises a twofold rotation axis.

2.10 Characterizing crystals using X-Ray diffraction

Diffraction techniques can be used to determine with great precision the arrangement of ions, atoms or molecules in a crystalline solid.

Diffraction is a phenomenon that arises from the interactions between a wave and a periodical object. When the incident beam of electromagnetic radiation interacts with electrons, the beam is scattered in all directions (coherent scattering). In a crystal, each periodically repeating element (repeating unit) acts as an identical secondary source of the wave. Summation of all the secondary waves gives rise to destructive interferences (in most directions) or constructive interferences. Globally, the result is that the beam is partially deflected in some specific direction, intrinsically related to the geometry and symmetry of the repeating unit, and orientation of the periodical object. Diffraction is a general phenomenon that can be observed when the size of the repeating unit is similar to the wavelength. Repeating units in crystals range from a few ångströms in inorganic salts to a few hundred ångströms in proteins. Therefore, X-ray radiation, which is typically monochromatic in most crystallography applications and has a wavelength around 1 Å, is the light of choice for diffraction on crystalline matter.

Phenomenological explanation :

A crystal is constructed from a periodic infinity of identical units (unit cells), each having the same electron density map.

X-ray diffraction is based on coherent scattering. This is a phenomenon that can be observed when an X-ray beam is sent on matter, due to the electronic cloud. Taken individually, each periodic unit would scatter part of the incident beam in all directions according to a continuous angular distribution depending on the distribution of the electron density within it and the angle of the incident light. A representation of this continuous scattering is shown in Figure 49a. If we placed a linear detector to analyze the scattered light (Figure 49b), waves around a central peak would be observed.

On a circular area detector (Figure 49c), fuzzy spots would be observed around a central peak. The central peak corresponds to light that has not interacted with matter.

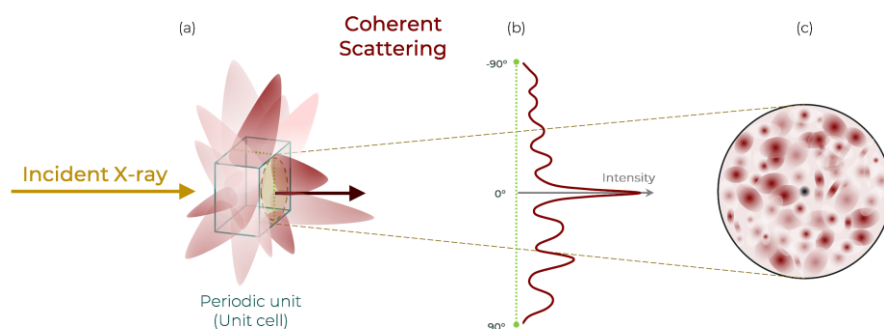


Figure 49 | (a) Coherent scattering of an isolated unit cell according to a continuous angular distribution. (b) Observation on a linear detector. (c) Observation on a circular area detector.

This description of the phenomenon on a periodic unit is purely “imaginary” in the sense that it is impossible to isolate a single unit cell and to collect its diffusion pattern on a detector. In reality, it is a gigantic number of unit cells which are irradiated at the same time and whose identical contributions, but offset in space, overlap, giving rise to the phenomenon of interference (a grain of salt with a side of 0.1 mm, barely visible, contains around 10^{15} unit cells!). It follows that the majority of the waves will be canceled (destructive interference), but that a small part will add up (constructive interference), forming a discrete diffraction pattern (Figure 50a). In a certain way, the continuous scattering is filtered by the interference phenomenon and a discrete diffraction pattern is isolated (Figure 50b). It is because the stacking of unit cells is regular that the phenomenon of diffraction can occur.

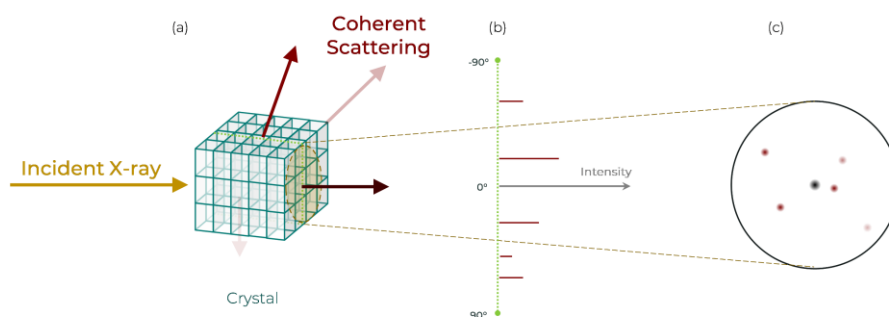


Figure 50 | (a) Coherent scattering of a crystal according to a discrete angular distribution. (b) Observation on a linear detector. (c) Observation on a circular detector.

The image observed on a circular area detector will be composed of points corresponding to the different constructive interference waves, diffracted by the crystal and reaching the detector (Figure 50c).

Mathematical explanation :

A spatial lattice can be cut by planes, called **reticular planes**, separated by a distance d . "A set of reticular planes" includes all the parallel reticular planes and intersects with all the nodes of the spatial lattice.

These planes are defined by hkl indices (Miller indices). h , k and l respectively designate the inverse of the intersection distances on the axes a , b and c . When h , k or $l = 0$ then the planes are respectively parallel to a , b or c . A representation in Figure 51 shows that the distance d between reticular planes is smaller the more the indices hkl increase.

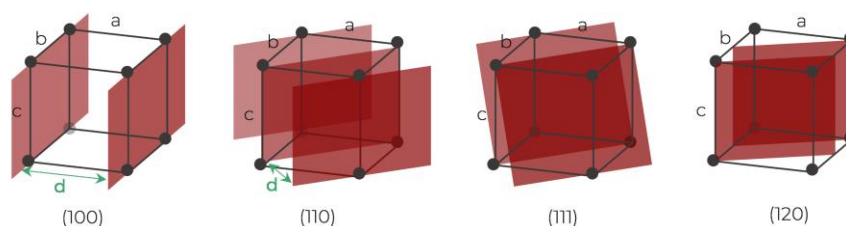


Figure 51 | Illustration of different reticular planes in a spatial lattice with orthogonal axes. Distance d is smaller the more hkl increase.

The notation (hkl) characterizes a reticular plane while the notation $\{hkl\}$ characterizes a set of equidistant planes (same d). Depending on the lattice geometry, some set of planes are equivalent. For example, in a cubic lattice, (hkl) , (hlk) , (khl) , (klh) , (lkh) , (lkh) and combinations with opposite sign are all equivalent, knowing that $(hkl) = (-h -k -l)$ for obvious geometric reasons.

Due to the periodic electron density map within a crystal, all the planes of a $\{hkl\}$ family cut this electron density map in the same way and are therefore chemically equivalent provided that their hkl indices are prime numbers between them. The other planes, which do not have prime indices between them, do not all share the same electron density map, but will generate harmonic reflections as we will see further. This stacking of parallel, equidistant, and chemically equivalent reticular planes makes interferences possible, and easy to understand using the Bragg's law.

The **Bragg's law** gives the condition for scattered waves to interfere constructively. Between two contributions, arising from different planes, the interference will be constructive when the difference in path traveled between two planes corresponds to an integer multiple of the wavelength. As shown in Figure 52, this difference in path traveled is equal to $2d \sin \theta$. The angle θ is called the Bragg angle. For most θ angles, the extra distance is not equal to an integer number of wavelengths and the waves interfere mostly destructively. This is described by Equation 8.

$$2d \sin \theta = n\lambda$$

(Eq. 8)

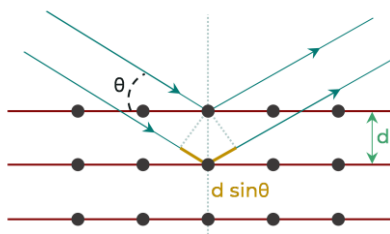


Figure 52 | Bragg diffraction. Two identical waves (of the same wavelength and same phase) approach a crystalline solid and are scattered by two different planes inside the material. The lower beam travels an additional length of $2d \sin \theta$. Constructive interference occurs when this length is equal to an integer multiple of the wavelength.

It follows that a set of equidistant planes $\{hkl\}$ (same d) will diffract at the same angle θ , and will mark a spot on the detector.

Each spot on the detector corresponds to a diffracted beam and can be characterized by an hkl position, an amplitude and a phase. The position of the spot on the detector, therefore the angle θ , gives information on the hkl planes. Information on the amplitude of the wave is obtained via the intensity of the spot. This value depends on the electron density distribution. However, the information about the phase of the wave cannot be measured. This is one of the mathematical problems in crystallography: solving the phase.

The information on the position of the spots obtained on the detector makes it possible to reconstruct a three-dimensional space called the reciprocal lattice. The reciprocal lattice is a mathematical construction consisting in all the points which could potentially diffract. It simplifies the interpretation of diffraction experiments. The symmetry and geometry of this network is directly linked to the spatial lattice, and not to its content. A visual representation of the equations can be obtained by placing the origin of this reciprocal lattice on the edge of the so-called Ewald sphere and the crystal at the center of this sphere. When the crystal is rotated, the reciprocal lattice also rotates. There will be a diffraction beam each time a node

of the reciprocal lattice intersects with the surface of the sphere (Figure 53).

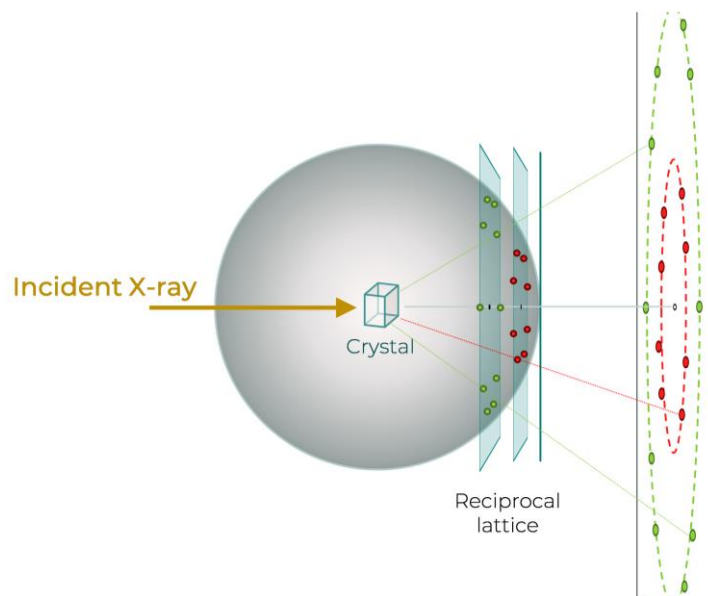


Figure 53 | Ewald sphere.

If the crystal is in a static position, only a small fraction (or even none) of the reciprocal lattice points will intersect with the sphere surface and very few (or no) diffraction spots will be visible on the detector (Figure 54a). Each family of reticular planes in our crystal needs to be brought into the Bragg/diffraction position. If the crystal is rotated along the axis of the incident beam, then each point will draw a circle on the detector as it rotates (Figure 54b). If it is rotated along other axes, then new diffraction points will appear on the detector while new points of the reciprocal lattice cross the Ewald sphere.

When analyzing a powder, it is not a single crystal that is analyzed but a very high number of crystals oriented in all possible directions. The pattern observed on the detector will therefore also be a set of circles, each corresponding to a series of diffraction points with the same θ value (same hkl /interdistance) (Figure 54b).

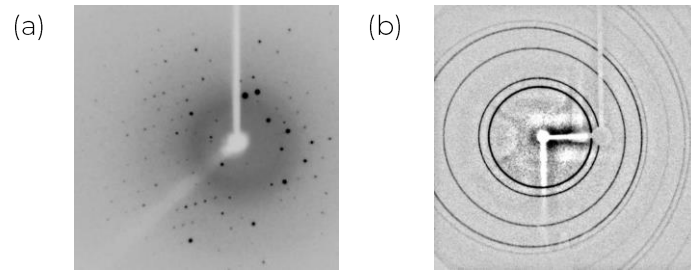


Figure 54 | (a) Image obtained during exposure of a single crystal to an X-ray beam. (b) Image obtained when exposing a crystalline powder to an X-ray beam. Or when a single crystal is rotated along the axis of the incident beam. (*Reproduced from [69]*)

The image observed on the 2D detector, when exposing a crystal to an X-ray, is an image of reciprocal space and therefore directly provides three-dimensional information about the crystal. When analyzing a powder, each ring obtained on the 2D detector corresponds to a diffraction angle and so to a set of equidistant hkl planes. The integration of each ring makes it possible to obtain a diffractogram. That is to say a graph giving the intensity of the beam as a function of the angle (Figure 55).

It follows that for each known crystal structure, it is possible to generate a diffractogram. A diffractogram can be considered as a digital fingerprint of a crystal phase.

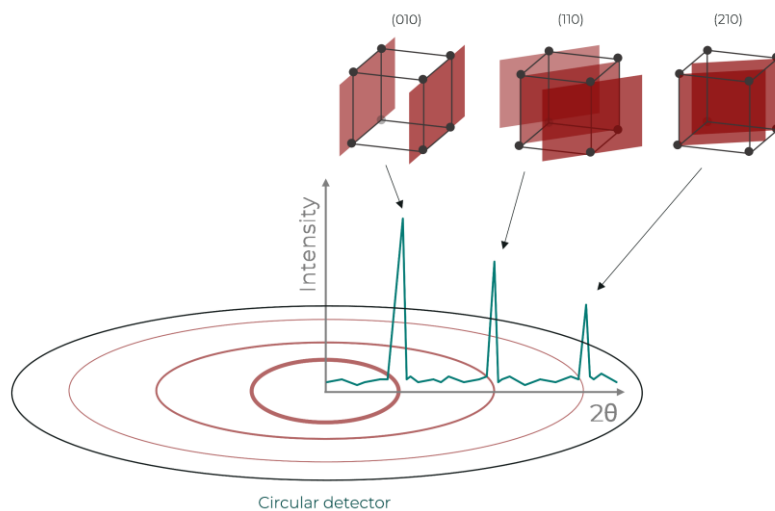


Figure 55 | Powder diffractogram obtained with the integration of each circle. Each pick corresponds to a hkl plan. (*Adapted from [70]*)

In crystallography, standardized file formats, CIF (Crystallographic Information File), are used to store and exchange data on the crystal structure of a material. These files contain detailed information about the asymmetric unit of a crystal, including atom positions, crystal symmetries, lattice parameters, etc. as well as information related to X-Ray diffraction analysis. This makes it possible to generate the entire atomic structure of the crystal. A CIF file can be read by either a scientist or a machine, allowing data sharing between researchers and crystal structure databases, such as the Cambridge Structural Database (CSD) maintained by the Cambridge Crystallographic Data Center (CCDC). In general, these CIF files are read directly in text by the researcher, or used in crystallography software to analyze and visualize crystal structures (eg. Using Mercury software package). A diffractogram can then be directly generated from this type of file.

In practice :

In the laboratory, X-ray diffraction can be carried out on a single crystal (SCXRD - three-dimensional information) or on a powder (PXRD - two-dimensional information). The wavelengths typically used in X-ray diffraction are those associated with copper ($1.5406 \text{ \AA}$) or molybdenum ($0.7093 \text{ \AA}$).

The first method consists of placing a single crystal on a support capable of rotating in all directions. A monochromatic X-ray beam is sent to the crystal, is diffracted and its image is received on a circular 2D detector placed on the other side of the crystal. This is the simplest method, however, it has an obvious limitation which is the need to have sufficiently large single crystals.

The second method consists of exposing a powder to a beam of X-rays, that is to say on a set of numerous small crystals disoriented in relation to each other. Some of these crystals will be correctly oriented to cause diffractions. The image obtained on a 2D detector is a set of circles, and corresponds to the sum of the diffraction images of a crystal rotated in all its possible orientations (Figure 56a). In a modern

powder diffractometer, the intensities of the diffraction spots (hence the rings) are recorded on a 1D detector, as it rotates around the sample in a plane containing the incident ray (Figure 56c). This rotation makes it possible to collect data on the diffraction angles of the different crystal planes present in the sample. When using a 1D detector for the analysis of crystalline powders, only part of the circles is intercepted by the detector (shown with a blue rectangle in Figure 56a and b) which can sometimes lead to a poor average on the resulting diffractogram. For example, if the majority of crystals in the sample are oriented in a preferred direction then the diffraction peaks corresponding to this orientation will be more intense than those of other orientations. This is one of the reasons why there may be differences between a diffractogram generated from a CIF file and a diffractogram resulting from a powder analysis.

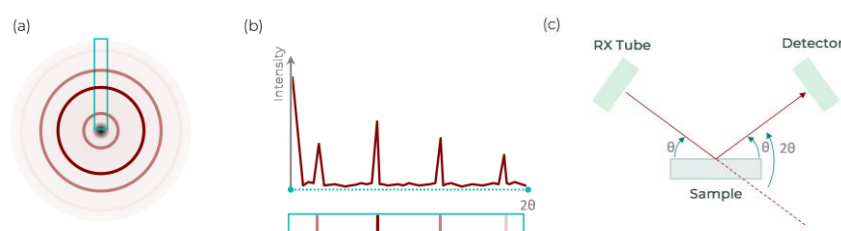


Figure 56 | (a) Circles on a detector which can appear following the analysis of a powder. (b) Resulting diffractogram. (c) modern powder diffractometer using a 1D detector.

Diffractograms generated from a CIF and those resulting from powder analysis have significant differences in terms of content and methodology. The first are based on idealized theoretical calculations of X-ray diffraction from the crystal structure. They are often used to predict the positions and intensities of diffraction peaks. The second comes from real experimental data. They capture the effects of grain size, crystal defects, impurities and other factors that can influence the observed diffraction profiles. They are used to characterize the crystal structure of samples, identify the phases present, assess purity, etc.

3. Phase diagrams

3.1 Introduction to phase diagrams

A phase diagram presents the different physical transformations of compounds and makes it possible to identify the most stable phase under certain conditions. These conditions can be any variable such as temperature, pressure, magnetic field, mole fraction, ...

- The spontaneous physical transformation from one phase to another is called **phase transition**.
- A **phase** is characterized by a uniform chemical composition and physical state throughout.

An important point in thermodynamics is that at constant temperature and pressure, systems tend to evolve so that their Gibbs energy is minimal. The thermodynamic description of a process must be distinguished from the study of the speed at which it occurs. The mobility of molecules in a gas or a liquid allows rapid phase transitions. On the contrary, in a solid the kinetics can prevent this transition, the phase is then thermodynamically unstable. This phase is called the **metastable** phase.

3.2 Physical transformation of pure compounds

For pure substances, the phase diagrams most often represented are diagrams of two variables (pressure and temperature) called PT diagrams or pressure-temperature diagrams as represented in Figure 57.

- Each pressure and temperature range represent the different **thermodynamically stable phases**.
- The curves separating the domains are the places where two phases coexist. They are called **phase boundaries**.
- The **triple point** is the place of conditions for which three different phases of a pure substance coexist in equilibrium.

- The **critical point** is the place where it is no longer possible to differentiate the liquid phase from the gaseous phase.

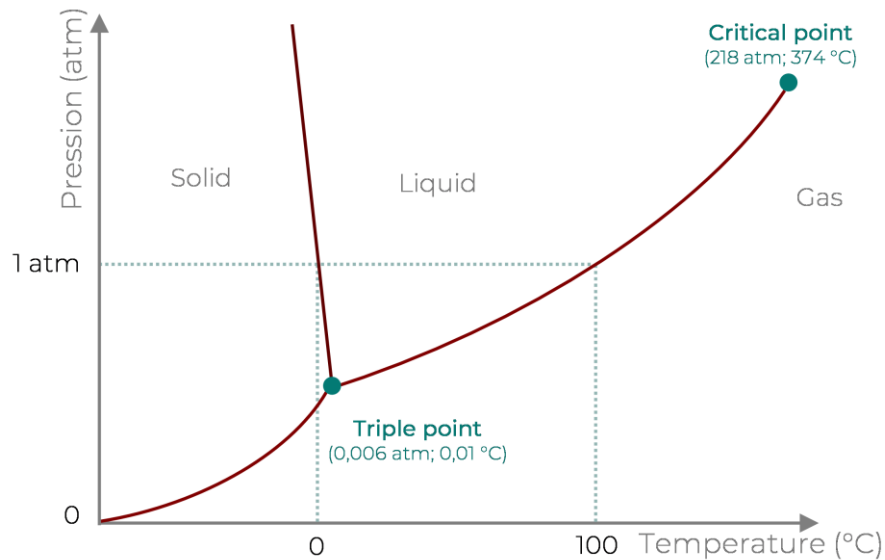


Figure 57 | Phase diagram for water.

3.3 Binary phase diagram

Compared to single-constituent phase diagrams, binary diagrams involve an additional variable which is the composition, thus giving 3D diagrams. For convenience, these diagrams are expressed as a function of composition and either temperature or pressure, which allows for a 2D representation.

We then find different types of temperature-composition diagrams:

- Liquid – vapor phase diagram
- Liquid – liquid phase diagram
- Solid – liquid phase diagram

3.4 Interpretation of binary phase diagrams

The interpretation of binary diagrams will be illustrated by two types of diagrams and holds for any type of binary phase diagram. First a liquid - vapor binary diagram is shown, then a solid - liquid binary diagram.

For a mixture of two constituents A and B, the *global molar composition* (**Z**) of the constituents is shown on the horizontal axis. This composition must respect Equation 9.

$$\mathbf{Z} = \mathbf{z}_A + \mathbf{z}_B = \mathbf{1} \quad (\text{Eq. 9})$$

In Figure 58 is shown a phase diagram for a mixture of two constituents: A having a higher boiling point than compound B. For a liquid-vapor phase diagram, the dew/steam condensation curve and boiling curves are expressed as functions of the composition of the phase in question and the temperature.

- The lower curve corresponds to the **boiling curve** of the liquid. It gives the boiling point of the mixture as a function of the *molar composition of the liquid phase* (**X**).

$$\mathbf{X} = \mathbf{x}_A + \mathbf{x}_B = \mathbf{1} \quad (\text{Eq. 10})$$

- The upper curve corresponds to the **dew/steam condensation curve**. It gives the condensation temperature of the mixture as a function of the *molar composition of the vapor phase* (**Y**).

$$\mathbf{Y} = \mathbf{y}_A + \mathbf{y}_B = \mathbf{1} \quad (\text{Eq. 11})$$

Matter is conserved. The global composition of a mixture therefore does not change with changes of state, regardless of how much liquid vaporizes or vapor liquefies. However, the composition of the individual phases varies.

A **tie-line** (isothermal line passing through the two curves) makes it possible to determine the composition of the liquid phase where it crosses the boiling curve and to determine the composition of the

vapor phase where it crosses the dew curve for a composition global given at a given temperature.

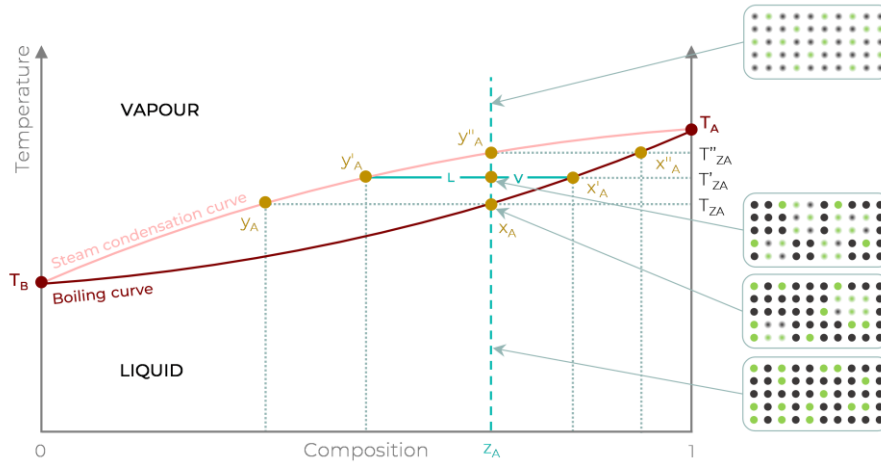


Figure 58 | Liquid – vapor binary phase diagram. As the mixture is heated, the isopleth z_A (straight line with constant composition) will first cross the boiling curve. At this point, i.e. at T_{ZA} , when the first molecules in the vapor phase appear, the composition of the liquid phase is given by x_A and the composition of the vapor phase is given by y_A . Then the line will cross the steam condensation curve. At this point, i.e. at T''_{ZA} , when the last molecules convert to the vapor phase, the composition of the liquid phase is given by x''_A and the composition of the vapor phase y''_A .

When a mixture in the liquid phase of molar fraction z_A is heated, it begins to boil at its boiling temperature T_{ZA} and finds itself in equilibrium with its vapor phase. At this time, the mole fraction at A in the liquid phase is given at the point x_A . In the vapor phase, it is given by the point y_A . B being more volatile, its content in the liquid phase decreases as it boils. That of A increases and the boiling point of the mixture approaches more and more that of pure A, T_A . Given the conservation of the material, once all the liquid has been vaporized, the vapor phase has a composition identical to the initial composition of the mixture.

It would now be interesting to determine from a known initial molar quantity ($\mathbf{N}$), the quantities of matter of A and B in the different phases.

$$\mathbf{N} = \mathbf{N}_L + \mathbf{N}_V \quad (\text{Eq. 12})$$

The overall number of moles of A $\mathbf{n}_A$ corresponds to the number of moles present in the liquid phase $\mathbf{n}_{A,L}$ and in the vapor phase $\mathbf{n}_{A,V}$. This relationship can also be written by involving the molar fractions in the liquid phase $\mathbf{x}_A$ and in the vapor phase $\mathbf{y}_A$:

$$\begin{aligned} \mathbf{n}_A &= \mathbf{n}_{A,L} + \mathbf{n}_{A,V} \\ \mathbf{n}_A &= \mathbf{x}_A \mathbf{N}_L + \mathbf{y}_A \mathbf{N}_V \end{aligned} \quad (\text{Eq. 13})$$

Another way to express the overall mole number of A is to express it in terms of its overall mole fraction. This relationship can also be written by involving the quantities of matter in each phase.

$$\begin{aligned} \mathbf{n}_A &= \mathbf{z}_A \mathbf{N} \\ \mathbf{n}_A &= \mathbf{z}_A \mathbf{N}_L + \mathbf{z}_A \mathbf{N}_V \end{aligned} \quad (\text{Eq. 14})$$

The combination of these two equations gives access to the molar quantities of A in the two phases. And consequently, the quantities of B too.

$$\begin{aligned} \mathbf{x}_A \mathbf{N}_L + \mathbf{y}_A \mathbf{N}_V &= \mathbf{z}_A \mathbf{N}_L + \mathbf{z}_A \mathbf{N}_V \\ \mathbf{N}_L (\mathbf{x}_A - \mathbf{z}_A) &= \mathbf{N}_V (\mathbf{z}_A - \mathbf{y}_A) \end{aligned} \quad (\text{Eq. 15})$$

As shown in Figure 58, the length V can be defined as $(\mathbf{x}_A - \mathbf{z}_A)$ and the length L as $(\mathbf{z}_A - \mathbf{y}_A)$. This new relationship is called the **Lever rule**. It can be applied to any phase diagram.

$$\mathbf{N}_L \mathbf{V} = \mathbf{N}_V \mathbf{L} \quad (\text{Eq. 16})$$

The quantities of matter of A and B in each of the phases can then be determined from the following relationships, developed from the Lever rule:

Amount of matter in the liquid phase

$$N_L = N \frac{L}{L+V} \quad (\text{Eq. 17})$$

Amount of matter in the vapor phase

$$N_V = N \frac{V}{L+V} \quad (\text{Eq. 18})$$

$L / (L + V)$ and $V / (L + V)$ are then respectively the proportions of the liquid and vapor phase.

In a solid – liquid phase diagram, the isobaric melting and solidification curves are expressed as functions of the composition of the phase in question and the temperature.

- The lower curve, labeled “**solidus**” corresponds to the **melting curve** of the solid. It gives the melting point of the mixture as a function of the *molar composition of the solid phase*.
- The upper curve labeled “**liquidus**” corresponds to the **solidification curve** of the liquid. It gives the solidification temperature of the mixture as a function of the *molar composition of the liquid phase (X)*.

In the case presented in Figure 59, the solidus curve is a bit abstract, it coincides with the ordinate axis, which means that the solid phase in equilibrium with the liquid phase, contains either 100% of A or 100% of B. The two curves meet at point E, called the eutectic point. At this point, the liquid phase is in equilibrium with two solid phases.

As shown in Figure 59, when a liquid phase mixture of mole fraction z_A is cooled, B begins to precipitate at the solidification temperature. A liquid phase containing A and B is in equilibrium with a solid phase containing B. As the cooling progresses, more and more B precipitates and the liquid concentrates in A. The composition of the liquid phase can be read on the liquidus line thanks to the tie-line just like in the liquid – vapor diagram.

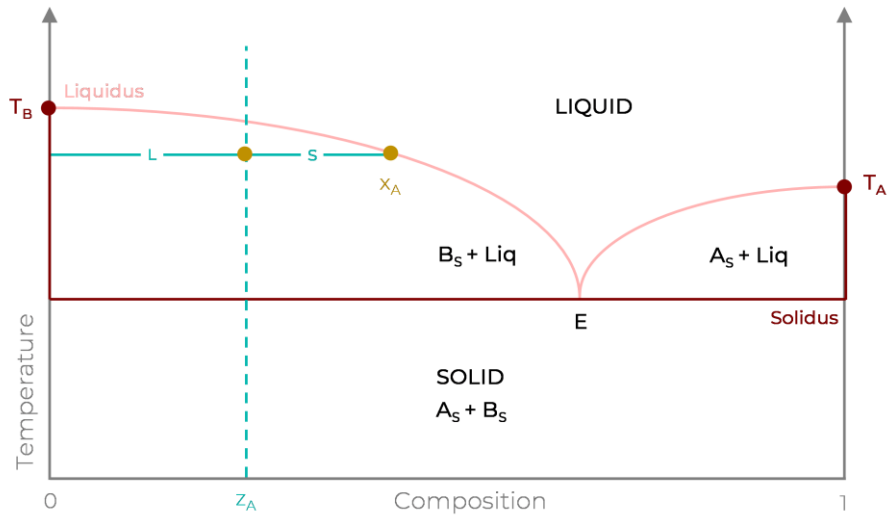


Figure 59 | Solid – liquid binary phase diagram. As the mixture is heated, the isopleth z_A (straight line with constant composition) will first cross the Solidus. At this point, the first molecules appear in the liquid phase. This liquid phase is composed of A and B. Throughout the rise in temperature, the composition of the liquid phase will be given by the tie-line. For example x_A on the figure. Until all molecules are in liquid phase and the composition correspond to the initial z_A .

The proportions of each phase can also be calculated from the Lever rule:

Amount of matter in solid phase

$$N_S = N \frac{S}{L+S} \quad (\text{Eq. 19})$$

Amount of matter in liquid phase

$$N_L = N \frac{L}{L+S} \quad (\text{Eq. 20})$$

$S / (L + S)$ and $L / (L + S)$ are then respectively the proportions of the solid and liquid phase.

3.5 Binary phase diagram: solids forms and enantiomers

When the two compounds A and B form a new solid form such as a cocrystal or a salt, two eutectic points appear on the phase diagram. This new solid phase AB will be composed of a well-defined stoichiometric quantity of the two compounds.

When the two compounds A and B are R and S enantiomers, and they form a new solid form RS, two eutectic points also appear. As enantiomers have the same physicochemical properties, the binary phase diagram is then symmetrical. The term **racemic** is used. The term **conglomerate** is used when the enantiomers crystallize individually, this is illustrated in Figure 60. This mixture presents a phase diagram with a eutectic with a racemic composition.

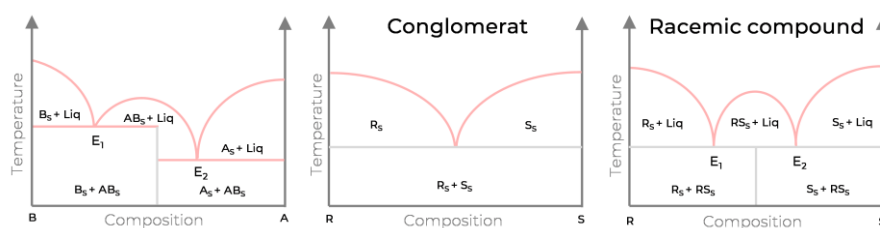


Figure 60 | Different types of solid-liquid binary phase diagram. **Left:** for a mixture of two different compounds which crystalized together. **Middle:** for a mixture of two enantiomer which so not crystalized together (Conglomerat). **Right:** for a mixture of two enantiomer which crystalized together (Racemic compound).

Enantiomeric systems can also be in the form of a solid solution. Since the majority of enantiomeric systems belong to the group of racemic compounds (i.e. ~ 90 %) and conglomerates (~ 5–10 %), only these will be presented here as well as in the ternary diagrams.

3.6 Ternary phase diagram

For a mixture of three components A, B and C, the mole fractions of these must always satisfy the relationship in Equation 21.

$$Z = z_A + z_B + z_C = 1 \quad (\text{Eq. 21})$$

This will automatically be satisfied if the phase diagram is drawn as an equilateral triangle, where each vertex represents a pure compound. If temperature is also taken as a variable, the phase diagram becomes a prism with a triangular base. Each side of the prism then corresponds to a binary diagram (mole fraction versus temperature). As shown in Figure 61, horizontal sections of the prism each correspond to a ternary phase diagram. Each point in the triangle represent a certain composition, and this composition can be read by projecting the point on each side of the triangle, by taking the parallel to the opposite side of each vertex.

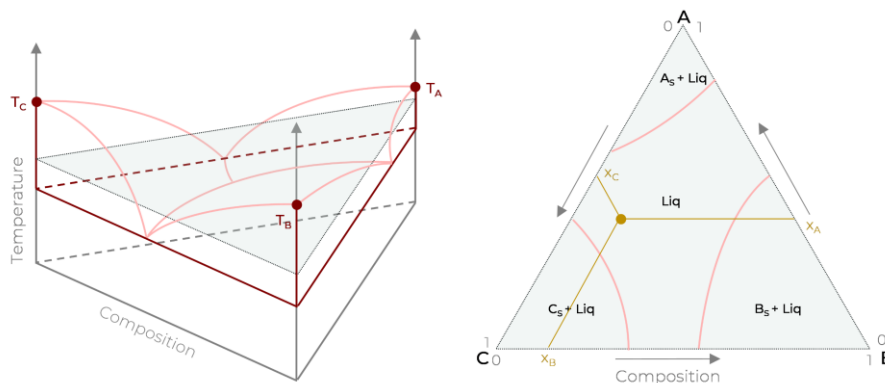


Figure 61 | Left: Phase diagram of three components as a function of temperature.
Right: Ternary phase diagram of three components at a given temperature.

In the field of crystallization of organic compounds, the third component will most often be a solvent, which remains liquid throughout the working temperature range. When one of the components is a solvent, the ternary diagram looks like Figure 62. In this figure, compound C is a solvent and compounds A and B are R and S enantiomers, leading to symmetric diagrams. On the left is the typical diagram of a ternary phase diagram when there is no

formation of a new solid phase AB (here RS). One eutectic point, one monophasic zone, one triphasic zone and two biphasic zones appeared. On the right is the typical ternary phase diagram when there is formation of a new solid phase AB (here RS). Two eutectic point, one monophasic zone, two triphasic zones and three biphasic zones appeared.

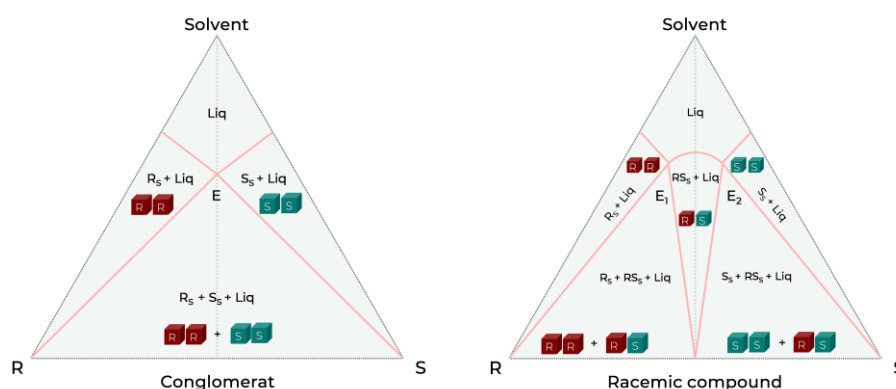


Figure 62 | Ternary phase diagrams for (left) a conglomerate and (right) a racemic compound. S and R are two enantiomers, RS is the racemic compound.

When a new solid form AB is formed, sometimes it happens that due to the large difference in the solubility of the compound A and B, the diagram bends, represented in Figure 63. In a practical point of view, it means that it is not so easy to obtain a pure new solid form. The system is said to be **incongruent**, meaning that starting from the stoichiometric ratio of the new solid form it is impossible to enter the zone where the new solid form is the only stable form in suspension. And consequently, a different starting ratio needs to be chosen. In the opposite case, the system is said **congruent** when starting with a stoichiometric ratio of components (ratio found in the new solid form), a pure new solid form can be obtained as a stable solid form in suspension.

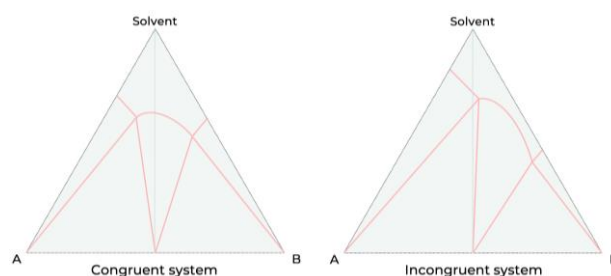


Figure 63 | Congruent and incongruent system.

Once the logic is understood, it is not so difficult to read a ternary phase diagram with solvent as one of the three components. It is based on the same principles as the binary phase diagrams. The composition of the liquid phase in biphasic zones (zones 1, 3 and 5 in Figure 64) is given by the intersection of the tie-line and the solubility line of the compound A, AB or B respectively (X_1 , X_3 and X_5). (The tie-line is the line starting from the pure form A, B or AB and passing through the composition of the mixture). It follows that the composition of the liquid phase in those three zones varies along the solubility curves. The composition of the liquid phase in triphasic zones (zones 2 and 5 in Figure 64) is given by the two eutectic points (X_2 and X_4).

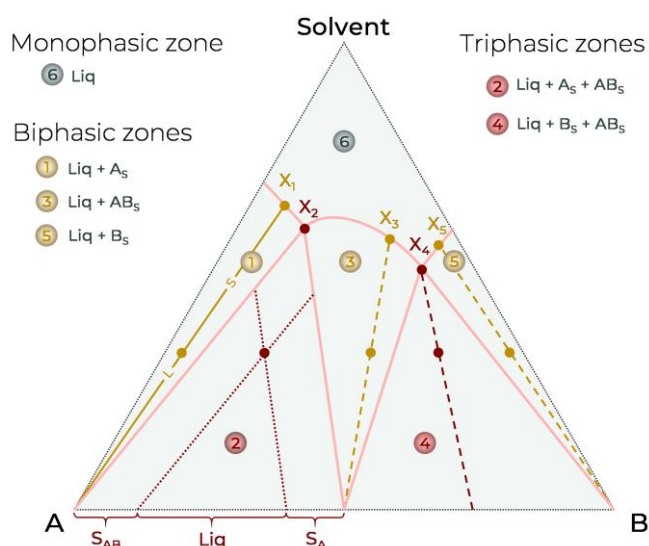


Figure 64 | Reading a ternary phase diagram.

In **biphasic zones** (zones 1, 3 and 5 in Figure 64), proportions of each phase can also be calculated from the Lever rule:

Amount of matter in solid phase

$$N_S = N \frac{S}{L+S} \quad (\text{Eq. 22})$$

Amount of matter in liquid phase

$$N_L = N \frac{L}{L+S} \quad (\text{Eq. 23})$$

$S / (L + S)$ and **$L / (L + S)$** are then respectively the proportions of the solid and liquid phase.

In **triphasic zones** (zones 2 and 4 in Figure 64), proportions of each phase can be calculated with drawn lines parallel to the edges of the triphasic field triangle:

Amount of matter in A solid phase

$$N_{S,A} = N \frac{S_A}{Liq + S_A + S_{AB}} \quad (\text{Eq. 24})$$

Amount of matter in AB solid phase

$$N_{S,AB} = N \frac{S_{AB}}{Liq + S_A + S_{AB}} \quad (\text{Eq. 25})$$

Amount of matter in liquid phase

$$N_{Liq} = N \frac{Liq}{Liq + S_A + S_{AB}} \quad (\text{Eq. 26})$$

$S_A / (Liq + S_A + S_{AB})$, **$S_{AB} / (Liq + S_A + S_{AB})$** and **$Liq / (Liq + S_A + S_{AB})$** are then respectively the proportions of the solid A, solid AB and liquid phase.

4. A deeper insight in mechanochemistry

4.1 A too restrictive definition

For more than ten years, mechanochemistry, that is to say the chemical and material transformations carried out under mechanical impact such as compression, shearing and friction, has aroused a lot of interest as a technique respectful of the environment. [71]

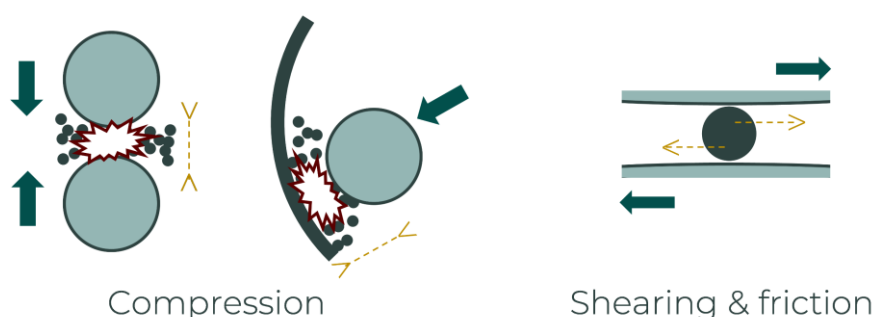


Figure 65 | Examples of compression, shear and friction in a ball mill.

In 1997, the International Union of Pure and Applied Chemistry (IUPAC) defined, in the context of polymers, a mechanochemical reaction as being a « *chemical reaction induced by the direct absorption of mechanical energy* ». [72] Reduced to the domain of polymers this definition covered all chemical reactions that use mechanical energy to directly break strong bonds which generates reactive centers, often radicals, which undergo other reactions. [73, 74] But this restrictive use does not really illustrate the latest advances and the extent of the applications of mechanochemistry. [75–79] It would, for example, exclude mechanochemical reactions taking place largely thanks to the increase in the number of contact surfaces between the reactants. However, taken in a broad sense, this definition does not restrict the mechanism to the atomic scale. In a broad sense, this definition can consider any transformation facilitated in one way or another by mechanical energy.

For the sake of simplicity, different names have been used over the years to describe the reactions that take place via mechanical energy: mecanochemistry, tribochemistry, mechanical alloying for example. This is due in part to the large number of researchers in the field of mechanochemistry. Today, they come from all branches of chemistry, physics, pharmaceutical sciences, biology, materials science and engineering. The name tribochemistry is more commonly found in the fields of engineering and materials, while the term mechanochemistry is more commonly found in the fields of organic and pharmaceutical chemistry. [80]

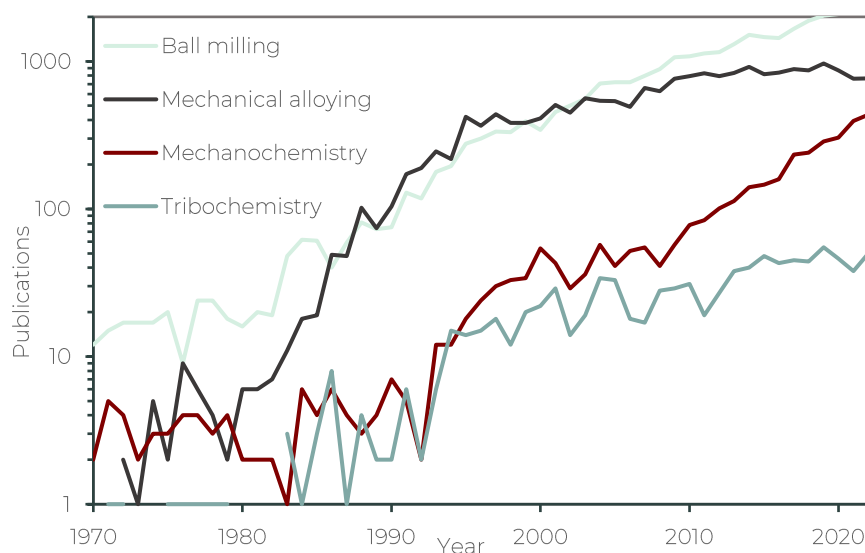


Figure 66 | Number of publications per year over the last five decades in which the terms related to chemical reactions of solids induced by mechanical treatment is present in title, abstract or keywords. (*Find in Scopus, adapted from [80]*)

4.2 History of mechanochemistry

Used since the Stone Age for food preparation and other purposes, the first traditional instrument of mechanochemical grinding is the mortar and pestle. The oldest preserved document linking grinding and chemistry is a small book entitled « On Stones », written in the 4th century B.C. by Theophrastus of Eresos. It describes the preparation of mercury (Hg) and covellite (CuS). These are obtained

through the reduction of cinnabar (HgS) by grinding using a copper mortar and pestle in the presence of vinegar. [81] This document shows that the possibility of initiating chemical reactions by grinding developed quite early. Few documents existed on the chemical effects of mechanical action, until the first extensive investigations by Walthère Spring and M. Carey Lea at the end of the 19th century. [82]

In the middle of the 20th century, the main fields of mechanochemistry were inorganic. The first articles on the applications of mechanochemistry to pharmaceuticals appeared in the 1980s. [83, 84] In 1870, for industrial production of mineral reductions to a size of less than a millimeter, the tumbler mill was invented. They used grinding bodies like balls which could be quite energetic if their drop height was large enough. [85] In 1923 Retsch developed the first motorized grinder which imitated manual grinding in a mortar. The vibratory mill was invented in 1930. As for the planetary mill, it was invented in 1961. [86]

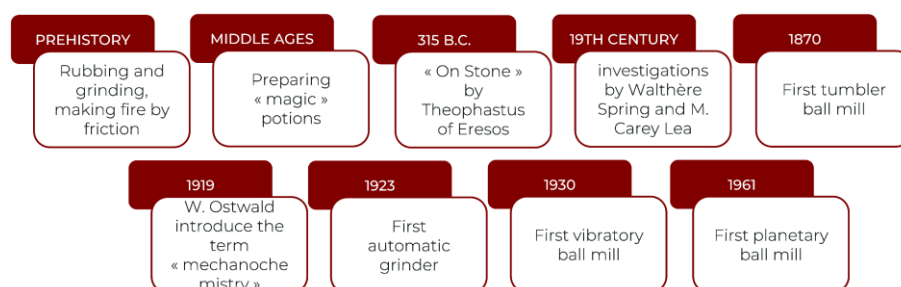


Figure 67 | A simplified timeline for various stages of mechanochemistry.

4.3 Mechanochemistry in a laboratory

Manual grinding using a mortar and pestle is the oldest approach to performing mechanochemistry and the first to appear in the laboratory. [87] This method is readily available in most laboratories, but it has various drawbacks. The reaction times are often long, the conversions often incomplete and the reactions are not very reproducible. Manual grinding force inevitably varies from one individual to another and continuous exposure of the sample to the

ambient atmosphere and humidity can influence the results (incorporation of atmospheric gases, CO₂ and humidity in the sample). [88–91] Today these limitations can be circumvented through the use of automated electric mills such as shaker mills, planetary mills, twin-screw extruders and others illustrated in Figure 68. The use of an electric grinder allows to isolate the sample from the environment and to grind for a fixed time with a controlled grinding frequency.



Figure 68 | Different types of milling. (Adapted from [92–95])

The two most common types of mills used in the laboratory are **ball mills** comprising; **shaker/vibratory mills** and **planetary mills**, due to their operational simplicity. They are used by solid-state scientists for the discovery, synthesis, and fabrication of solid forms of compounds, such as salts, polymorphs, and cocrystals and by organic scientists as a tool for organic synthesis. Mechanochemistry is used in various fields such as organic synthesis, pharmaceutical crystal phase synthesis, mineralogy, inorganic synthesis, catalysis,...

The movements of these two types of crushers are different. In a vibratory ball mill (1 dimension), the jar is shaken in one dimension, from side to side. In some shaker ball mills (3 dimensions), the container undergoes several movements at the same time, for example rotation, vibration and oscillation. In a planetary ball mill, jars are arranged eccentrically on a plate which rotates in the opposite direction to the rotation of the grinding bowls. In some planetary ball mill, this plate is itself placed eccentrically on another plate which rotates in the opposite direction to the first plate.

A neat vision of mechanochemistry would be to use flasks coated with various immobilized chiral catalysts for enantioselective reactions. This would make it possible to have no catalyst recovery step at the end of the reaction in the mixture. This is already the case for certain reactions, called direct mechanocatalysis, where the grinding equipment is itself the catalyst. [96] One of the first papers on this subject dates back to 2009, when J. Mack *et al.* attempted a mechanochemical Sonogashira reaction using copper balls as a co-catalyst. The reaction catalyst, palladium, was added in powder form. [97] Recently, L. Borchardt *et al.* performed Suzuki reactions by coating conventional steel grinding balls with a palladium layer. [98] The results were comparable or superior, to the use of palladium powder or palladium balls. This coating was also applied to the vial. Compared with balls surfaces, coating the vial increased the catalyst surface area by 14 times. Similar yields with coated balls and coated vial show that the only important factor is the presence of catalyst at

the impact point. However, it is possible to achieve more cycles by covering the vial rather than the balls, as the surface area is greater in the vial and will therefore be destroyed less quickly. The use of higher density balls had the effect of increasing yield. However, too high a density resulted in higher abrasion of the catalyst layer, reducing yield.

4.4 Energy transfer in ball mill

Energy transfer within a ball mill is influenced by grinding conditions. This is mainly due to the impact of the balls against each other and against the walls of the vial. Milling time, milling frequency, the number, type and size of the grinding balls, as well as the amount of sample (relative to the volume of the bowl) are adjustable parameters that have an effect on the compression and friction forces during grinding. They directly affect the kinetic energy of balls and the functioning of mechanochemical reactions.

Grinding elements, i.e. vial and balls are usually made from various materials, such as stainless steel, zirconia (ZrO_2), tungsten carbide (WC). Each material has a certain density and hardness (Table 6).

The density will influence the amount of energy released on impact ($E = mv^2 / 2$). The different hardness scales of materials demonstrate the diversity of the criteria analyzed. The Mohs scale, for example, focuses on resistance to abrasion and wear, providing insight into a material's durability. This scale applies to minerals, placing talc, the softest material, on its lowest rung, while diamond, the hardest material, occupies the highest position on this scale. In contrast, the Vickers scale focuses on penetration resistance, revealing a material's ability to withstand specific stresses. In mechanochemistry, these scales become crucial tools for evaluating the resistance of a material to wear under mechanical stress. This type of scale is empirical. The Young's module is a fundamental physical property which evaluates the resistance of a material to plastic deformation. This kind of hardness plays a crucial role in impact dynamics, influencing the time

scale at which materials deform and release energy. In general, the harder a material is, the less it will deform upon impact, thereby reducing the duration of the interaction and increase of the impact pressure.

The classification of materials in mechanochemistry according to their hardness will depend on the specific properties evaluated, when subjected to dynamic mechanical forces or shocks. [99–102]

Table 6 | Characteristics of grinding bowl/grinding ball materials. For hardness, values are general estimates and may vary depending on various factors, including material quality and purity, as well as specific testing conditions. The Mohs scale is not really applicable to metals and ceramics. However, WC hardness is comparable to that of diamond, which is classified as the hardest mineral with a hardness of 10 on the Mohs scale. ZrO₂ is slightly less scratch resistant than corundum, which is rated 9 on the Mohs scale.

Material	Density (g/cm ³)	Hardness (Vickers)	Hardness (Mohs)	Possible contamination by abrasion
Agate	2,65	700-900	6-7	SiO ₂
stainless steel	7,7	200-1000	N/A	Fe – Cr
zirconia	5,7	1200-1400	(8,5)	ZrO ₂ , Y ₂ O ₃ (minimal)
tungsten carbide	14,3	1300-2200	(10)	WC, Co (minimal)

During ball milling, various stress events can occur, such as head-on and oblique collisions (shear/static and rolling friction). [103] These events occur more or less frequently (Stress frequency **SF**) and are more or less energetic (Stress energy **SE**). While ball density and size will have an impact on stress energy, rotation speed and ball number will have an impact on stress frequency.

For reaction to occur, a certain minimum energy must be supplied to the reactants. The mean stress energy (**SE**) must be higher than this minimum energy. [104, 105]

$$\text{Energy transfer } E = \sum SE = \overline{SE} \cdot SN = \overline{SE} \cdot SF \cdot t \quad [J] \quad (\text{Eq. 27})$$

$$\text{Power } P = \frac{E}{t} = \overline{SE} \cdot SF \quad [W] \quad (\text{Eq. 28})$$

A small number of large balls will result in fewer, higher-energy collisions than a large number of small balls, which will result in more, lower-energy impacts. When the frequency is increased, the number of collisions increases. In a planetary mill, it would be normal to think that at too high a frequency, the balls would stick to the wall, reducing impact and grinding efficiency. [106] However, this assertion was contradicted by a study of ball movements within a planetary mill, which were tracked by camera. [107] Ball movement is strongly influenced by friction (static and rolling), and therefore by the filling ratio and the nature of the powders and is not influenced by the frequency.

4.5 What happens in a mechanochemical reaction ?

Understanding the fundamental nature of mechanochemical reactions is an important goal for both theorists and experimentalists. But there is no clear, detailed understanding of how chemical reactions take place in a grinder.

Several models exist today to try to explain the mechanistics of mechanochemical reactions. These different models are developed in parallel in various communities, each bringing a unique perspective to the phenomena, but there is still a significant lack of communication between them. It's not unusual for well-documented phenomena to be regularly rediscovered. It is worth noting that more interaction between fields can be expected for the near future, which is likely going to impact the vision on the mechanistic models. As in the words of N. Copernicus : « *To know that we know what we know, and that we do not know what we do not know, that is true knowledge.* » [80]

When compounds are subjected to mechanical treatment (milling: compression/impact and shearing/friction), the relaxation of the stress field can be accompanied by various effects, such as heat

release, the emergence of new interfaces, the accumulation of defects in the crystals, polymorphic transition, amorphization or chemical transformations. [108] Mechanical treatment (mixing) improves contacts between particles. [109]

It is interesting to highlight here some of the results obtained by V. V. Boldyrev and E. V. Boldyreva *et al.*, who revealed fascinating findings regarding the cocrystal system of piroxicam-succinic acid, demonstrating that impact and shear treatments induce distinct processes in the same system. While impact processing favors the synthesis of a cocrystal, shear processing instead leads to the separation of the cocrystal. These observations offer an innovative approach to optimize grinding conditions, highlighting the importance of the choice of device and operating mode. A variation in the impact-to-shear ratio during grinding can not only interrupt, but also reverse the mechanochemical synthesis process. [110] For example, in a vibratory mill, the impact-to-shear ratio will be different on the walls and on the end of the jar. As a result, products in different areas of the jar may have different compositions. [111, 112]

Heat in planetary and vibratory mills :

The effects of heat developed within the ball mills play a definite role in the reactions. [113–115] L. Takacs et J.S. McHenry compared the average temperatures of the vial of vibratory and planetary mills. [116] To do this, they carried out direct calorimetric measurements on the grinding balls of a vibratory mill SPEX 8000 and a planetary mill Pulverisette 5 from Fritsch. After empty grinding, the balls were placed directly into a calorimeter containing water. Temperatures below 100°C were observed in the vibratory mill, and above 200°C in the planetary mill, operating at similar grinding intensities. This is why it is not uncommon to schedule rest intervals to cool down after a period of grinding in planetary mills.

These temperature differences are explained by the different collisions found in these two types of mill. Whereas in the vibratory

mill there are mainly head-on collisions (provided the bottom of the vial is flat), in the planetary mill, in addition to head-on collisions, there are oblique collisions, which generate friction and shear forces. E. V. Shelekhov *et al.* have also identified in their simulation these two types of contribution to heat increase in a planetary mill. More oblique collisions lead to greater heating. [117]

The maximum temperatures reached increase as the total mass of balls increases. For the same total ball mass, the maximum temperature reached is relatively similar, but the speed of reaching it is greater with a large number of small balls than with a small number of large balls. If the number of balls is increased too much, this reduces the movement of the other balls and therefore the maximum temperature. A linear correlation was found between maximum temperature and grinding ball density. [118] As frequency increases, so does temperature. Depending on the friction of the ball, a too high speeds, in a planetary mill, can lead to a lower temperature as the balls would remain against the vial. [107]

First model explaining mechanochemical reactions :

For a long time, it was assumed that any chemical change in mechanochemistry was the result of local heating. Two descriptions have been developed to explain these local heating phenomena. The first model, the hot-spot theory, was established in 1952 by F. P. Bowden *et al.* Based on oblique collisions, it suggests that high temperatures are produced by friction, triggering the mechanochemical reaction. [119] The second model, Thiessen's magma-plasma model, established in 1967, is based on head-on collisions. It suggests that at the point of contact of the collision, the high temperatures produced are responsible for the formation of a plasma state. [120, 121] But ample evidence points to the need for a deeper understanding of direct mechanochemical phenomena. For example, these models cannot be the reactive sites of mechanochemical organic synthesis reactions, in which case significant decomposition should be observed. Although many

scientists have accepted those models, others have argued that the slip directly breaks the bonds and the resulting loose bonds cause the reaction. [122]

In-situ and *ex-situ* monitoring :

Various *in-situ* and *ex-situ* techniques can be used to fully understand the behavior and mechanism of mechano-chemical reactions. These techniques can all be used individually or in combination. [123]

In-situ observations of a mechanochemical reaction were achieved by T. Friščić *et al.* by using synchrotron X-ray diffraction techniques. X-ray diffraction, only sensitive to highly crystalline materials, has been used to show that solids in mechanochemistry can accumulate lattice defects which can sometimes even lead to amorphization. [124, 125] In the same way, Fourier-transform infrared spectroscopy (FTIR) and Raman spectroscopy were achieved by D. Gracin *et al.* It directly measure the relative energy of chemical bond. [126] Using sensors in the grinding bowl/jars, *in-situ* monitoring of temperature and pressure can also be carried out. The development of *in-situ* monitoring is important because *ex-situ* measurements suspend the process, which can interfere with the process itself. Furthermore, reactions do not necessarily stop as soon as grinding is stopped. [127, 128] *In-situ* monitoring is facilitated with the use of transparent bowls/jars poly(methyl)methacrylate (PMMA). For X-ray diffraction, colorless bowls/jars polylactic acid (PLA) can also be used. [129]

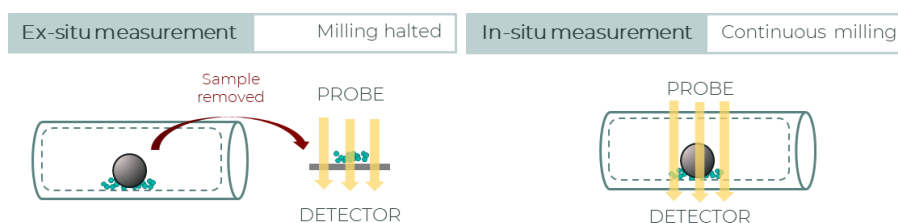


Figure 69 | *Ex-situ* and *in-situ* measurement. (Adapted from [127])

Mechanochemical organic syntheses :

Mechanistic studies of organic reactions would require NMR spectroscopy to bring mechanistic studies to the same level as those in solution, which is complicated *in-situ*.

In the case of mechanochemical organic syntheses, in addition to the temperature increase, the high concentration of the reactants as well as the vigorous mixing in the grinding bowl are probably important components. Some experiments show that reactions occur in semi-molten phase due to an eutectic states. [130]

Mechanochemical crystalline phases syntheses :

In the case of syntheses of crystalline phases, a recent article [131] shows that there could be at least three different mechanisms for the formation of eg. cocrystals: vapor diffusion (where the intermediate is in gaseous form), the liquid eutectic phase (where the intermediate is liquid) and the amorphous phase (where the intermediate is amorphous). It is nowadays assumed that each grinding reaction is a combination of the three types of mechanisms. [132]

Molecular diffusion This mechanism can occur when the solid reactants have a high vapor pressure. This mechanism can be easily achieved when the two reagents are in contact and can even occur without grinding. Without grinding, the cocrystal is created in the vapor phase at the surface of solid reactants. Grinding would just bring some facilities to the reaction. Grinding can mix volatile reagents, or it can increase the number of reactive surfaces, by overcoming the intermolecular forces that maintain molecules in reactive solids.

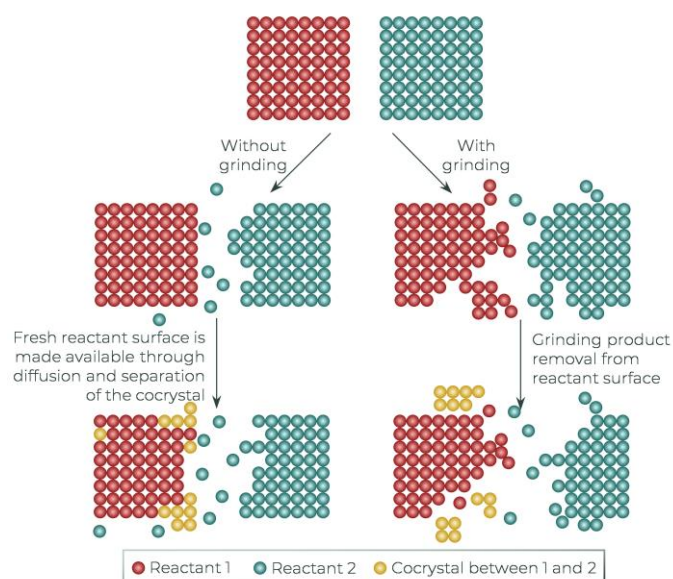


Figure 70 | Molecular diffusion mechanism. (Adapted from [131])

Eutectic formation This mechanism occurs also on the surface of solid reactants in a liquid phase. The two solid reactants, which form a eutectic, melt on their surface. Then, the melt crystallizes to form the cocrystal. Grinding can break the solid reactants, which would increase the number of reactive surfaces. In addition, it can serve to initiate the formation of cocrystals by inducing nucleation.

Amorphous phase formation In this mechanism, the long range order is broken completely. The amorphous ground material can however crystallize forming the cocrystal. Amorphization does not need to occur over the entire sample but can occur locally.

4.6 Really without solvent ?

It is not uncommon to categorize mechanochemical reactions as « solventless » or « solid-state » but in reality, some mechanochemical reactions occur with the presence of solvent. Hydrated reactants and atmosphere humidity are examples of unintentional presence of solvent. When a solvent is intentionally added in a small amount (negligible compare to the classical chemistry) it is called LAG (liquid

assisted grinding) also known as solvent-drop grinding. These amounts of solvent are so small that the compounds react as if they were dry powders or sticky solids rather than solutions.

It has been shown that the reactions in LAG are not affected by the relative solubilities of the reactants in the solvents. The factor η [$\mu\text{L}.\text{mg}^{-1}$], an empirical parameter proposed by Frisčić, is used to characterize the amount of solvent per unit mass of reactive in the reaction. In a neat grinding reaction, $\eta = 0 \mu\text{L}.\text{mg}^{-1}$, whereas $\eta > 12 \mu\text{L}.\text{mg}^{-1}$ in solution reactions. The values of η are between 0 and 1 $\mu\text{L}.\text{mg}^{-1}$ for LAG. [133] Figure 71 shows the η scale.

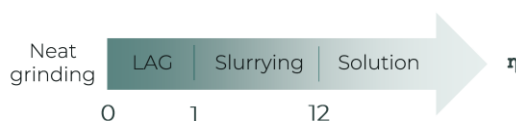


Figure 71 | The η scale. (Adapted from [134])

The mechanism of LAG remains unknown although it is usually found to accelerate reactivity. Some studies have shown, however, that the properties of the solvent can have an impact on the reactivity of the grinding. For example, the cocrystallization of theophylline with benzamide will lead to two different polymorphic forms depending on whether the solvent used is polar or not. [135]

Other grinding approaches have also been developed:

- POLAG (polymer assisted grinding), addition of polymer, eliminates the risk of undesirable solvates forming. [136]
- ILAG (ion and liquid assisted grinding), addition of inorganic salt ions and solvent. [137]
- Ion and ionic liquid assisted grinding, addition of an ionic liquid. [138]
- DES (deep eutectic solvent), mixture between two or more compounds in an exact proportion that corresponds to the eutectic point. [139]

CHAPTER II

ALDOLIZATION IN THE SOLID-STATE

ALDOLIZATION IN THE SOLID-STATE

1. A brief review of organocatalyzed asymmetric aldol reaction

1.1 Timeline of the organocatalyzed asymmetric aldol reaction

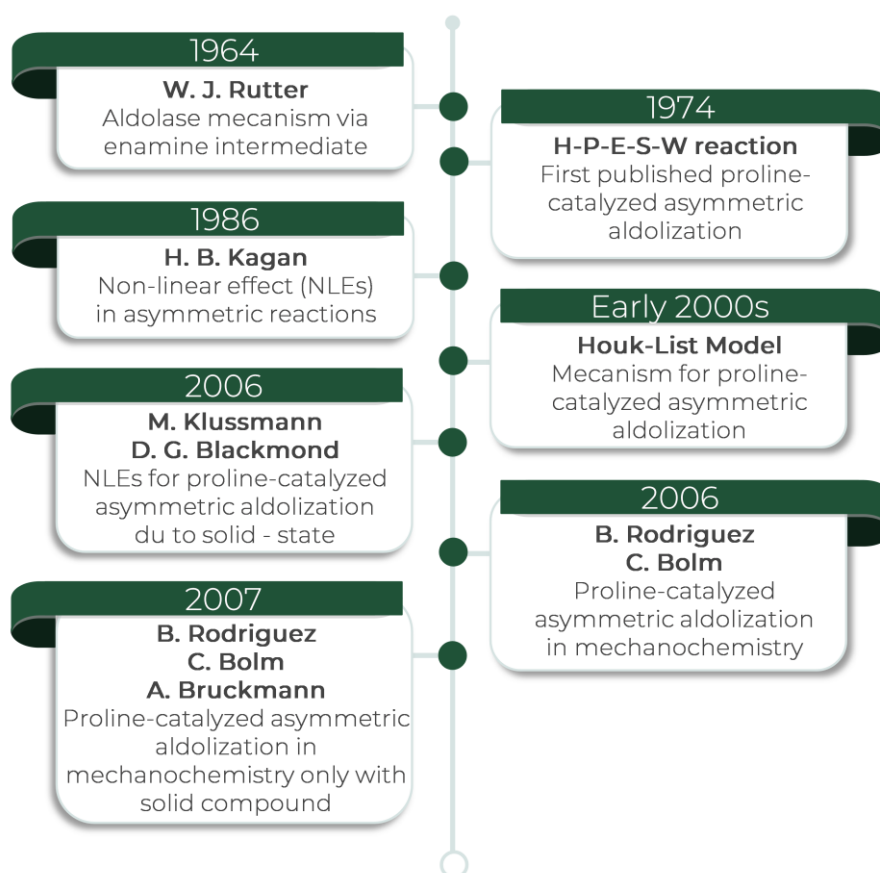


Figure 72 | Chronology of the Organocatalyzed Asymmetric Aldol Reaction: Key Developments Outlined Below.

1.2 Aldol addition reaction mechanism

Mechanism with acid or basic catalyst :

The aldol reaction is a reaction in which a carbon-carbon bond is formed between two carbonyl compounds, to form a new β -hydroxycarbonyl compound (aldol product). This bond is formed between the electrophilic carbon of a first carbonyl group and the α -nucleophilic carbon of a second carbonyl group, as shown in Figure 73.

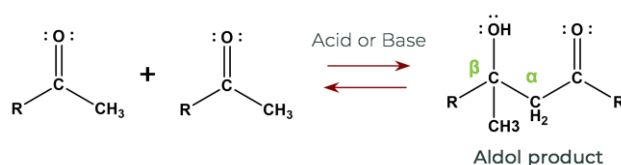


Figure 73 | An aldol addition reaction. Here the two carbonyl compounds are ketone and the product, β -hydroxyketone, is a ketol product.

The term « aldol » comes from the fact that the first such reaction discovered was with aldehydes (in the 1870s). [140] In general, the word aldolization is used regardless of the type of carbonyl compound involved. And it is not uncommon to come across the word « ketol » when ketones interact.

The aldol reaction takes place with the aid of an acidic or basic catalyst. In a basic medium, the conjugate base, the enolate (nucleophilic carbon), will be formed and will attack another carbonyl group in the medium. In an acidic medium, the conjugated acid (electrophilic carbon) is formed and can be attacked by a carbonyl group in enol form, as shown in Figure 74.

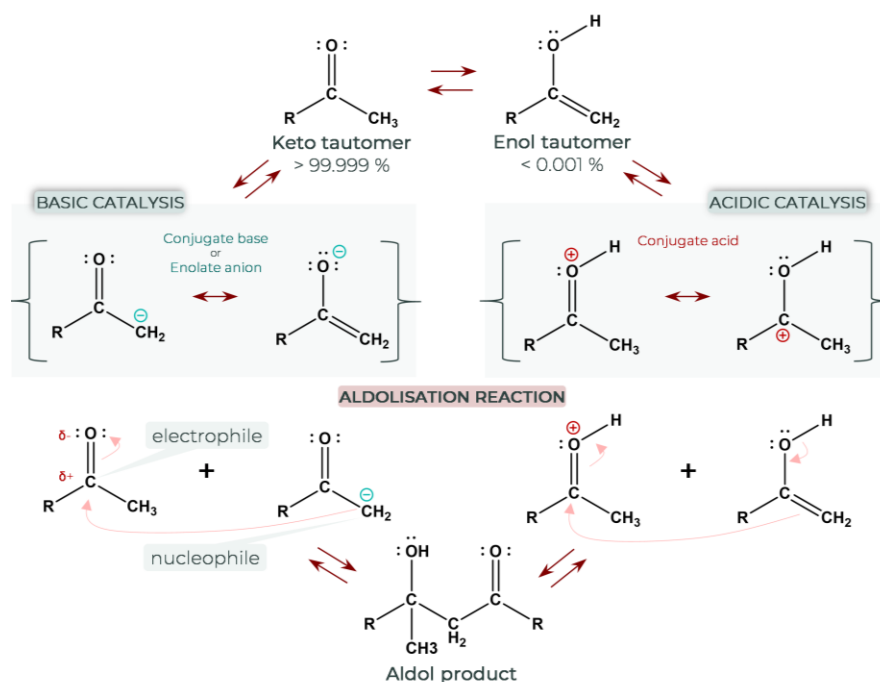


Figure 74 | Aldolization reaction mechanisms.

When two different carbonyls are involved in the aldol reaction, the term cross-aldolization is used. In these cases, one carbonyl acts as nucleophile (enol or enolate form) and the other acts as electrophile. In general, the carbonyl with the most electrophilic carbon will play the role of the electrophile. Figure 75 ranks the electrophilicity of different carbonyls in descending order.

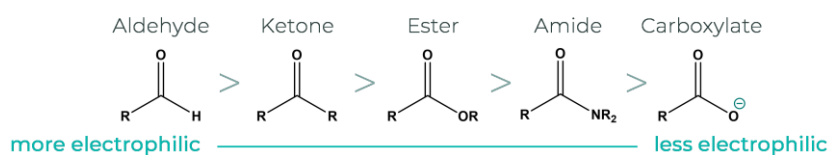


Figure 75 | Reactivity of the electrophilic carbonyl carbon towards a given nucleophile.

The aldol product can dehydrate (elimination of a water molecule) forming an α - β unsaturated carbonyl compound. When this dehydration takes place, the term aldol condensation is used. **Crotonisation** is the name given to the combination of **aldolization** + **condensation**, as shown in Figure 76.

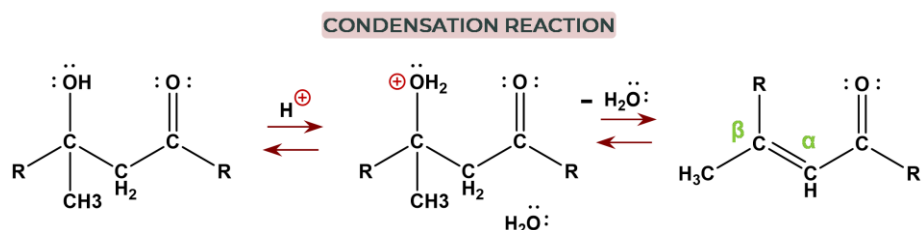


Figure 76 | Condensation reaction.

In an acidic medium this dehydration occurs simply. However, in basic media, this elimination does not occur as easily. But since the double bond resulting from the dehydration is conjugated with the carbonyl group, the stability of the product is increased. Therefore, dehydration with removal of OH^- can also take place in basic medium under strong conditions (strong base, high temperature, long reaction time).

Mechanism with an enzyme catalyst – Aldolase :

Aldolic reactions are found in many biological systems. A well-known example is the formation of D-fructose 1,6-bis(phosphate) from dihydroxyacetone phosphate and D-glyceraldehyde 3-phosphate, which is an aldol addition catalyzed by an enzyme: fructose 1,6-bis(phosphate) aldolase (Figure 77). [141]

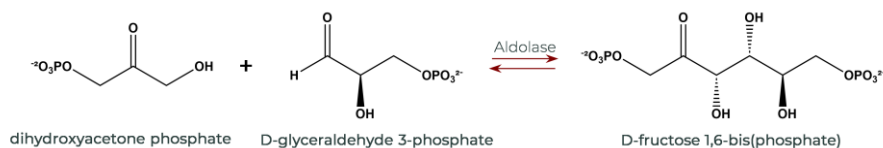


Figure 77 | A catalyzed reaction by an aldolase.

Aldolase are a class of enzymes that accelerate aldol and retro-aldol reactions in a reversible manner. The mechanism of the aldolase-catalyzed aldol addition reaction has been known for 60 years and was proposed by W. J. Rutter in 1964. [142] In this mechanism, the **aldolase** combines the two carbonyl compounds directly, without modifying them beforehand, by passing through an **enamine intermediate** (unsaturated organic compound obtained by the condensation of an aldehyde or a ketone with a secondary amine). This mechanism, valid for Type I aldolases, is still accepted today. Type II aldolases, on the other hand, work by a mechanism, discovered in the early 1940s, involving a Zinc cofactor as a Lewis acid promoter to generate the **enolate**. [143, 144] Both mechanisms are illustrated schematically in Figure 78.

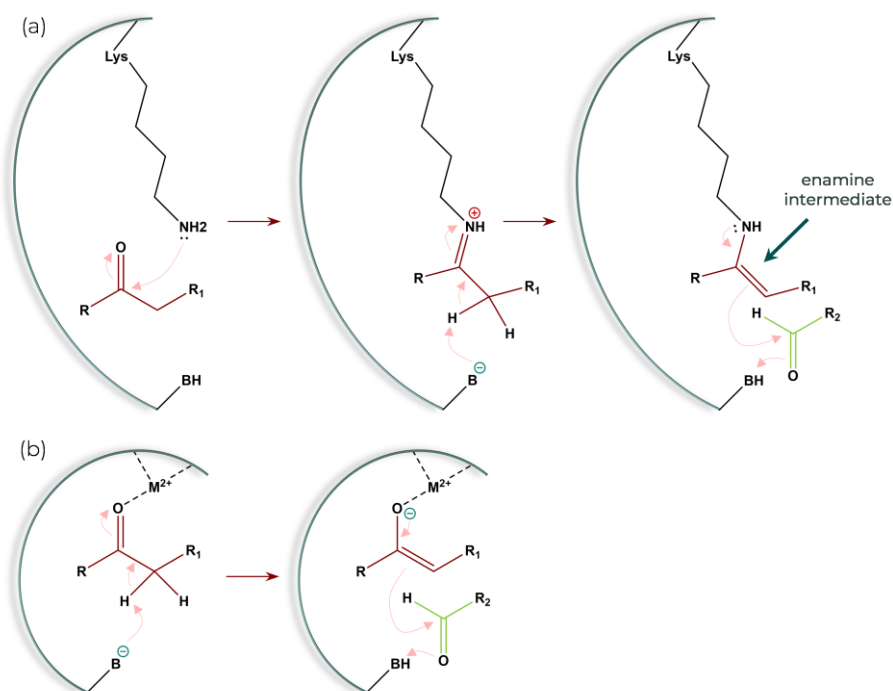


Figure 78 | (a) Mechanism of aldolase type I. (b) Mechanism of aldolase type II.

Aldolases have an asymmetric active site, meaning that they can promote the formation of specific carbon-carbon bonds in specific positions and spatial configurations. Enzymes, nature's catalysts, have been essential for the development of organic catalysts for asymmetric synthesis, a field defined by IUPAC as: « *A chemical reaction (or reaction sequence) in which one or more new elements of chirality are formed in a substrate molecule and which produces the stereoisomeric (enantiomeric or diastereoisomeric) products in unequal amounts.* » [145] Within this field, proline stands out as a prominent example of an organic catalyst, playing a pivotal role in asymmetric synthesis. Its increasing use as a chiral catalyst over recent decades underscores its significance in this area of research.

Mechanism with organic catalysts – Proline :

Proline is a chiral amino acid with two distinct enantiomers: L-proline and D-proline. In aldol reactions, proline acts as a catalyst promoting the formation of a product with a specific stereochemical configuration.

The proline-catalyzed asymmetric aldolization dates back to the 1970s. While the mechanistic foundations of aldolases were well established by the 1960s, the mechanism involving proline remained elusive up until the 2000s.

This is likely explained by the fact that organic chemists and biochemists usually worked separately. This made understanding the mechanism of proline in asymmetric catalysis difficult for a long time. Indeed, proline acts in a similar way to aldolase. [146]

The following paragraph briefly retraces the history of the different mechanisms proposed for aldolization catalyzed by proline.

1.3 Asymmetric aldol reaction catalyzed by proline

Asymmetric intramolecular aldolization :

One of the first published proline-catalyzed asymmetric aldolization reactions is the Hajos-Parrish reaction, now called the Hajos-Parrish-Eder-Sauer-Wiechert (H-P-E-S-W) reaction. [147] Discovered in 1974, this reaction is considered as a prototype of asymmetric catalysis. Illustrated in Figure 79, this intramolecular reaction was mainly used for the synthesis of steroids. This reaction paved the way for **asymmetric syntheses catalyzed by small asymmetric organic molecules**, now known as **organocatalysis**. [146] The search for an asymmetric catalyst is of great interest, especially to produce chiral pharmaceutical compounds. For about thirty years, the enantioselective mechanism of this reaction remained unclear.

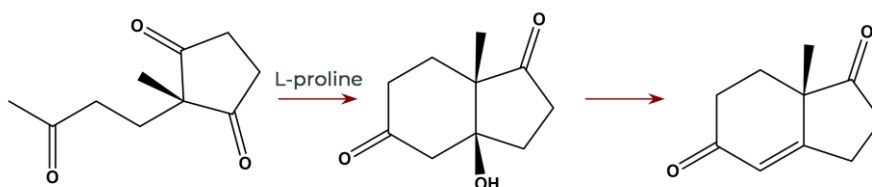


Figure 79 | (1974) Hajos-Parrish-Eder-Sauer-Wiechert reaction (H-P-E-S-W). The first published intramolecular proline-catalyzed asymmetric aldolization reactions.

In 1974, Z. G. Hajos proposed a nucleophilic substitution mechanism involving a **carbinolamine intermediate**. [148] In 1986 a mechanism was proposed by C. Agami and C. Puchot, involving an **enamine intermediate**, but non-linear effects of enantiomeric excesses (effects detailed later) led them to propose a 2-proline mechanism. [149–151] In 2001, K. N. Houk applied to the intramolecular H-P-E-S-W reaction, mechanistic ideas from works of B. List and C. F. Barbas, who based themselves on intermolecular reactions (a mechanism passing through a chair-like transition state with an enamine intermediate, as described below). [152] The different transition state models proposed for the H-P-E-S-W reaction are illustrated in Figure 80.

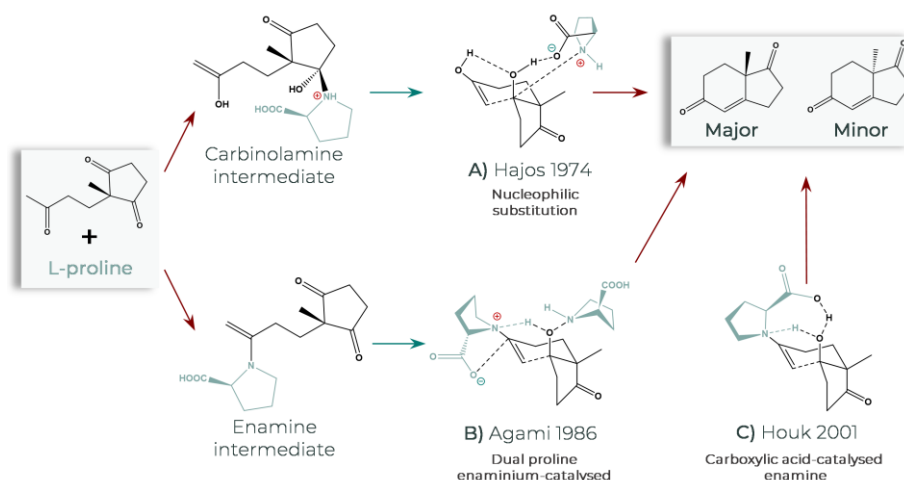


Figure 80 | Different transition state models proposed to explain enantioselectivity for the H-P-E-S-W reaction. Carbinolamine intermediate: **A** Hajos 1974 (Nucleophilic Substitution). Enamine Intermediate: **B** Agami 1986 (Dual proline enaminium-catalyzed), **C** Houk 2001 (Carboxylic acid-catalyzed enamine). (Adapted from [148])

Asymmetric intermolecular aldolization :

Asymmetric intermolecular aldolizations were previously carried out via pre-formed enolates combined with a chiral ligand and generally using a metal. [153–155]

Following studies of asymmetric intermolecular aldolization catalyzed by proline (or proline derivatives), B. List and C. F. Barbas proposed in 2000 a mechanism via a Zimmerman-Traxler type transition state (via a chair-like and not boat-like transition state) involving a single proline (Figure 82). [156, 157] The reaction they studied is illustrate in Figure 81.

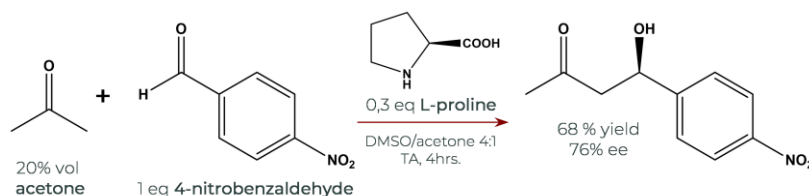


Figure 81 | (2000) Reaction studied by B. List and C. F. Barbas. An intermolecular proline-catalyzed asymmetric aldolization reaction, proposed with a mechanism involving a chair-like transition state. (0.3 eq proline, 1 eq 4-nitrobenzaldehyde, +/- 27 eq acetone). (Adapted from [156])

Subsequent studies in the early 2000s on intra- and intermolecular reactions, mainly by B. List, K. N. Houk, C. F. Barbas and S. Bahmanyar, supported this one-proline model. This earned List the Nobel Prize in Chemistry in 2021. The Zimmerman-Traxler transition state model to explain enantioselectivity is now named after its two main authors; Houk-List. [158–163] It is shown in Figure 82 for an intermolecular reaction.

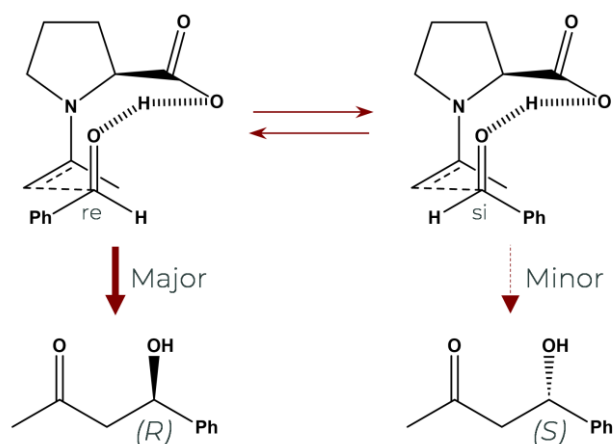


Figure 82 | Houk – List model through Zimmerman-Traxler transition state. The reaction proceeds via a chair-like, pericyclic process. The re-facial attack is favoured because the Ph group is in equatorial position.

In this model, **proline** provides a **double activation**: first, the formation of a **nucleophilic enamine intermediate** with the nitrogen. And secondly, the **increase in the electrophilicity of the aldehyde**, via the formation of a hydrogen bond with the carboxyl group. The favoured transition state is the one where the Ph group is distant (so-called equatorial), which leads to a re-facial selectivity. [164–166]

When the final product contains 2 chiral centres, 2 diastereomers with each their enantiomers are possible. [167, 168] An example is shown in Figure 83 by reacting cyclohexanone and an aldehyde together.

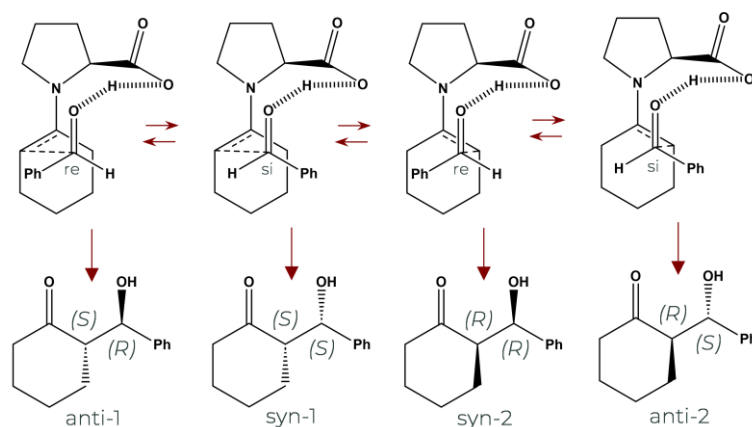


Figure 83 | Representation of the possible transition states in L-proline catalyzed asymmetric aldolization, with 2 chiral centers on the final product.

The mechanism of an intermolecular aldolization reaction catalyzed by proline (Figure 84) taking into account the latest mechanistic aspects highlighted in 2022 by E. J. Mattioli *et al.* on the intramolecular H-P-E-S-W reaction, is detailed in Figure 85. [169] An interesting aspect specified is the catalytic role of the water molecule formed during iminium formation (first step). It will serve as a proton shuttle during the formation of the enamine and the C-C bond (second step). In this figure, the mechanism and molecular representations should be used and interpreted with caution as the three-dimensional structures are shown in a single plane. The mechanism can be divided into three steps: i) iminium ion formation, ii) enamine and C-C bond formation, iii) aldol intermediate formation. A fourth step can be added, iv) final aldol dehydration, if there is dehydration at the end of the reaction.

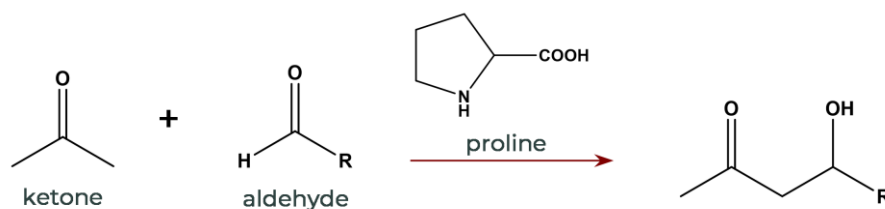


Figure 84 | Intermolecular aldolization reaction catalyzed by proline.

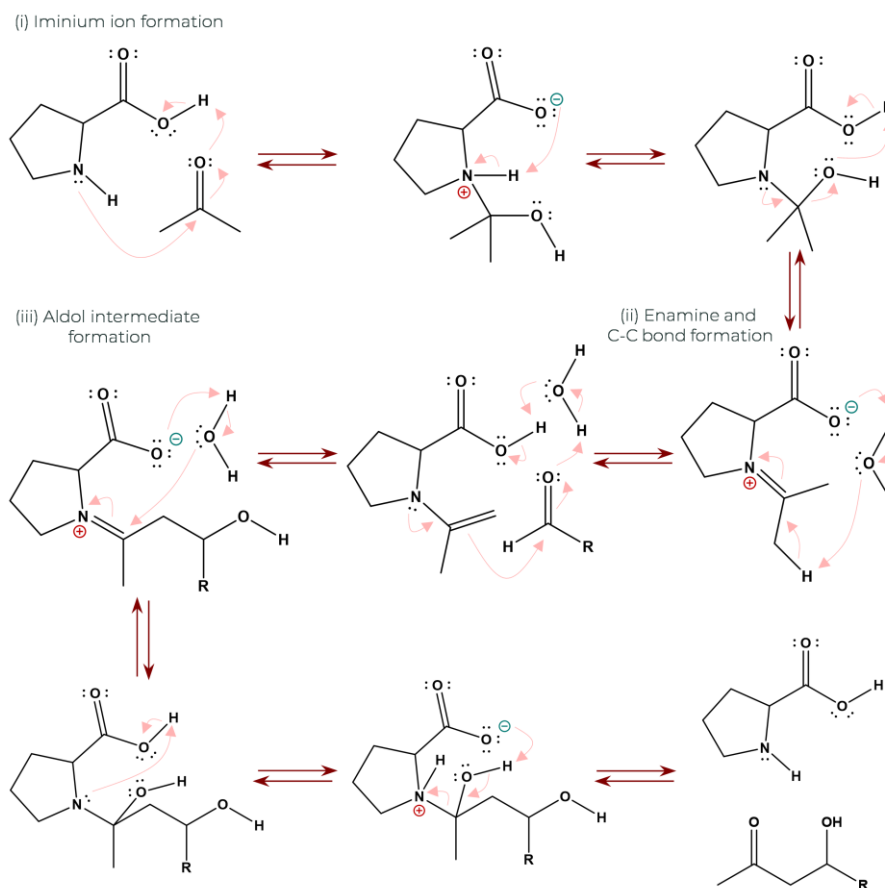


Figure 85 | Mechanism of an intermolecular aldolization reaction catalyzed by proline.

All the steps have been noted here as reversible, this is the case in solution. However, depending on the reaction conditions, this reversibility will occur or not. Also the aldol condensation step does not necessarily occur.

In solution, when different diastereotopic products are present, interconversions between them can occur. Since this interconversion takes place only in the liquid phase, it will depend on the solubility of the different products formed. [170]

1.4 Challenge in asymmetric synthesis: Asymmetric amplification /depletion.

In an asymmetric synthesis reaction, one would expect to observe linearity between the enantiomeric excess of the product obtained and the enantiomeric excess of the chiral catalyst used. Indeed, it is difficult to believe that an enantiomerically impure chiral catalyst could give a stereoselection higher than its own ee or even equivalent to the pure catalyst. However, an increasing number of reactions in asymmetric synthesis have shown non-linearity in this relationship. One of the first reports on non-linear effects (NLEs) in asymmetric catalysis was published by C. Puchot, C. Agami, H. B. Kagan *et al.* in 1986. [149] H. B. Kagan, a true pioneer in the field, has contributed considerably to the development of models associated with non-linear effects in asymmetric synthesis. These non-linear effects reflect molecular interactions and the complexity of the reaction mechanisms.

Plotting the enantiomeric excess of the product against the enantiomeric excess of the catalyst is a simple way of obtaining information about the pattern of the non-linear effect taking place, as illustrated in Figure 86. In practice, the chiral catalyst used is enantiomerically pure to maximize the enantiomeric yield of the reaction. If this catalyst is not available in a pure form, then its enantiomeric excess becomes the limiting factor for chiral induction. The linear correlation between the enantiomeric excess of the catalyst ee_{cat} and the enantiomeric excess of the product ee_{prod} results in the Equation 29 below where ee_{max} represents the enantiomeric excess of the product when a pure chiral catalyst is used. A linear relationship is in principle expected as represented by curve A in Figure 86.

$$ee_{prod}(\%) = ee_{max} ee_{cat} \quad (\text{Eq. 29})$$

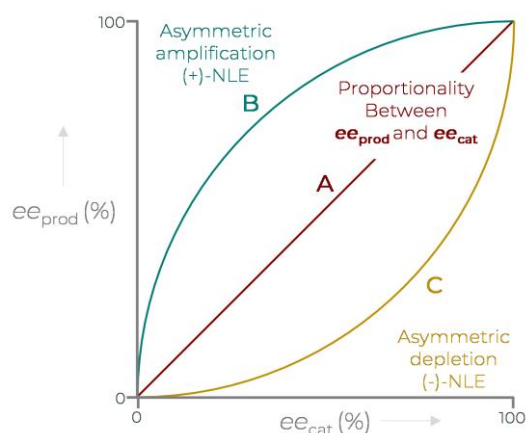


Figure 86 | Typical curves for positive (B) and negative (C) non-linear effects.

In cases where non-linear effects are observed, the enantiomeric excess of the product and the enantiomeric excess of the catalyst are correlated by the Equation 30 below, where **f** is the correction factor and accounts for deviations from linearity.

$$ee_{\text{prod}}(\%) = ee_{\text{max}} ee_{\text{cat}} f \quad (\text{Eq. 30})$$

In Figure 86, curve B represents a positive non-linear effect, abbreviated as (+)-NLE, also called asymmetric amplification, [171] and curve C represents a negative non-linear effect, (-)-NLE, called asymmetric depletion.

Asymmetric amplification is of great interest. Probably the most interesting application is the synthesis of products presenting high enantiomeric excesses from a chiral catalyst that is enantiomerically impure and therefore often cheaper to prepare. [172, 173] Asymmetric amplification can also be used in autocatalysis with this effect playing in the discussion related to the origin of homochirality of life. Currently, research is oriented towards understanding whether it would be possible to force or prevent a non-linear effect by varying certain experimental parameters. In literature, parameters such as the nature of the solvent, temperature, relative concentrations, etc. have an impact on the development of NLEs. [174] This wide variety of parameters makes it difficult to anticipate an NLE. Furthermore,

certain factors favoring a (+)-NLE in one situation may disadvantage it in another context.

Since most of the models (based on several interconnected aspects and different from one situation to another) that can explain the non-linear effects are described for reactions in solution, they will not be developed in this project. The non-linear effects observed in the solid phase can be explained by the phase behavior of the catalysts and will be detailed later.

1.5 Can the solid-state also participate to asymmetric amplification?

In 2006, M. Klussmann and D. G. Blackmond highlighted a mechanism giving rise to asymmetric amplification, based on the solid - liquid phase equilibrium behavior of the organocatalyst. To do this, they worked on an aldolisation between acetone and 2-chlorobenzaldehyde using amino acids as a catalyst, show in Figure 87. [175]

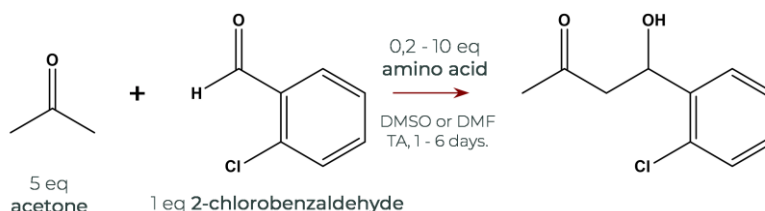


Figure 87 | Studied reaction by M. Klussmann and D. G. Blackmond in 2006.
(Adapted from [175])

As proline is a well-known catalyst, it was the first to be analyzed. Using low proline concentrations (to such extent that the entire amount of proline is dissolved) the observed relationship between ee_{cat} and ee_{prod} is linear. However, when higher concentrations are used, so that not all proline is dissolved, and a solution-solid equilibrium is installed for proline, the ee_{prod} is largely independent of the ee_{cat} , as shown in Figure 88a. This unusual non-linear relationship cannot be explained by existing models of non-linear effects in asymmetric catalysis. However, this relationship reflects the trend of

the enantiomeric excess of dissolved proline as a function of the enantiomeric excess of total proline: The enantiomeric excess of proline in solution remains constant at about 50 % even as the enantiomeric excess of overall proline varies, illustrated in Figure 88b.

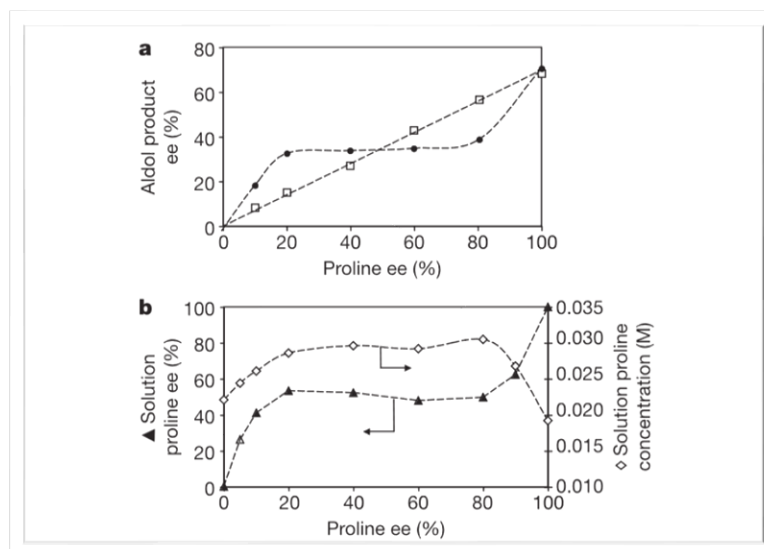


Figure 88 | a) Product enantiomeric excess versus proline enantiomeric excess. **Square**, dissolve proline with a global concentration of 0,025 M. **Circle**, solid-liquid proline with a global concentration of 0,1 M. **b) Triangles**, solution proline enantiomeric excess and **diamonds**, solution proline concentration, as a function of the overall enantiomeric excess for proline at 0.1 M. All experiments in DMSO with 0.8 wt% H₂O at 25°C. (Reproduced from [175])

Proline is a racemic compound; it crystallizes in 1 : 1 ratio DL crystals. Its ternary phase diagram in dimethylsulfoxide (DMSO) is shown in Figure 89. For suspensions containing only one solid form (e.g. only D-proline, L-proline or DL-proline), the solution ee varies with the overall proline ee. If two solid forms are present in suspension, the proline concentration and solution ee, no longer vary, regardless of the overall proline ee. This is due to the existence of a eutectic. [176, 177] The solution enantiomeric excess at this eutectic point is 49,6 % in DMSO. [178]

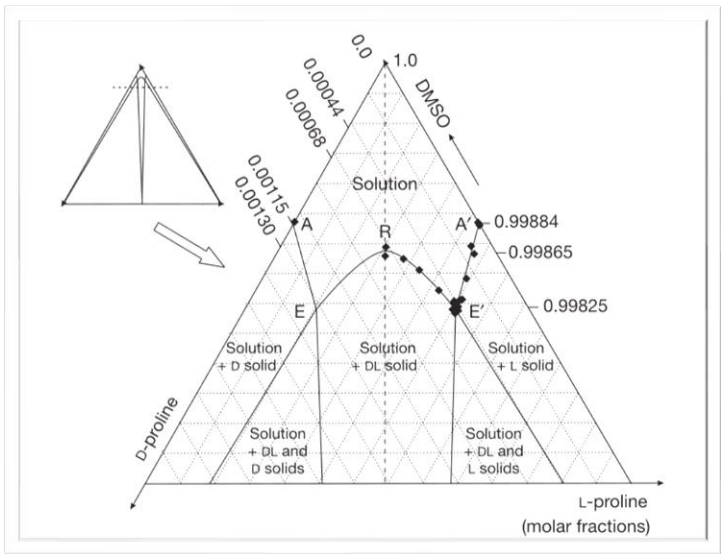


Figure 89 | Ternary phase diagram of D-proline, L-proline and DMSO at 25°C.
(Reproduced from [175])

This prompted M. Klussmann and D. G. Blackmond to examine the phase behavior of several amino acids. To explore their potential for asymmetric amplification, which for some amino acids could be higher than with proline, which has a eutectic positioned at about 50 % ee. Amino acids forming conglomerates, such as threonine and arginine, show a 0 % enantiomeric excess at the eutectic. [179] The eutectic enantiomeric excess measurements in water at 25 °C of racemic amino acids by Klussmann and Blackmond are shown in Table 7. The eutectic values are high for several amino acids.

Table 7 | Solution enantiomeric excess for some amino acids at the eutectic point in water at 25°C. (Adapted from [175, 178])

Amino acid	ee of solution at eutectic (%)	Amino acid	ee of solution at eutectic (%)
Threonine	0	Methionine	85
Valine	46	Leucine	87
Alanine	60	Histidine	93
Phenylalanine	83	Serine	>99

Figure 90 shows how the enantiomeric excesses of the product obtained vary with different amino acids used as catalysts in the aldolization reaction shown in Figure 87. The results indicate quite visually that the position of the eutectic dictates the selectivity of the product. Conversely, conversions were generally lower than with proline, ranging from 25-60 % depending on the amino acid used compared to values above 90 % with proline.

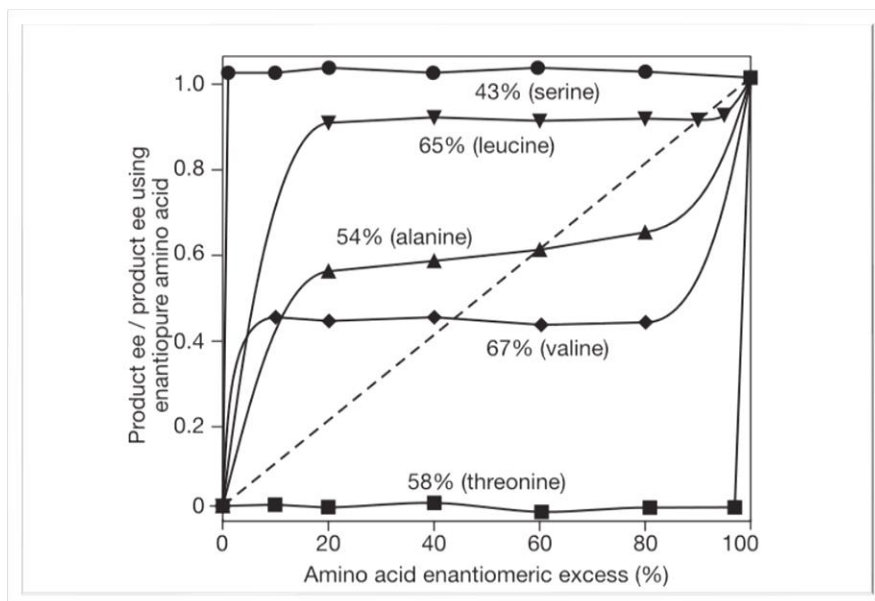


Figure 90 | Non-linear effects in an amino-acid mediated aldol reaction. All experiments in DMF. (Reproduced from [175])

One year later, in work related to homochirality of life, the same group demonstrated that the eutectic composition of mixtures of L and D amino acids could be adjusted by the addition of achiral dicarboxylic acids that cocrystallize with these chiral amino acids. In several cases, the new eutectic compositions were 98 % ee or more. [178, 180] Table 8 presents their results.

Table 8 | Solution ee at the eutectic for amino acids in the presence of Carboxylic acid in water at 25°C. Thr: Threonine, Val: Valine, Ile: Isoleucine, Met: Methionine, Phe: Phenylalanine, Leu: Leucine, His: Histidine. (Adapted from [180])

	Thr	Val	Ile	Met	Phe	Leu	His
None	0	47	52	85	88	88	94
Oxalic acid	50	66	82	43	23	98	63
Malonic acid	11	50	51	69	86	91	91
Succinic acid	2	93	52	42	79	89	56
Maleic acid	34	69	71	55	7	81	82
Fumaric acid	24	99	59	72	99	92	98
Adipic acid	0	48	51	66	94	92	77

The possible mechanisms of asymmetric amplification due to the solid-liquid phase behavior of the catalysts, as well as interactions between a chiral compound and an achiral compound can enrich the discussion on one of the most incredible examples of asymmetric amplification: the development of a strong enantiomeric excess in biomolecules originating from a presumed racemic prebiotic world, also coined the evolution of the homochirality of life. [175]

1.6 Aldol reaction catalyzed by proline through mechanochemistry

Until now, proline-catalyzed aldolization reactions were generally carried out in highly polar solvents, such as dimethylsulfoxide (DMSO). [181] Only a few examples of reactions performed in the absence of solvent can be found in the literature. [182] For these, good yields and stereoselectivity were obtained, however, an excess of liquid ketone had to be used (greater than or equal to 3 equivalents). In most cases, the ketone appeared to act both as reactant and as reaction medium.

In 2006, the planetary mill was used for the first time to perform asymmetric organocatalysis reactions under solvent-free conditions. B. Rodriguez and C. Bolm studied, among others, the asymmetric aldol addition reaction, illustrated in Figure 91. [183]

They compared the results obtained with simple magnetic stirring (which is considered to be conventional stirring in the remainder of this text) to those obtained with a planetary mill under solvent-free conditions. In both cases, high yields are obtained with enantiomeric (ee) and diastereomeric (ed) excesses of up to 99%. On the other hand, the reaction times are much shorter in planetary milling (5 to 36 hours) compared to reactions carried out using a magnetic stirrer bar (1 to 4 days). Furthermore, these good yields are obtained using almost equimolar ratios of starting reagents, which avoids the use of excess ketone as practiced in solution. Conventional magnetic stirring without solvent is therefore insufficient to achieve efficient mixing of all products and thus high conversion.

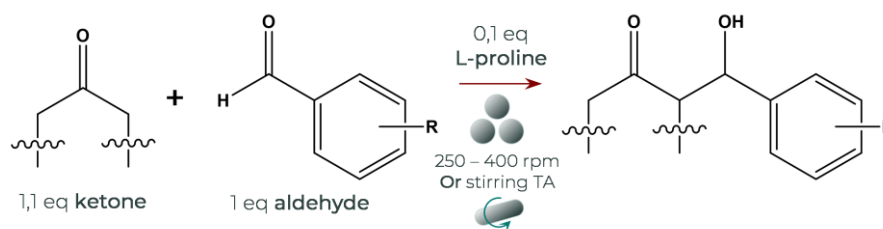


Figure 91 | Used liquid ketone: cyclohexanone, cyclopentanone, cycloheptanone and acetone. Used solid ketone: 4-tert-butylcyclohexanone, Tetrahydro-4H-thiopyran-4-one, 1-Boc-4-piperidone, 4-phenylcyclohexanone. Used aldehyde: R = NO₂, OMe or Cl. (Adapted from [183])

It was also observed, as expected, that reactions between cyclohexanone and aldehydes with electron-withdrawing substituents, such as the NO₂ group, gave products with high stereoselectivities in short reaction times. On the contrary, aldehydes with electron-rich groups, such as Cl or OMe groups, decreased both reactivity and stereoselectivity. These trends in electronic effects are like those observed in aldol reactions in organic or aqueous solvents. [184–188]

Initially, the ketones used were liquid, but it was shown in 2007 by B. Rodriguez, A. Bruckmann and C. Bolm that this reaction can also work with solid starting reagents (using 4-tert-butylcyclohexanone or Tetrahydro-4H-thiopyran-4-one for ketone). [189] They note that the

reactions take place in an intermediate melt, visible both when performing conventional stirring and with the mill. This melt is a prerequisite for the reaction to proceed but does not always imply that a reaction is taking place. When this liquefaction occurs at room temperature, it implies the existence of a eutectic mixture whose melting point is below room temperature (even when the melting points of the reactants are above room temperature). Obviously, the reaction times were longer than with liquid ketones (1 to 1,5 days for reactions performed in a planetary mill, but 5 to 7 days for reactions performed with conventional stirring). The small increase of the temperature inside the jars during the milling is likely one of the reasons why ball milling outperforms conventional stirring.

More than a year later, the same group studied this type of reaction with only solid reagents combined to a variation in proline ee. [190] The reaction is described in Figure 92.

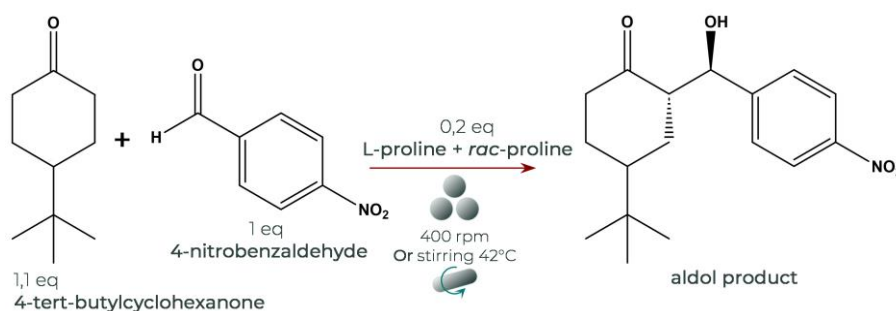


Figure 92 | Solid-state aldol reaction between 4-tertbutylcyclohexanone and 4-nitrobenzaldehyde using a variation of proline ee as catalyst. (Adapted from [190])

They observed a significant non-linear relationship between the enantiomeric excess of proline and that of the aldol product as shown in Figure 93. They speculate that the nature of this non-linear effect stems from the ternary phase behavior of the scalemic proline because the non-linearity was similar to the observation by M. Klussmann and D. G. Blackmond in 2006. [175]

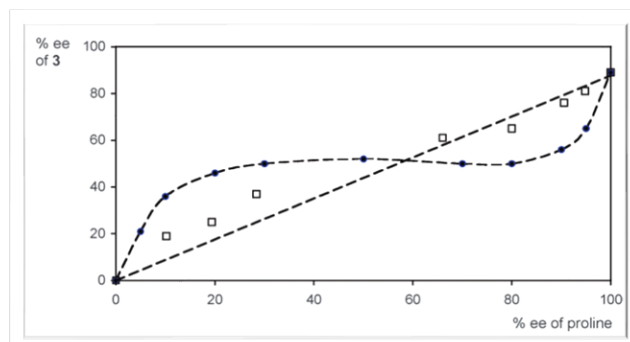


Figure 93 | a) Circles, ee of aldol product versus ee of proline in the ball mill. b) Squares, under conventional stirring at 42°C. (Reproduced from [190])

In their work, B. Rodriguez, A. Bruckmann and C. Bolm also investigated the effect of starting with a physical mixture of L-proline and D-proline instead of starting with a mixture of DL-proline and L-proline. They noted a significant difference, due to the inherent transformation to DL-proline, when starting with a physical mixture. Solid proline requires a significant period to reach the equilibrium state in the reaction mixture, where DL-proline is formed. During this period, between the initial conglomerate state (L-proline + D-proline) and the thermodynamic racemic state (DL-proline + L-proline or D-proline), the enantiomeric excess of the product formed at each instant is changing over time. In addition, as the solubility of a conglomerate is higher than that of the racemic compound, the global catalyst concentration is also affected, which will decrease during the transition period. This further supports the hypothesis that the ratio of proline available to the reaction comes from the eutectic mixture formed.

2. Goals and methodology

2.1 Crystal engineering to control aldol product enantioselectivity

The objective of this part of my thesis was to develop a tool to act on the enantiomeric excess of organocatalyzed aldolization products, by playing on the physicochemical properties of the catalyst without changing the nature of the catalyst. For this, we will use a crystal engineering tool: cocrystallization (Figure 94).

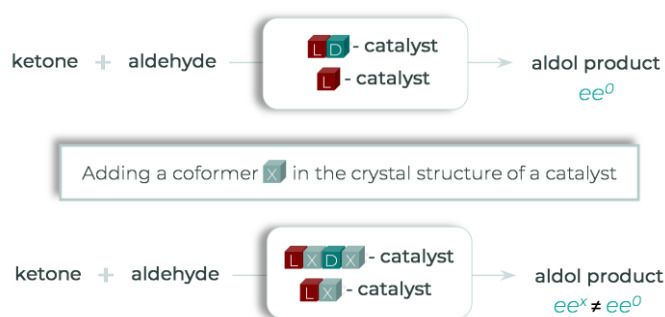


Figure 94 | General scheme to act on the enantiomeric excess of the aldol product by adding a conformer to the catalyst to form a cocrystal of this latter.

This project is based on the various studies described above, carried out by M. Klussmann, D. G. Blackmond, B. Rodriguez, A. Bruckmann and C. Bolm, who note a non-linear effect in asymmetric aldolization reactions organocatalyzed either purely working with solids or when using solids suspended in a solvent. In both cases, the evolution of the enantiomeric excess of the aldol product does not vary linearly with the enantiomeric excess of the catalyst and this deviation is not explained by the different models developed for asymmetric amplification. They therefore assumed that this non-linearity was due to the solid – liquid phase behavior of the catalyst in the reaction medium. The reaction would occur in both cases in the liquid phase, either in solution or in the concentrated molten phase. The easiest way to visualize this phenomenon is to use a ternary diagram, which shows us that in a solid – liquid equilibrium, an initial ratio of L/D

catalyst leads to a different ratio in the liquid reactive phase. See Figure 95.

In Figure 95, the catalyst is suspended in solvent S. When thermodynamic equilibrium is reached, all the initial compositions on the red segment will lead to the same ratio of catalyst in the liquid reactive phase corresponding to the eutectic, point E in Figure 95a1. This implies that for all these initial ratios of proline, the aldol products will have the same ratio, hence the observation of a plateau on the graph in Figure 95a2.

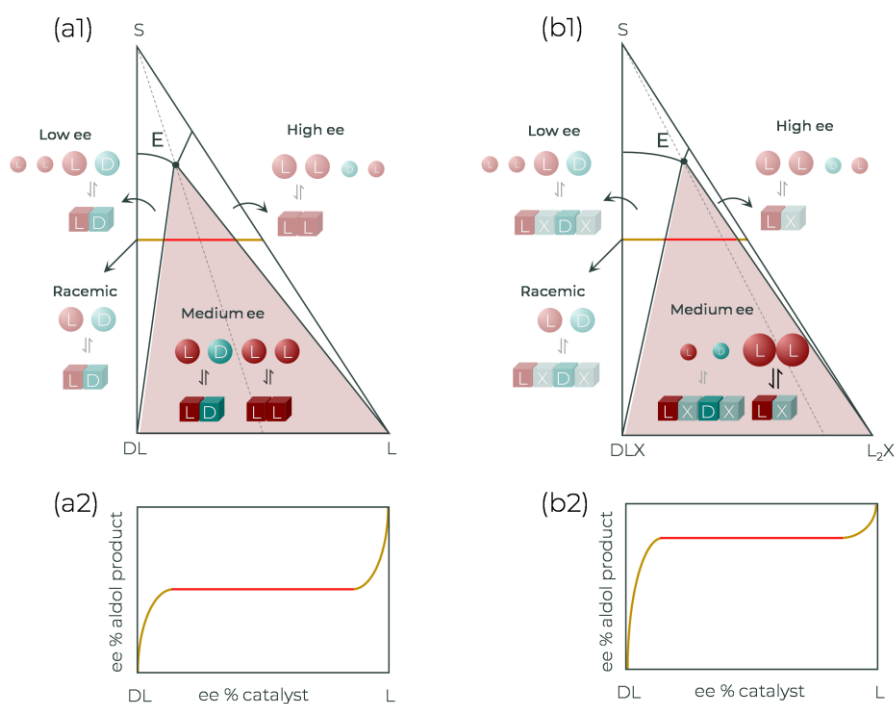


Figure 95 | a) Ternary diagram and dependence of the enantiomeric excess of the final product on that of catalyst. The composition of the eutectic determines the position of the plateau in the enantiomeric dependence. **b)** Ternary diagram modified by cocrystallization and dependence of the enantiomeric excess of the final product on that of catalyst. The composition of the eutectic is different from that shown in (a). It implies a higher enantiomeric excess plateau position (qualitative data).

What we will attempt to do here is to play with these phase diagrams, by cocrystallizing catalyst with various coformers. The cocrystallization of catalyst will strongly impact the ternary diagram and influence the composition of the eutectic determining the final enantiomeric excess in solution, as shown in Figure 95b1.

The work of B. Rodriguez, A. Bruckmann and C. Bolm (NLEs in aldolization organocatalyzed reaction in mechanochemistry) [190] combined with work of M. Klussmann and D. G. Blackmond (new eutectic compositions of amino acid due to de formation of a cocrystal) [180] form the basis of our first project "Controlling selectivity by crystal engineering on aldolization in the solid-state".

2.2 Methodology

Figure 96 illustrates the asymmetric aldolization reaction that we will use to conduct this research on. Since we wanted to play with the eutectic of the reaction mixture, we needed to use a ketone, an aldehyde and a solid catalyst at room temperature.

This reaction was chosen simply because it had already been well established in the previously cited work by B. Rodriguez, A. Bruckmann and C. Bolm. The use of 4-nitrobenzaldehyde is based on the fact that the electrophilicity of the carbonyl group is increased by the presence of the nitro group in the para position, which increases reactivity. Tetrahydro-4H-thiopyran-4-one and 4-tert-butylcyclohexanone are the only two solid ketones used by B. Rodriguez, A. Bruckmann and C. Bolm, as will be explained, they presented a certain challenge in the identification of the different possible aldol products/stereoisomers. Proline is one of the most extensively described catalysts in the literature for organocatalyzed aldolisation reactions and offers good reactivity for this type of reaction.

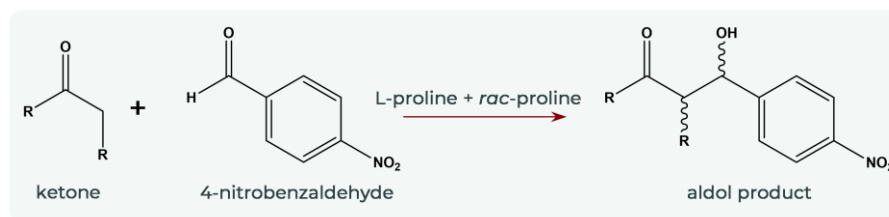


Figure 96 | Asymmetric aldol reaction catalyzed by proline.

The use of tetrahydro-4H-thiopyran-4-one can lead to four different products in an aldolization reaction (two diastereotopic pairs of enantiomers), shown in Figure 97. In contrast, the use of 4-tert-butylcyclohexanone can lead to eight different products (four diastereotopic pairs of enantiomers), shown in Figure 98. Indeed, during an aldolization reaction, a 4-substituted achiral cyclohexanone can be easily desymmetrized. This results in an increase in complexity giving access to products with three stereocenters.

The results obtained during this project will be presented in 2 parts. First, an investigation of the different solid forms of L- and DL-proline will be carried out. An analysis of three different coformers forming cocrystals with proline will then be performed. These three coformers are 2,5-dihydroxybenzoic acid, fumaric acid and succinic acid. Second, asymmetric aldol reactions will be carried out in the solid-state. For each ketone used, an HPLC method has been developed beforehand. Subsequently, these aldol reactions will be carried out using a proline cocrystal as a catalyst.

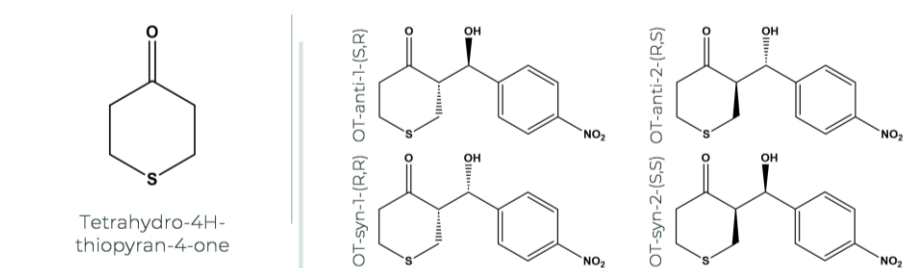


Figure 97 | Various stereoisomers accessible when using scalemic proline with tetrahydro-4H-thiopyran-4-one.

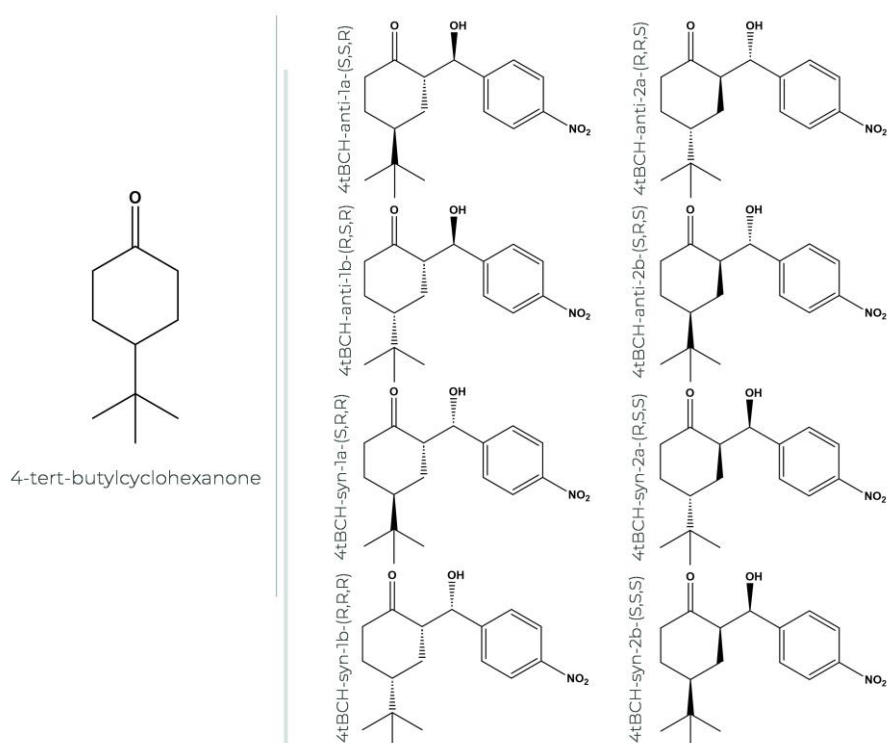


Figure 98 | Various stereoisomers accessible when using scalemic proline with 4-tert-butylcyclohexanone.

3. Investigating the proline solid-state

3.1 Proline solid phase: hydrates and polymorphs

In biological environments, proline is commonly found in zwitterionic form (proline[±]). Proline can exist in protonated (prolinium) or deprotonated (prolinate) form depending on the pH of the medium (Figure 99).

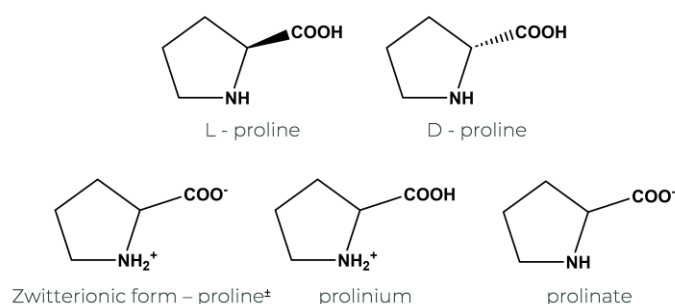


Figure 99 | Different forms of proline.

Carbon-oxygen bond distances in carboxyl (COOH) groups can provide clues to the form in which proline is present in a crystal. When the carboxyl of proline is present in neutral form, the C-O and C=O bond distances are respectively about 1.3 and 1.2 Å. On the other hand, when the carboxyl of proline is present in carboxylate form, the C-O bond distances are generally equal and their value is intermediate between that of the C=O and C-O bond.

Since the eutectic directly depends on the nature of the two solid phases put in presence one of the other, it is of utter importance to completely understand the various phases that exist of a given compound. We therefore started by researching the different known solid-states of proline, as well as its solvates that could be of interest in this research. The first part consisted of a search for the different solid phases already described in the CSD. Then the different commercial proline solid phases used were analyzed by X-ray powder diffraction before grinding, after grinding and after drying in an oven.

A database search shows several solid forms of proline already identified. Up to now, two different polymorphic forms of enantiopure proline as well as a hydrate have been characterized. As for the racemate DL-proline, only one solid form has been characterized, as well as a hydrate.

The first polymorphic form of L-proline, which we will call **L-prol-FI**, was described by Kayushina *et al.* (PROLIN). [191] and the second form, which we will call **L-prol-FII**, was described by our group (PROLIN04). [192] The hydrate form, which we will call **L-prol-HyI**, was described by Janzcak *et al.* (RUWGEV). [193]

Myung *et al.* described the anhydrous solid form of DL-proline, which we will call **DL-prol-FI** (QANRUT). [194] The hydrated solid form, which we will call **DL-prol-HyI**, was described by Padmanabhan *et al.* (DLPROM01). [195] A second hydrated form was discovered by F. Zhou *et al.*, and is termed **DL-prol-HyII**. [196]

Table 9 | L-proline and DL-proline solid forms, found in CSD.

Solid-state	Name	CSD Code	Space Group	References
Polymorph I	L-prol-FI	PROLIN	P 2 ₁ 2 ₁ 2 ₁	[191]
Polymorph II	L-prol-FII	PROLIN04	P 1	[192]
Hydrate	L-prol-HyI	RUWGEV	C 2	[193]
Polymorph I	DL-prol-FI	QANRUT	P 2 ₁ /c	[194]
Hydrate I	DL-prol-HyI	DLPROM01	P b c a	[195]
Hydrate II	DL-prol-HyII	N/A	P 2 ₁ /c	[196]

Knowing the different hydrates and polymorphs of proline, we checked the solid phases of the L- and DL-prolines by X-ray diffraction. We verified the commercial product prior to use, after drying and after grinding. The L-proline used (from Bachem, Switzerland - 1000017110) showed only one solid phase, that of polymorph I. Even after 90 min of grinding in a vibratory mill or after 48 h of grinding in a planetary mill (conditions for the aldolization reaction) the hydrate did not appear.

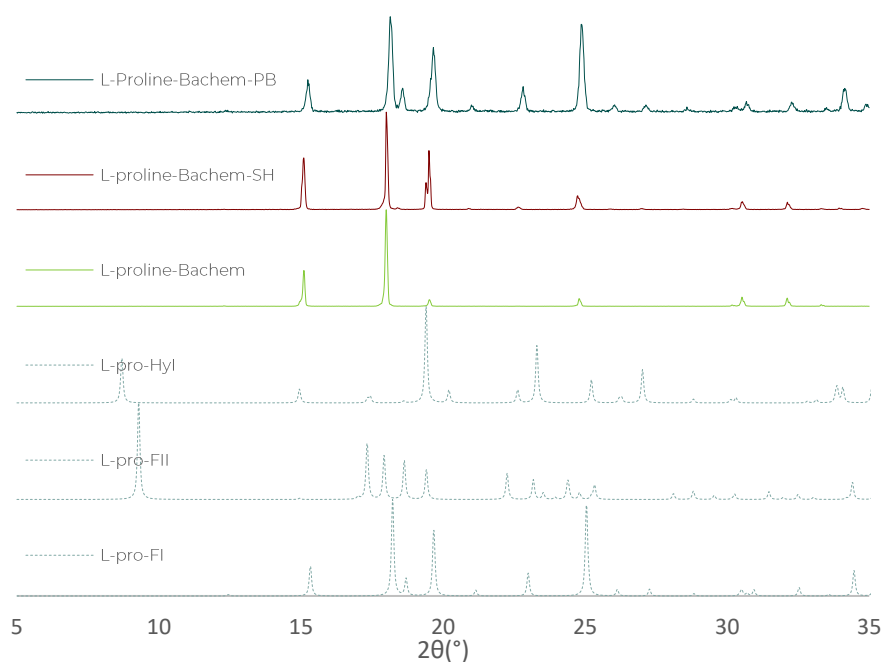


Figure 100 | Diffractograms of L-proline solid phase. SH: Shaker mill, PB: Planetary ball mill. Simulated patterns in dashed line and experimental one in full line.

The DL-proline jar, on the other hand, contains the hydrate DL-pro-Hyl (Alfa Aesar, Germany - 1018420). After 24 hours in the oven at 120°C, the hydrate disappears. However, after 48h of grinding the anhydrous form in a planetary mill, the hydrate reappeared. A similar observation was made grinding for 90 min in a shaker mill. In addition, new peaks can be observed on the XRPD, suggesting a new, unknown form. For all aldolization reactions performed in the context of this work, we decided to heat DL-proline for 24 hours at 120°C to avoid the presence of a DL-hydrate at the beginning of the reaction. However, we are aware that during the course of the reaction it is plausible that the DL-hydrate partially appears.

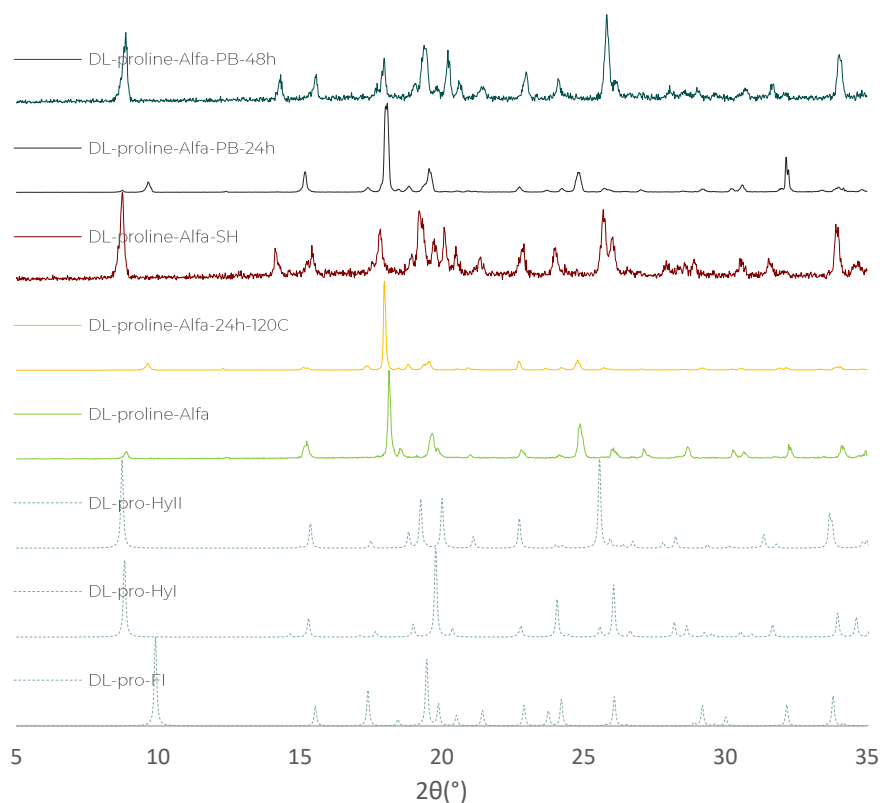


Figure 101 | Diffractograms of DL-proline solid phase. SH: Shaker mill, PB: Planetary ball mill. Simulated patterns in dashed line and experimental one in full line.

3.2 Proline cocrystals in the CSD

A search of the CSD database shows that some cocrystals based on L-proline or DL-proline have already been identified. In the context of this work, we were interested in finding achiral cocrystallization agents (coformer) which cocrystallize both with L-proline and DL-proline, forming a coformer-L-proline, coformer-DL-proline pair. For this pair we hope the eutectic point is substantially altered. Furthermore, we aimed for identical stoichiometry of the enantiopure and racemic cocrystals, to allow easily mixing the cocrystals in various ee and avoiding any stoichiometry effect. Indeed, if a 1 : 1 and 2 : 1 cocrystal would exist, we would need to adapt the amount of coformer according to the ee of the overall catalyst, which

would prove experimentally challenging. This led us to select three cocrystal formers identified in the database, which could be potential candidates for our work, and which are readily available in the lab: 2,5-dihydroxybenzoic acid (25DHBA), fumaric acid (FUMA) and succinic acid (SUCA), represented in Figure 102.

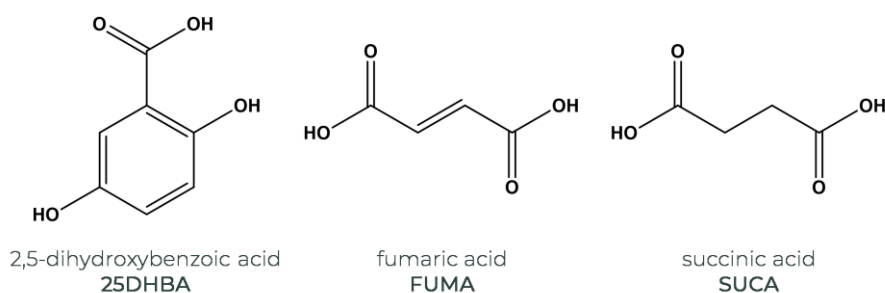


Figure 102 | Cocrystallization agents found in CSD which form a cocrystal with L-proline and/or DL-proline.

To confirm these four coformers are true candidates for our work, we needed to verify they form cocrystals with both the enantiopure as well as the racemic compound. To do so, we complemented the CSD results with experimental work, when the solid form was missing. Typically, we worked in a three-step procedure.

Firstly, liquid assisted grinding (LAG) was carried out between proline (enantiopure and racemate) and the cocrystallizing agents to see if a cocrystal exists. To do this, equimolar or 2 : 1 amounts of proline (0.1 mmol or 0.2 mmol) and cocrystallizing agent (0.1 mmol) were put into an Eppendorf tube, then 3 x 3 mm stainless steel balls and 10 μL of methanol were added ($\eta = \pm 0,3 - 0,4 \mu\text{L} \cdot \text{mg}^{-1}$). Once the jars were filled, the milling was run for 90 min at 30 Hz. The different grindings were then analyzed by X-ray powder diffraction.

Secondly, to confirm the stoichiometry of the obtained cocrystal, single crystals were grown. These were mainly obtained by solvent evaporation (solvent readily available in the lab). Equimolar or 2 : 1 amounts of proline and cocrystallizing agent were completely dissolved in different solvents. The different solutions were placed in

open vials in a refrigerator (5°C) for slow evaporation or left to evaporate at room temperature. The evaporation time varied from 3 to 7 days. Alternatively, cooling crystallization was used. This technique consists of saturating a solvent with equimolar or 2 : 1 quantities of proline and crystallizing agent and then decreasing the solubility by placing the samples in a refrigerator to decrease the temperature. The different single crystals obtained were then analyzed by X-ray diffraction and the simulated pattern verified to correspond to the ground product obtained in step one.

Finally, using these cocrystals in the aldolization reaction, implies having them in sufficient amount. To produce both the enantiopure and racemic cocrystal. Various slurries in different solvents (common used for crystal form screening and readily available in the lab) were performed. These allow us to determine one or more potential solvents to prepare cocrystal material in large quantities for subsequent use in the aldolization reaction. To do this, equimolar or 2 : 1 amounts of proline (1 mmol or 2 mmol) and cocrystallization agent (1 mmol) were suspended in about 1 to 2 ml of solvent ($\eta = \pm 2,9 - 7,4 \mu\text{L.mg}^{-1}$). After 7 days of stirring (seeding furthermore with the ground product) the different samples were filtered, washed with the corresponding solvent and analyzed by X-ray powder diffraction to verify they corresponded with the forms identified in step one and two.

3.2.1. 2,5-dihydroxybenzoic acid

Aakeroy *et al.* described the cocrystal between L-proline and 2,5-dihydroxybenzoic acid (ZEZHIV). [197] The cocrystal is a 1 : 1 cocrystal containing one equivalent of proline to one of 2,5-dihydroxybenzoic acid. The cocrystal with the racemate DL-proline was not yet described and found and identified in this work.

Grinding between L-proline and 2,5-dihydroxybenzoic acid leads as expected to the previously described cocrystal (ZEZHIV), as do the slurries in acetonitrile, dichloromethane and methanol. The grinding between DL-proline racemate and 2,5-dihydroxybenzoic acid leads to

a new, unexplained solid form that could be a potential cocrystal. This new solid form is seen in the slurries made with acetonitrile and methanol. However, the slurry in dichloromethane shows the same powder diffractogram as the ZEZHIV cocrystal! This could mean that in dichloromethane, proline forms a solvated cocrystal conglomerate with 2,5-dihydroxybenzoic acid. This solid form is expected to desolvate quite rapidly upon removal from the suspension, leading to the formation of the conglomerate. Such a cocrystal conglomerate could be further used for the development of a preferential crystallization in dichloromethane and if confirmed, can be part of some future work. ¹H-NMR analyses were carried out on these three slurries and showed a 1 : 1 ratio for each of the three samples (see Supporting Information p.231). Various methods were used to try and obtain a single crystal form between the racemic DL-proline and 2,5-dihydroxybenzoic acid. Evaporation in methanol allowed us to identify and characterize the new solid form between DL-proline racemate and 2,5-dihydroxybenzoic acid. The crystal structure confirms that the ratio between the two compounds is 1 : 1. The Scale Up of this system was then carried out by slurrying in acetonitrile in a 1 : 1 ratio (See p.160 for more details). The choice of this solvent was made in view of the quality of the powder obtained in methanol and acetonitrile. In methanol some peaks are unexplained, neither by parents nor by one of the known cocrystals.

Table 10 shows the different results obtained by grinding, slurry and crystal growth experiments between the 2,5-dihydroxybenzoic acid coformer and enantiopure as well as racemic proline. The diffractograms of grindings as well as slurries are presented in Figure 103 with L-proline and Figure 104 with DL-proline. Simulated patterns of cocrystals (the new form with DL-proline and the form with L-proline (ZEZHIV)) are in dashed line.

Table 10 | Cocrystal form screening performed on L- and DL-proline with 2,5-dihydroxybenzoic acid. A new form identified and characterised between DL-proline and 2,5-dihydroxybenzoic acid with a ratio of 1:1, by evaporation in MeOH. Crystallization method: LAG ($\eta = 0,37 \mu\text{L}.\text{mg}^{-1}$) Slurry ($\eta = 3,71 - 7,43 \mu\text{L}.\text{mg}^{-1}$).

Proline	Solvent	Crystallization method	Crystal form (XRD – XRPD)
L	MeOH	Ball-milling LAG	ZEZHIV
L	ACN, MeOH, DCM	Slurry	ZEZHIV
DL	MeOH	Ball-milling LAG	New form
DL	ACN, MeOH	Slurry	New form
DL	DCM	Slurry	Same pattern as ZEZHIV
DL	ACN, MeOH, DCM	Cooling (5°C)	N/A
DL	DCM	Cooling (-60°C)	N/A
DL	ACN, DCM	Evaporation (RT)	25DHBA
DL	MeOH	Evaporation (RT)	New form characterised
DL	ACN, MeOH, DCM	Evaporation (5°C)	25DHBA

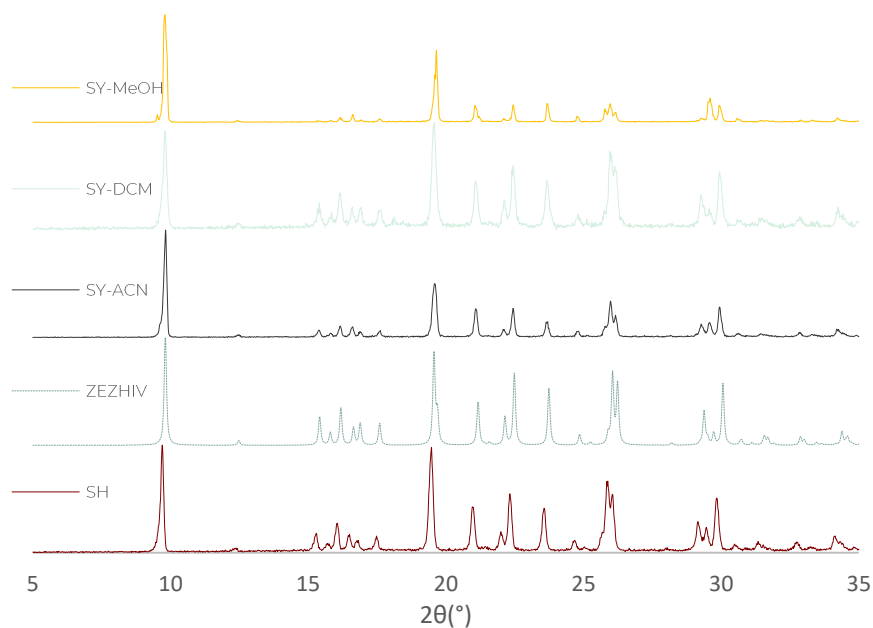


Figure 103 | Diffractograms of shaker milling (SH) and slurry (SY) (in ACN, DCM and MeOH) between L-proline and 2,5-dihydroxybenzoic acid. Simulated patterns from CSD in dashed line and experimental one in full line.

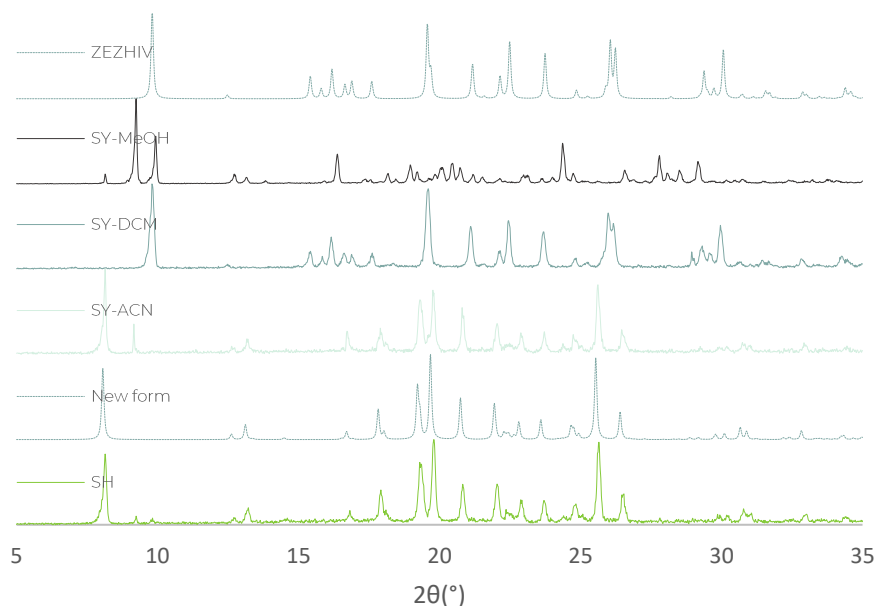


Figure 104 | Diffractograms of shaker milling (SH) and slurry (SY) (in ACN, DCM and MeOH) between DL-proline and 2,5-dihydroxybenzoic acid. Simulated patterns from single crystal in dashed line and experimental one in full line.

The asymmetric unit of the cocrystal obtained by evaporation from methanol is illustrated in Figure 105. The cocrystal crystallizes in the monoclinic system with a $P2_1/c$ space group, containing one molecule of 2,5-dihydroxybenzoic acid and one molecule of D or L-proline in the asymmetric unit. Crystal parameters are shown in Table 11. Proline is disordered with half in zwitterionic form (D or L – pro[±]) and half in prolinium form (D or L – pro⁺). 2,5-dihydroxybenzoic acid form dimers where the carboxylic acid moieties share one proton with an overall single negative charge per dimer. The cocrystal has a fifty per cent of salt character. Contrary to the empirical guideline, we are here in the presence of a cocrystal salt continuum while the $\Delta pK_a < 0$. Here ΔpK_a is -1,17 (pK_a for proline is 1,8 and pK_a for 2,5-dihydroxybenzoic acid is 2,97).

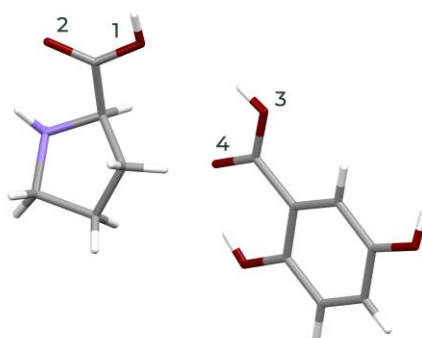


Figure 105 | Asymmetric unit of cocrystal between DL-proline and 2,5-dihydroxybenzoic acid, view along a axis. Number are references to C-O bond distances: 1 = 1,223 Å; 2 = 1,275 Å; 3 = 1,279 Å; 4 = 1,248 Å.

Table 11 | Main crystallographic data of new cocrystal form between DL-proline and 2,5-dihydroxybenzoic acid. From a single crystal growth in MeOH.

Compound	DL-proline 2,5-dihydroxybenzoic acid
Identification code	cb_A9DL_meOH
Empirical formula	C ₅ H _{9.5} NO ₂ , C ₇ H _{5.5} O ₄
Formula weight (g/mol)	269.25
Temperature (K)	297(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P2₁/c</i>
a,b,c (Å)	a 12.0218(10) b 8.5578(5) c 13.4006(12)
α, β, γ (°)	β 114.249(10)
Volume (Å ³)	1257.03(19)
Z	4
Density calculated (Mg/m ³)	1.423
Absorption coefficient (mm ⁻¹)	0.115
Crystal size (mm ³)	0.30x 0.25 x 0.15
F(000)	568
Theta range for data collection (°)	3.020 to 26.258
Reflections collected	8693
Independent reflections	2510 [R(int) = 0.0233]
Completeness to theta = 25.96°	99.4
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.77379
Data / restraints / parameters	2510 / 3 / 182
Goodness-of-fit on F ²	1.084
Final R indices [I>2sigma(I)]	R1 = 0.0413, wR2 = 0.1077
R indices (all data)	R1 = 0.0474, wR2 = 0.1114
Largest diff. Peak and hole (e.Å ⁻³)	0.263, -0.171

3.2.2. *Fumaric acid*

A. Tilborg *et al.* described the cocrystal between L-proline and fumaric acid (GIHSOH), as well as that with D-proline (GIHSUN). The cocrystal contains two equivalents of proline to one of fumaric acid. They also described the cocrystal with the racemate DL-proline (GIHSAT), again in an overall ratio of two molecules of proline to one molecule of fumaric acid. [198]

Milling in a 2 : 1 ratio between the L-proline enantiomer or DL-proline racemate and the crystallizing agent fumaric acid leads as expected to the forms GIHSOH and GIHSAT. Various slurries were performed with L-proline in ethyl acetate, dichloromethane, ethanol, acetone, tetrahydrofuran and methanol. All recovered powders showed a single solid phase corresponding to the cocrystal between L-proline and fumaric acid. Concerning the DL-proline racemate, the slurries made in ethanol and methanol showed the pure solid phase corresponding to the cocrystal between the DL-proline racemate and fumaric acid. On the other hand, the slurries in ethyl acetate and dichloromethane show only the presence of a mixture of DL-proline and its first hydrated form. The system therefore behaves incongruently in these solvents, which will therefore not be used to produce cocrystal material on a larger scale. The Scale Up of this system is carried out by slurring a 2 : 1 ratio in ethanol (See p.160 for more details).

Table 12 shows the different results obtained by grinding, slurry and crystal growth experiments between the fumaric acid coformer and the enantiopure proline as well as the racemate. The diffractograms of grindings as well as slurries are presented in Figure 106 with L-proline and Figure 107 with DL-proline. Simulated patterns of cocrystals are in dashed line.

Table 12 | Cocrystal form screening performed on L- and DL-proline with fumaric acid. Crystallization method: LAG ($\eta = 0,29 \mu\text{L.mg}^{-1}$) Slurry ($\eta = 2,89 - 5,77 \mu\text{L.mg}^{-1}$).

Prolin e	Solvent	Crystallization method	Crystal form
L	MeOH	Ball-milling LAG	GIHSOH
L	ACN, MeOH, DCM, EtOAc, EtOH, Acet, THF	Slurry	GIHSOH
DL	MeOH	Ball-milling LAG	GIHSAT
DL	EtOH, MeOH	Slurry	GIHSAT
DL	EtOAc, DCM	Slurry	DL-prol-FI, DL-pro-Hyl

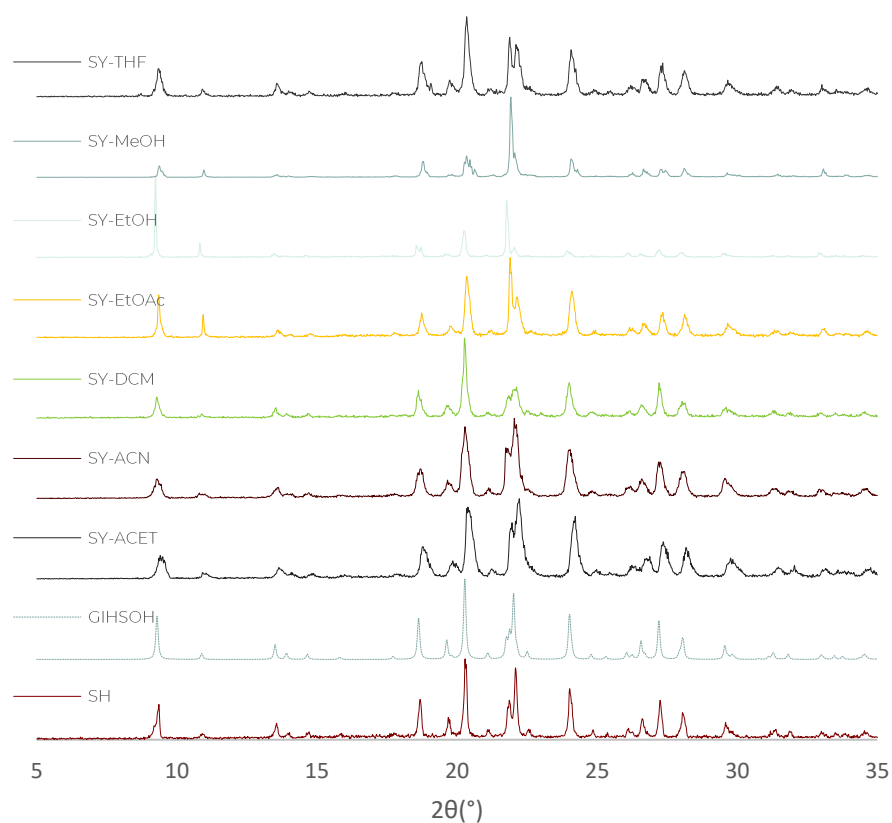


Figure 106 | Diffractograms of shaker milling (SH) and slurry (SY) (in Acet, ACN, DCM, EtOAc, EtOH, MeOH and THF) between L-proline and fumaric acid. Simulated patterns from CSD in dashed line and experimental one in full line.

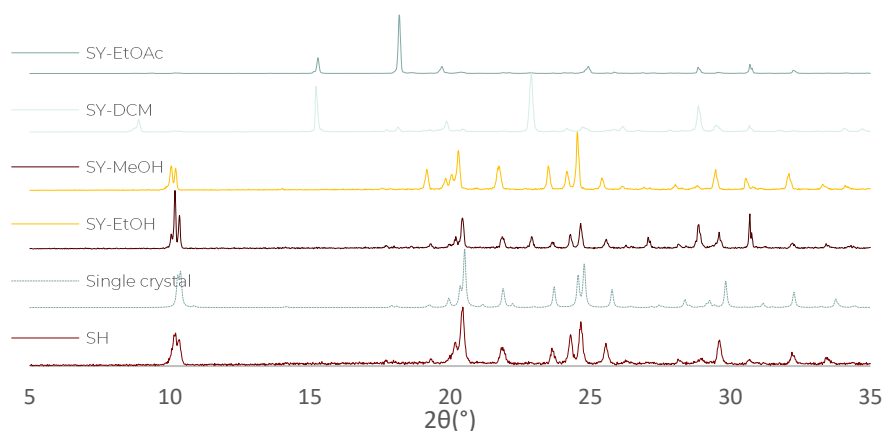


Figure 107 | Diffractograms of shaker milling (SH) and slurry (SY) (in EtOH, MeOH, DCM and EtOAc) between DL-proline and fumaric acid. Simulated patterns from a single crystal in dashed line and experimental one in full line (See the side-note which explains why it is the reference of an experimental single crystal that was used and not the CSD reference).

As a side-note, we noticed during this thesis, that care should be taken when using diffractograms simulated from a crystal structure published and downloaded from the CSD. Figure 108 shows the difference between a simulated diffractogram from the data available in the CSD and the simulated diffractograms obtained from the experimental single crystal structure, for the cocrystal between DL-proline and fumaric acid. This is due to the fact that, sometimes there is no information about the occupancy of atoms for a disordered structure in the CSD while in the experimental file the occupancy of each atom is given. For example, the occupancy of two oxygens will be at 1 in the CSD while they will be 0,7 and 0,3 in the experimental file.

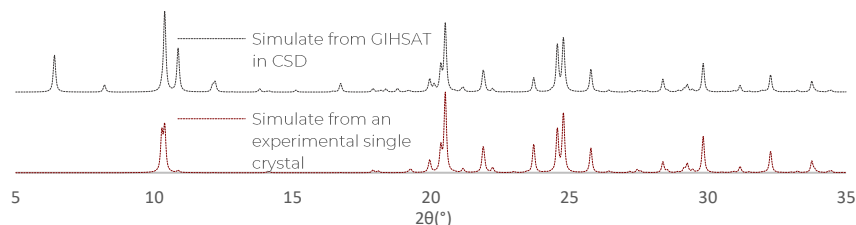


Figure 108 | Difference between a powder pattern simulated from a crystal structure published on the CSD and a powder pattern simulated from an experimental single crystal of DL-proline and fumaric acid.

3.2.3. Succinic acid

Prasad *et al.* described the cocrystal between the racemate DL-proline and succinic acid (LABZUJ). [199] The cocrystal contains two equivalents of proline to one of succinic acid. The cocrystal with the L-proline enantiomer is not yet described. Two polymorphic forms of this cocrystal will be characterized in this thesis.

Grinding between DL-proline and succinic acid leads, as expected, to the previously described cocrystal (LABZUJ), as does the slurry in methanol. The slurries in ethyl acetate, dichloromethane and ethanol, on the other hand, show traces of the hydrated DL-proline. Milling between the L-proline enantiomer and succinic acid leads to a new, unexplained solid form that could be a potential cocrystal. However, slurries in dichloromethane, ethyl acetate, methanol, ethanol and acetonitrile show peaks not overlapping with the grinding experiment, indicating a potential other solid form. Various methods were carried out in an attempt to obtain single crystals between the L-proline enantiomer and succinic acid. Evaporation in methanol allowed us to identify and characterise the first form between L-proline and succinic acid and evaporation in acetone led to the second form. The crystal structure confirms the ratio between the two compounds is 2 : 1 in both cases. Figure 109 and Table 13 show ball-milling to lead to FII of the cocrystal, whereas slurry experiments always yield FI. Crystallographic data of both forms is given in Table 14. As shown by this table FI is also the densest polymorph, leading us to believe that FI is the most stable form.

Table 13 shows the different results obtained by grinding, slurry and crystal growth experiments between the succinic acid coformer and the enantiopure proline as well as the racemate. The diffractograms of grindings as well as slurries are presented in Figure 109 with L-proline and Figure 110 with DL-proline. Simulated patterns of cocrystals (the two new forms I and II with L-proline and the form with DL-proline (LABZUJ)) are in dashed line.

Table 13 | Cocrystal form screening performed on L- and DL-proline with succinic acid. Two new forms identified and characterised between L-proline and succinic acid with a ratio of 2 : 1. One by evaporation in MeOH and one by evaporation in Acet. Crystallization method: LAG ($\eta = 0,29 \mu\text{L.mg}^{-1}$) Slurry ($\eta = 2,87 - 5,74 \mu\text{L.mg}^{-1}$).

Proline	Solvent	Crystallization method	Crystal form
L	MeOH	Ball-milling LAG	New Form II
L	MeOH, EtOH, DCM, ACN	Slurry	New Form I
L	EtOAc	Slurry	New Form I, L-pro-Hyl
L	MeOH, Acet, DCM	Cooling (5°C)	N/A
L	MeOH	Evaporation (RT)	New Form I characterized
L	Acet	Evaporation (RT)	New Form II characterized
L	DCM	Evaporation (RT)	N/A
L	MeOH, Acet, DCM	Evaporation (5°C)	SUCA
DL	MeOH	Ball-milling LAG	LABZUJ
DL	MeOH	Slurry	LABZUJ
DL	EtOH, DCM, EtOAc	Slurry	LABZUJ, DL-pro-Hyl

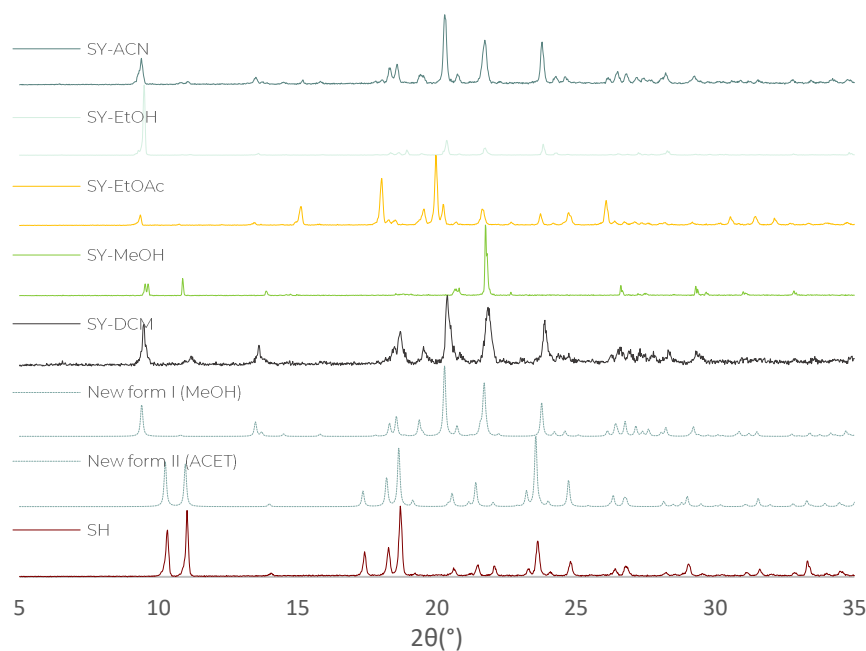


Figure 109 | Diffractograms of shaker milling (SH) and slurry (SY) (in DCM, MeOH, EtOAc, EtOH and ACN) between L-proline and succinic acid. Simulated patterns from single crystals in dashed line and experimental one in full line.

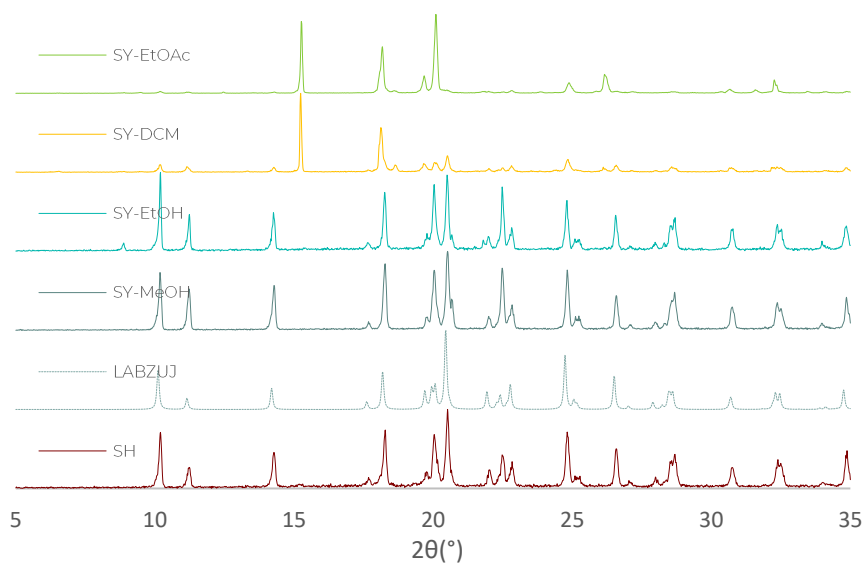


Figure 110 | Diffractograms of shaker milling (SH) and slurry (SY) (in MeOH, EtOH, DCM and EtOAc) between DL-proline and succinic acid. Simulated patterns from CSD in dashed line and experimental one in full line.

The asymmetric unit of the cocrystal obtained by evaporation from methanol (Form I) is illustrated in Figure 111. The cocrystal crystallizes in the monoclinic system space group $P2_1$, containing one molecule of succinic acid and two molecules of L-proline in the unit cell.

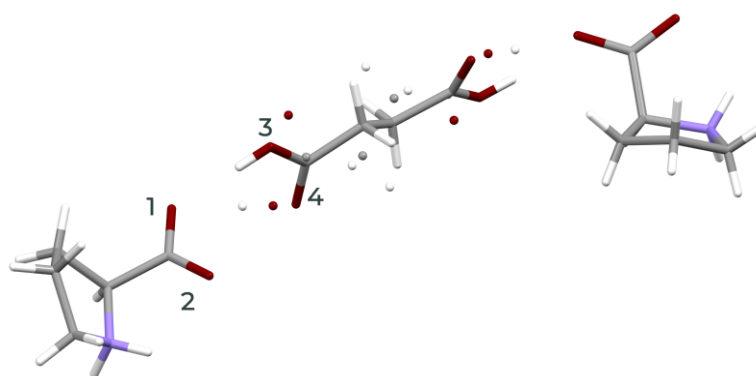


Figure 111 | Asymmetric unit of L-proline/Succinic acid Form I, view along c axis. Number are references to C-O bond distances: 1 = 1,252 Å; 2 = 1,226 Å; 3 = 1,335 Å; 4 = 1,276 Å.

The asymmetric unit of the cocrystal obtained by evaporation from acetone (Form II) is illustrated in Figure 112. The cocrystal crystallizes in a monoclinic system with a $P2_1$ space group, containing also one molecule of succinic acid and two molecules of L-proline in the unit cell. Crystal parameters for the two forms are shown in Table 14.

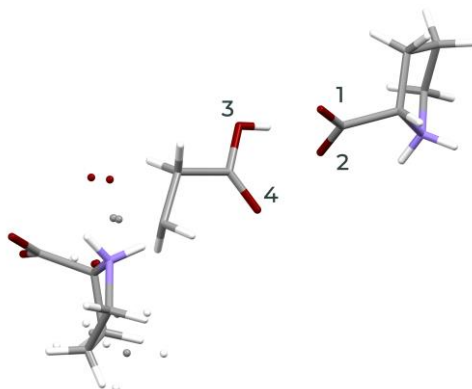


Figure 112 | Asymmetric unit of L-proline/Succinic acid Form II, view along c axis. Number are references to C-O bond distances: **1** = 1,234 Å; **2** = 1,228 Å; **3** = 1,300 Å; **4** = 1,207 Å.

In both cases, proline is in zwitterionic form ($L\text{-pro}^{\pm}$) and succinic acid in a neutral form. Analyses of C-O bond distance of carboxyl show that it is therefore not a salt which is obtained. This statement aligns with the empirical guideline predicting that there is no formation of a salt, but cocrystal formation, when the $\Delta pK_a < 0$. Here ΔpK_a is -2,4 (pK_a for proline is 1,8 and pK_a for succinic acid is 4,2)[198, 200].

Table 14 | Main crystallographic data of new cocrystal forms between DL-proline and 2,5-dihydroxybenzoic acid. From a single crystal growth in MeOH, and from a single crystal growth in Acet.

Compound	L-proline Succinic acid Form I	L-proline Succinic acid Form II
Identification code	cb_A4_L_MeOH	cb_A4_L_acet
Empirical formula	C ₅ H ₂₄ NiO ₂ , C ₅ H ₂₄ NiO ₂ , C ₄ H ₆ O ₄	C ₅ H ₂₄ NiO ₂ , C ₅ H ₂₄ NiO ₂ , C ₄ H ₆ O ₄
Formula weight (g/mol)	348.35	348.35
Temperature (K)	297(2)	297(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁
a,b,c (Å)	a 9.7716(4) b 9.1606(3) c 10.0987(5)	a 5.16117(15) b 16.1347(5) c 10.3098(3)
α, β, γ (°)	a 90 b 111.282(5) g 90	a 90 b 97.639(3) g 90
Volume (Å ³)	842.33(7)	850.91(4)
Z	2	2
Density calculated (Mg/m ³)	1.373	1.360
Absorption coefficient (mm ⁻¹)	0.113	0.112
Crystal size (mm ³)	0.38x 0.20 x 0.20	0.50x 0.50 x 0.25
F(000)	372	372
Theta range for data collection (°)	3.154 to 26.288	3.217 to 26.262
Reflections collected	7364	6025
Independent reflections	3316 [R(int) = 0.0209]	3232 [R(int) = 0.0233]
Completeness to theta = 25.96°	98.3	98.0
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90140	1.00000 and 0.87766
Data / restraints / parameters	3316 / 79 / 290	3232 / 73 / 273
Goodness-of-fit on F ²	1.048	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0578, wR2 = 0.1554	R1 = 0.0446, wR2 = 0.1185
R indices (all data)	R1 = 0.0629, wR2 = 0.1597	R1 = 0.0465, wR2 = 0.1202
Largest diff. Peak and hole (e.Å ⁻³)	0.426, -0.176	0.277, -0.130

3.2.4. Cocrystals of interest

Table 15 summarizes the cocrystals of interest for this project. The three coformers selected do align with the desired criteria: existence of both L- and DL-cocrystals, identical stoichiometry for L- and DL-cocrystals, easily up-scalable method to obtain bulk material of both.

Table 15 | Summary table of cocrystals already described (white), characterized during this project (green).

Code CSD	Proline	Coformer	Ratio
ZEZHIV	L-proline	25DHBA	1:1
	DL-proline	25DHBA	1:1
GIHSOH	L-proline	FUMA	2:1
GIHSUN	D-proline	FUMA	2:1
GIHSAT	DL-proline	FUMA	2:1
(FI)	L-proline	SUCA	2:1
(FII)	L-proline	SUCA	2:1
LABZUJ	DL-proline	SUCA	2:1

Given that fumaric acid and succinic acid are two molecules distinguished simply by the presence or absence of a double bond, it seems interesting to compare their unit cell parameters. As shown by Table 16, Form I of the L-Proline Succinic acid cocrystal is isostructural to the L-Proline Fumaric acid cocrystal. For this system, likely a solid solution between both cocrystals can be formed varying the amount of Fumaric acid vs Succinic acid. No such isostructural cocrystal was observed when looking at DL-Proline.

Table 16 | Comparison of unit cell parameters of cocrystals of succinic acid and fumaric acid with L-proline.

Compound	L-proline / Succinic acid I	L-proline / Succinic acid II	L-proline / Fumaric acid
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$
a, b, c (Å)	a 9.7716(4) b 9.1606(3) c 10.0987(5)	a 5.16117(15) b 16.1347(5) c 10.3098(3)	a 9.5896(4) b 9.0386(3) c 10.1964(5)
α, β, γ (°)	a 90 b 111.282(5) g 90	a 90 b 97.639(3) g 90	a 90 b 110.845(5) g 90

Table 17 | Comparison of unit cell parameters of cocrystals of succinic acid and fumaric acid with DL-proline.

Compound	DL-proline / Succinic acid	DL-proline / Fumaric acid
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$Pbc2_1$
a,b,c (Å)	a 5.254(1)	a 17.2025(6)
	b 17.480(1)	b 9.7993(3)
	c 10.230(1)	c 27.6106(19)
α, β, γ (°)	a 90	a 90
	b 119.60(6)	b 90
	g 90	g 90

4. Mechanochemical aldolization catalyzed by proline

4.1 Setting the mechanochemical conditions

Mechanochemical reactions can be performed under different conditions (LAG, neat grinding, amount of material, ball-size, ...) and with different equipment (vibratory mill, planetary mill, ...). To define the conditions used for the rest of the work, we first started by investigating the set-up that led to a successful reaction. To do so we focused on the system 4-tert-butylcyclohexanone and 4-nitrobenzaldehyde using L-proline as a catalyst (Figure 113). This system was chosen because it led to good yields as shown by B. Rodriguez, A. Bruckmann and C. Bolm (85% yield and enantiomeric excess of 91 %). [189] Furthermore, it is a system on which non-linear effects have been observed when using different ratios of L and D proline. [190]

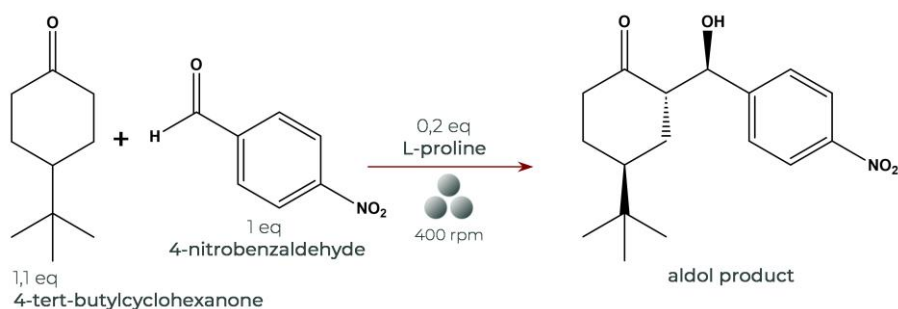


Figure 113 | Reaction used to define mechanochemical reaction conditions.

In literature, this experiment was carried out with 45 mL grinding bowls containing 60 x 5 mm diameter balls, both composed of zirconium oxide, in a Fritsch Pulverisette 7 premium planetary mill (2 experiments can be run at the same time). They used approximately 690 mg of compounds with milling conditions of 15 min at 400 rpm + 5 min break for a total duration of 33 h. [189, 190] However, only stainless steel and tungsten carbide bowls and balls (10 mm) were available in the lab. So initial experiments were carried out using a

Pulverisette 7 with 45 mL stainless steel or tungsten carbide bowls and 3 x 10 mm stainless steel or 3 x 10 mm tungsten carbide balls. Using this set-up, with $\approx$ 690 mg of compounds and the same milling condition, we were unable to make the reaction work correctly. It is not possible to draw a conclusion about non-reactivity with this grinding device, given the difference between the number (3 vs 60) and size (10 vs 5 mm) of balls and the grinding material used. The lack of reactivity when grinding with a steel bowl and balls can be due to the low hardness of this material, damping the impact of the balls which would prevent formation of the molten state. With the much harder tungsten carbide, reactions occurred but the bowl deteriorated and the powder was black at the end of the reaction (We supposed it was tungsten carbide particles). See Table 6 for hardness and density scale of the materials.

When switching to 45 mL zirconium oxide bowls and to 60 x 5 mm zirconium oxide balls, promoting a better mixing and homogenization of the reaction mixture, with $\approx$ 690 mg of material and the same milling condition used in literature, we were effectively able to make the reaction work.

This allowed us to set-up a general procedure. In order to perform the impressive amount of experiments which laid ahead of us, we decided to switch to two Tencan XQM-0.4A planetary mills, with which we were able to run 8 experiments at the same time. We used 50 mL zirconium oxide bowls and 60 x 5 mm zirconium oxide balls ($\pm$ 30 g). Typically, the milling was carried out using about 690 mg of material for 48 hours at a speed of 400 rpm in 15 minutes milling cycles, followed by a 5 minutes pause to avoid overheating the bowl. In the literature, an adequate reaction time was 33 hours, but we chose to work with 48 hour milling sessions to simplify work planning. (After a reaction monitoring, the reaction seemed to stagnate between 30 and 48 hours).

Following grinding, the solid product was washed off the reaction bowls with several fractions of diethyl ether. The different fractions

were then collected and concentrated using a rotavapor. Finally, chiral HPLC analysis was used to determine the enantiomeric excess of the aldol product. We used first diethyl ether like in the literature, but we will see that a part of the product did not dissolve (suspended in the solvent). Even though this initially, enabled us to isolate products and characterize them (description in next point), we turned to dichloromethane afterwards as it allowed solubilizing all the products.

Figure 114 shows the overall number of experiments performed in the context of this thesis. This figure sums up the experiments done using two different types of ketones, and three different types of prolines (native proline and two proline cocrystal systems) varying the overall ee. This figure is just illustrative, and highlights the amount of work underlying this chapter.

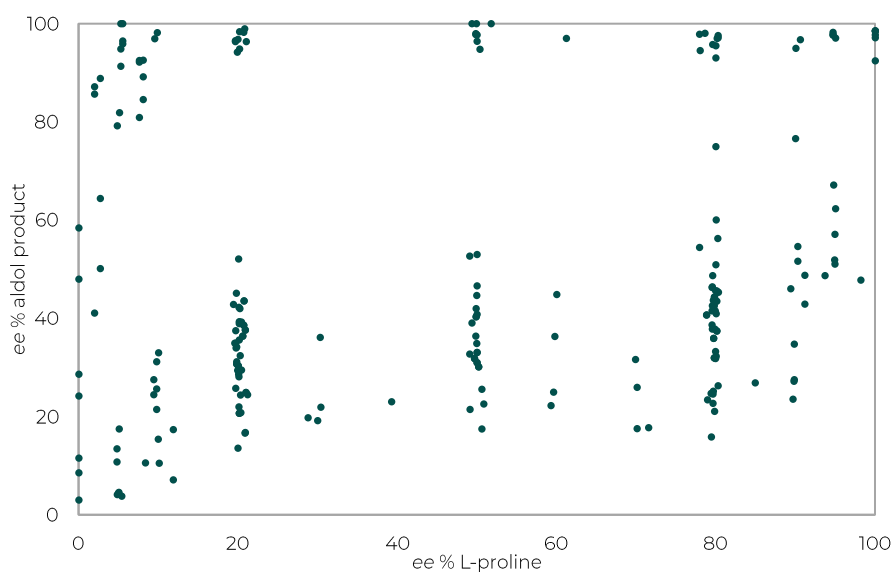


Figure 114 | Grinding experiments performed in the context of this work, highlighting the high number of experiments performed.

4.2 Puzzling out a complicated chPLC pattern working with 4-tert-butylcyclohexanone

Above we were merely interested in setting up the conditions for the mechanochemical reaction to work. Once this established, we needed to analyze the stereochemistry of the obtained products using a chiral HPLC.

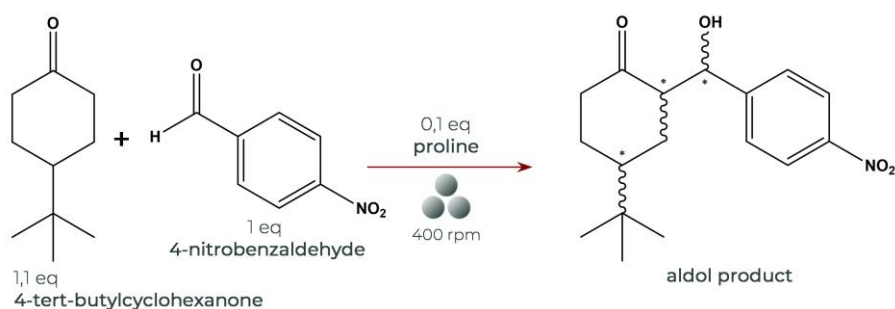


Figure 115 | Reaction conditions used to determine the 8 possible stereoisomers when working with 4-tert-butylcyclohexanone.

Aldolization reactions with 4-tert-butylcyclohexanone can lead to 8 different products (4 couples of enantiomers), as shown above in Figure 97 or in one go in Figure 115. These 8 products are visible in chiral HPLC (see Figure 119), but in the context of this work, we focus only on the enantiomeric ratio of the main couple of enantiomers. These correspond to the two enantiomers obtained using pure L-proline or D-proline, respectively named 4tBCH-anti-1a-(S, S, R) and 4tBCH-anti-2a-(R, R, S), showed in Figure 116.

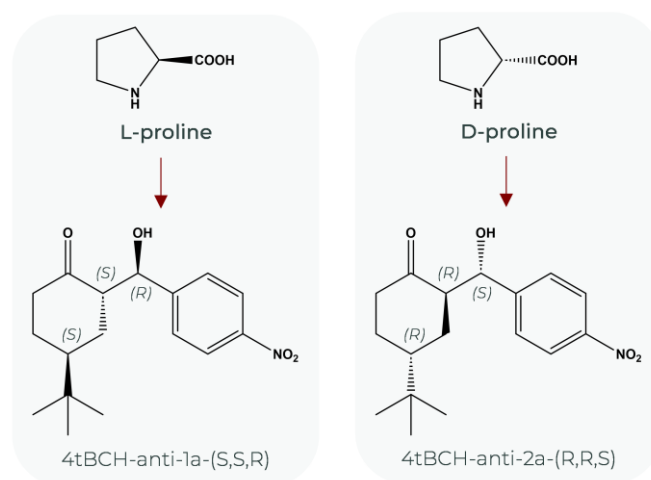


Figure 116 | Main enantiomers obtained using pure L- and D-proline.

To be sure to identify these two peaks in chiral HPLC we isolated them after a ball milling reaction. To do so, 1.1 eq of 4-tert-butylcyclohexanone (2.2 mmol), 1 eq of 4-nitrobenzaldehyde (2 mmol) and 0.1 eq of *rac*-proline (0.2 mmol) were weighed and put in a 50 mL zirconium oxide bowl together with 60 x 5 mm zirconium oxide balls ($\pm$ 30 g). Grinding was started for 48 hours at 400 rpm with intervals of 15 min grinding in one direction, 5 min pauses, 15 min grinding in the other direction and 5 min pause. At the end of the 48 hours, the resulting solid was recovered in 4 fractions of about 40 mL of diethyl ether. A solid part was then found suspended in the diethyl ether. The liquid part, compound dissolved in diethyl ether, was concentrated with a rotavapor. The different samples were analysed by chiral HPLC and ^1H -NMR.

Since the ^1H -NMR were carried out in DMSO, these data cannot confirm whether the reaction was complete or not. In DMSO, an aprotic polar solvent, the aldolization reaction could continue to take place. [156] During the HPLC analysis, the apolar solvents isohexane, or acetonitrile, were not favorable for the reaction to continue. Furthermore, the absence of 4-nitrobenzaldehyde confirmed that the reaction was complete. See Supporting Information p.232 for ^1H -NMR results of this part.

For chiral HPLC, samples were first diluted using a mixture of isohexane and ethanol (90 : 10). Analysis were performed using the following HPLC parameters: Column: DAICEL Chiralcel-OJ-H, 4.6x250 mm, 5 μ m; T° = 25 °C; Flow: 1 mL.min⁻¹; Mobile phase 85 % isohexane, 15% Ethanol; Equilibrate time of 30 min; Stop time: 30 min.

The solid part (suspended in the diethyl ether) showed in ¹H-NMR that it contained a single diastereomer. Chiral HPLC analysis of the solid showed the presence of two enantiomers with an absorption at 266,5 nm, see Figure 117.

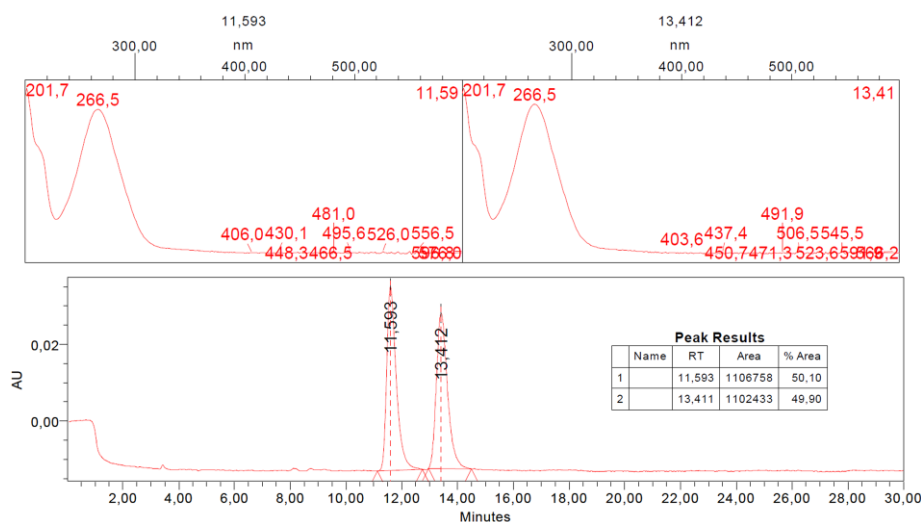


Figure 117 | Chiral HPLC of the solid compound in suspension in diethyl ether, showing two enantiomers.

Recrystallisation of the solid product by evaporation in ethyl acetate allowed the two enantiomers to be characterized by XRD and their stereochemistry to be identified (see Figure 118). These correspond to the expected products using pure L-proline and D-proline.

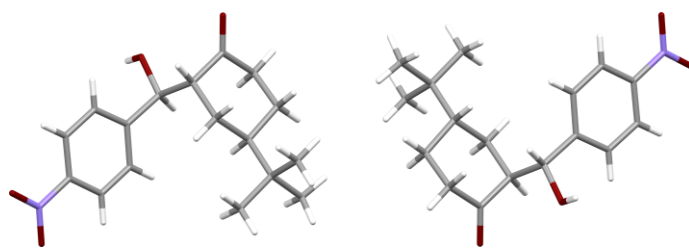


Figure 118 | Crystal structure of the racemate obtained by the asymmetric aldolization catalyzed by a racemic mixture of L- and D-proline. The enantiomers obtained are 4tBCH-anti-a1-(S, S, R) (right) and 4tBCH-anti-a2-(R, R, S) (left).

On the other hand, the compounds dissolved in the diethyl ether showed in ^1H -NMR the presence of at least two diastereomers, one of which is the diastereomer also present in the solid. It is assumed that the remaining two diastereomers were in too low concentration to be observable in ^1H -NMR or embedded in the signals of the other two diastereomers. Chiral HPLC confirmed the solid indeed contains eight peaks that could correspond to the four diastereotopic pairs of enantiomers, see Figure 119. Two of which corresponded to the same peaks as the pair of enantiomers observed from the initial solid with a retention time of 11.501 and 13.330 min. Even in the remaining liquid these form the major stereoisomers present.

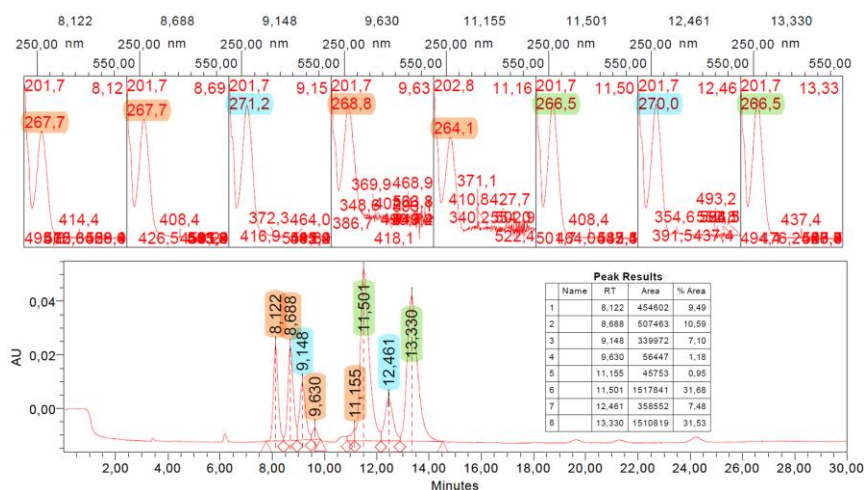


Figure 119 | Typical pattern obtained in chiral HPLC using 4-tert-butylcyclohexanone. Chiral HPLC of the dissolved compound in diethyl ether, showing certainly eight products including the pair of enantiomers present in the solid suspension (peaks at 11,501 and 13,330 min).

A silica chromatographic column performed with 100 % dichloromethane, on these compounds dissolved in the diethyl ether allowed the isolation of two pairs of enantiomers. One pair correspond to the one found in the solid with a retention time around 11.5 and 13.3 min (Figure 120) and the other pair with retention time 9.1 and 12.4 min (Figure 121).

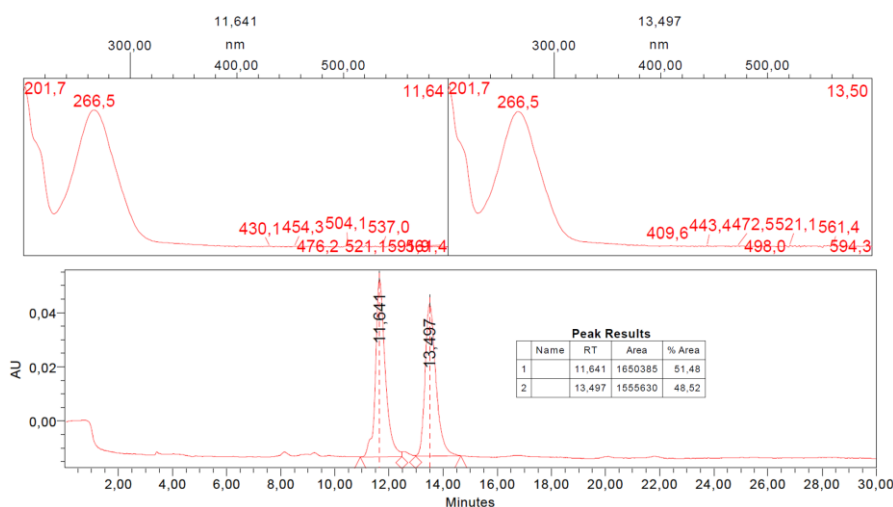


Figure 120 | Chiral HPLC of a second fraction collected after a silica chromatographic column, showing the same pair of enantiomers than in the solid suspension.

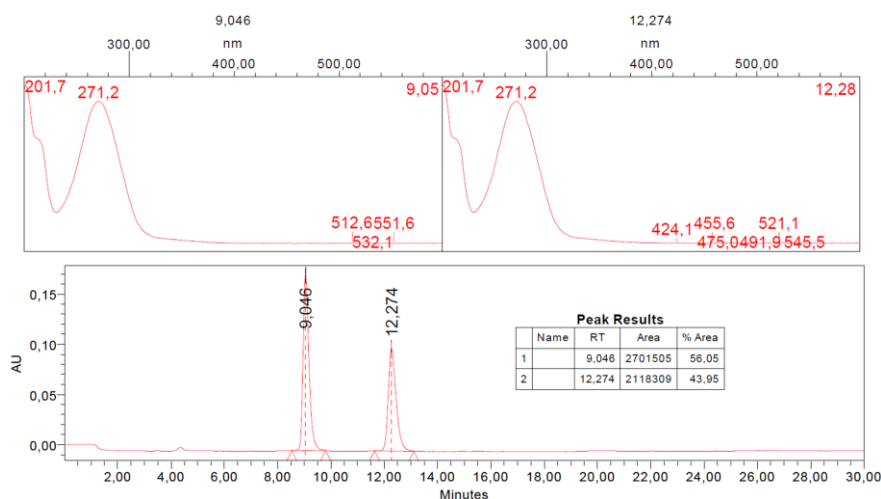


Figure 121 | Chiral HPLC of first fraction collected after a silica chromatographic column, showing a new pair of enantiomers.

Unfortunately, we were not able to identify the stereochemistry of this new pair, nor of the four other products. However, as the solids with retention time at 11.5 and 13.3 min, are the major compounds obtained both in the solid and the remaining liquid phase, this pair of enantiomers is clearly the major form, and is the main focus of this work.

The grinding experiment was repeated using the same methodology, in the same conditions, but this time using enantiopure L-proline and D-proline. This allowed the peaks to be associated with each of the enantiomers. This time, only the compound suspended in the diethyl ether was analysed in chiral HPLC. This allowed to confirm the major left peak corresponds to 4tBCH-anti-a1-(S, S, R) with a retention time around 10,868 min (Figure 122) and the right peak corresponds to 4tBCH-anti-a2-(R, R, S) with a retention time around 12,489 min (Figure 123).

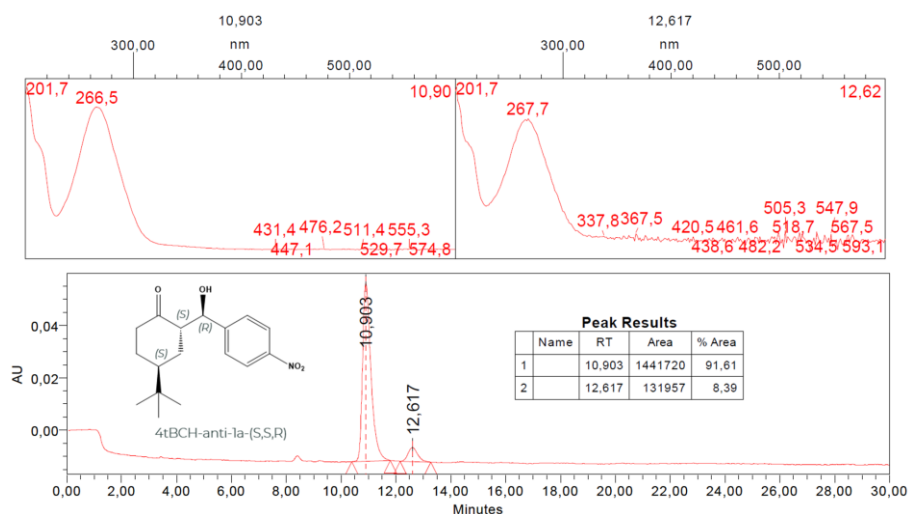


Figure 122 | Chiral HPLC results for the solid in suspension in diethyl ether using L-proline.

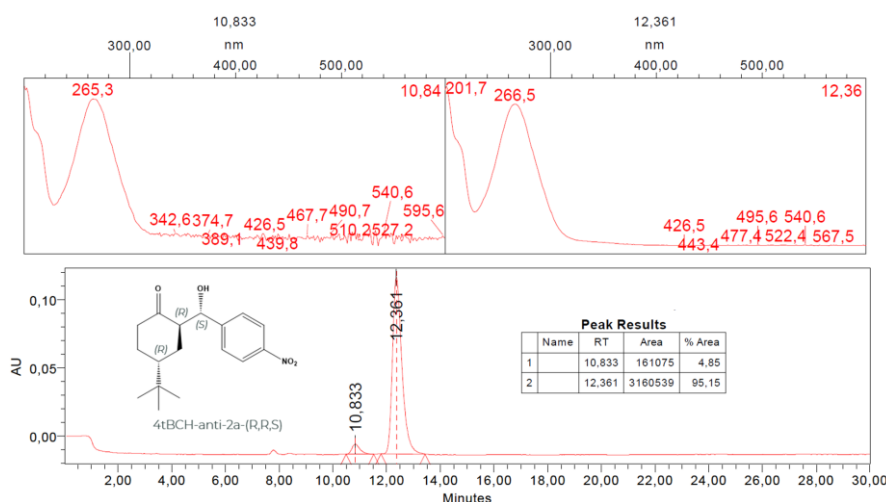


Figure 123 | Chiral HPLC results for the solid in suspension in diethyl ether using D-proline.

The solid obtained in suspension in diethyl ether after grinding with L-proline was recrystallized by evaporation in ethyl acetate. The single crystal thus obtained made it possible to confirm the stereochemistry of the product obtained mainly with L-proline, showed in Figure 124.

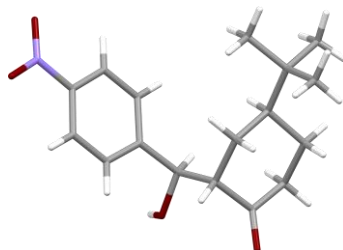


Figure 124 | Crystal structure of the aldol product obtained by the asymmetric aldolization catalyzed by a L-proline. The compound obtained is 4tBCH-anti-a1-(S, S, R).

At this stage of our work, a failure occurred on the chiral HPLC, forcing us to develop a new method on a chiral reverse HPLC. For this new method, samples were first diluted using a mixture of acetonitrile and H₂OmQ (90 : 10). Analysis were performed using the following HPLC parameters: Column: PHENOMENEX Lux Amylose, 4.6x250 mm, 5 μ m; T° = 25 °C; Flow: 1 mL.min⁻¹; Mobile phase 95 % acetonitrile, 5% H₂OmQ; Equilibrate time of 30 min; Stop time: 30 min.

A rest of the solid samples found suspended in diethyl ether, collected during the three previous reactions (aldolization with *rac*-proline (Figure 125), L-proline (Figure 126) and D-proline (Figure 127)) were analyzed to reattribute the peaks. With this new column, product 4tBCH-anti-a1-(S, S, R) shows a retention time around 5,117 min (Figure 126) and 4tBCH-anti-a2-(R, R, S) shows a retention time around 4,213 min (Figure 127).

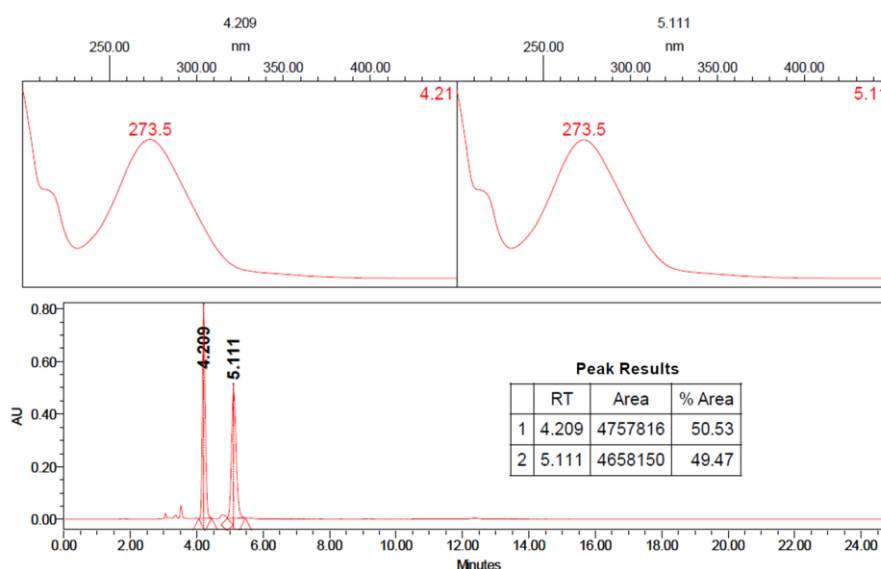


Figure 125 | Chiral reverse HPLC results for the solid in suspension in diethyl ether using *rac*-proline.

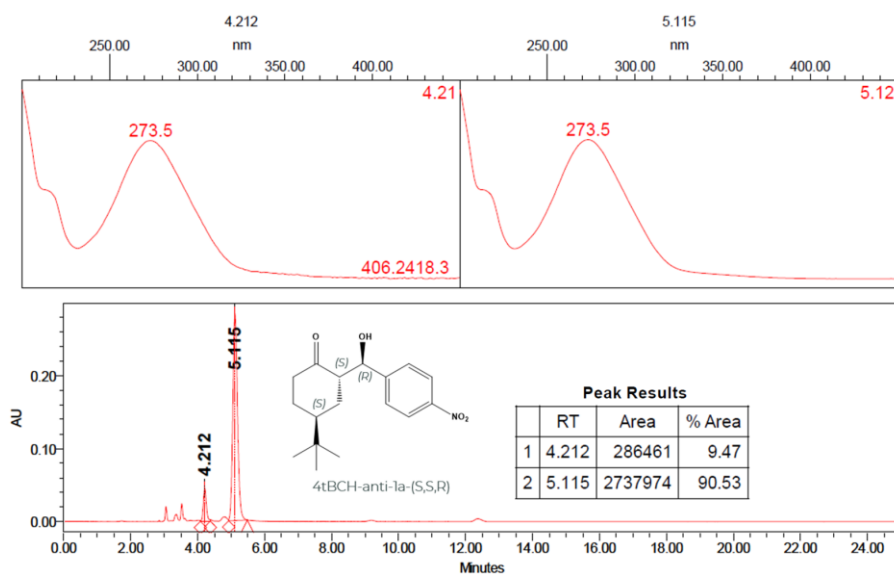


Figure 126 | Chiral reverse HPLC results for the solid in suspension in diethyl ether using L-proline.

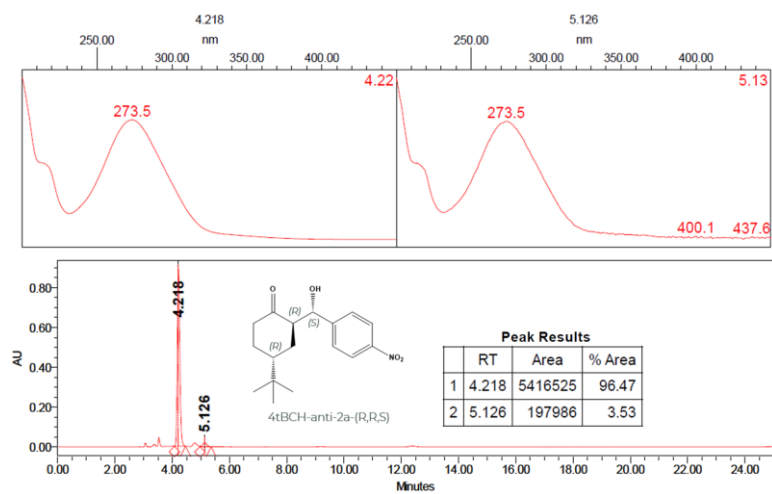


Figure 127 | Chiral reverse HPLC results for the solid in suspension in diethyl ether using D-proline.

For the remainder of the work, the entire sample was kept after the ball-milling, dissolved in dichloromethane and extracted. The typical pattern obtained in chiral HPLC is shown in Figure 128, showing that the two enantiomers of interest, peaks at 4.220 and 5.126 min, make up 79,33 % of the overall compound. Peaks at 4.754 and 7.293 min belong to the two enantiomers recovered after the silica chromatographic column and are shown in Figure 121 with the other HPLC method.

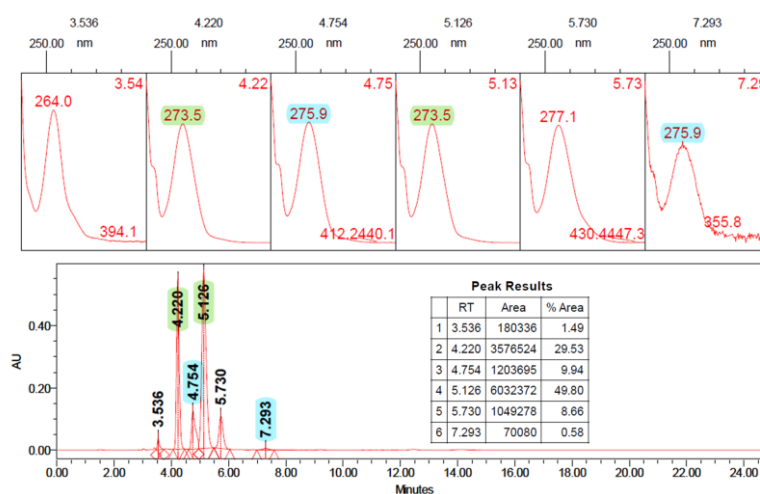


Figure 128 | Typical pattern obtained in chiral reverse HPLC using 4-tert-butylcyclohexanone.

4.3 Studying the impact of the proline ee working with 4-tert-butylcyclohexanone

Knowing which signal correspond to which enantiomer in chiral HPLC, we then turned to a first series of experiments to verify the results obtained by B. Rodriguez, A. Bruckmann and C. Bolm. [190] To do so, 1.1 eq of 4-tert-butylcyclohexanone (2.2 mmol), 1 eq of 4-nitrobenzaldehyde (2 mmol) and 0.2 eq of proline (0.4 mmol) were weighed and put in a 50 mL zirconium oxide bowl together with 60 x 5 mm zirconium oxide balls ($\pm$ 30 g). The ee of proline was varied by varying the amount of *rac*-proline and L-proline. One should not use varying amounts of L-proline and D-proline to avoid any phase transitions (*in-situ* formation of *rac*-proline as explained in the introduction p.108). The different millings were run for 48 hours at 400 rpm with intervals of 15 min of milling in one direction, 5 min of breaks, 15 min of milling in the other direction and 5 min of breaks (Reaction in Figure 129).

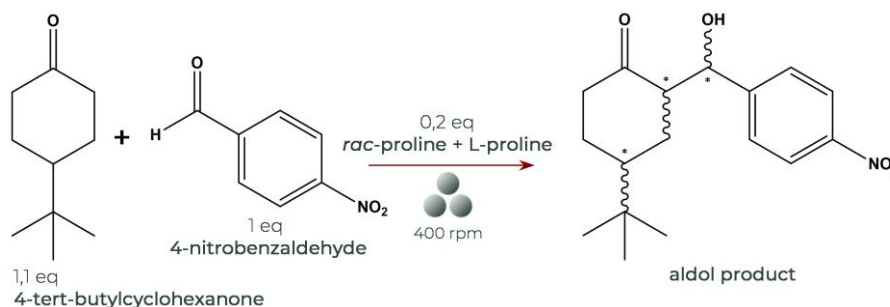


Figure 129 | Reaction using to see the impact of the proline ee with 4-tert-butylcyclohexanone.

After 48 hours, the resulting solid in the different bowls was not always spread in a homogeneous manner, see Figure 130. This was true throughout the research. Only those products which were visually homogeneous, were kept, and the powder completely dissolved in dichloromethane and then evaporated with a rotavapor.



Figure 130 | Example of three non-homogeneous bowls and therefore not taken into consideration (left). Example of a homogeneous bowl and therefore taken into consideration (right).

A chiral reverse HPLC was performed on each recovered solid. For this samples were first diluted using a mixture of acetonitrile and H₂OmQ (90 : 10). Analysis were performed using the following HPLC parameters: Column: PHENOMENEX Lux Amylose, 4.6x250 mm, 5 μ m; T° = 25 °C; Flow: 1 mL.min⁻¹; Mobile phase 95 % acetonitrile, 5% H₂OmQ; Equilibrate time of 30 min; Stop time: 30 min. A table shows the different retention times and peak areas of the two enantiomers in Supporting Information p.233.

A graph expressing the enantiomeric excess of the product 4tBCH-anti- α l-(S, S, R) as a function of the enantiomeric excess of the L-proline was plotted. As seen in Figure 131, the trend observed by B. Rodriguez, A. Bruckmann and C. Bolm is indeed there, but a large variation between the different points is present!

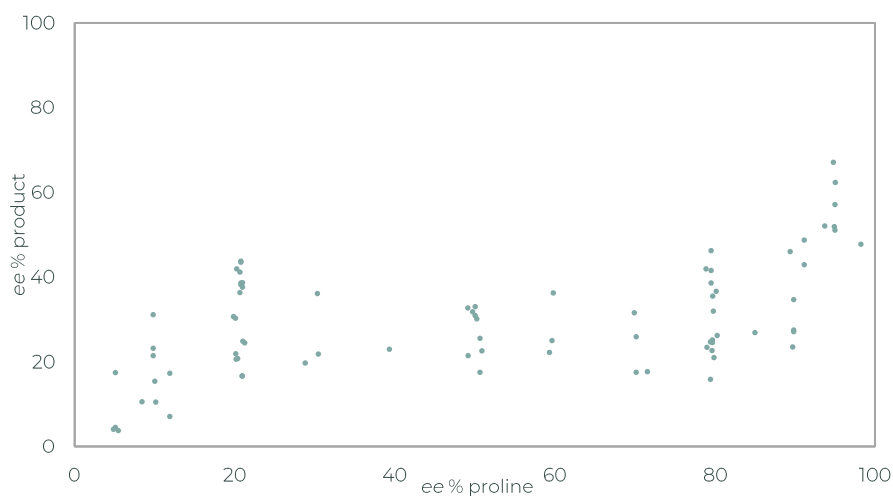


Figure 131 | Enantiomeric excess of the product 4tBCH-anti- α 1-(S, S, R) versus the enantiomeric excess of the L-proline.

After careful analysis of all experimental parameters, the strong variation in outcome for a given ee % of proline, was shown to be due to the origin of the 4-nitrobenzaldehyde material used. Figure 132, shows the data of Figure 131 using different colour coding according to the starting material used. Careful analysis of the starting material (HPLC, NMR, Mass, ...) did not allow us to identify the nature of the impurity in the material explaining this strong variation.

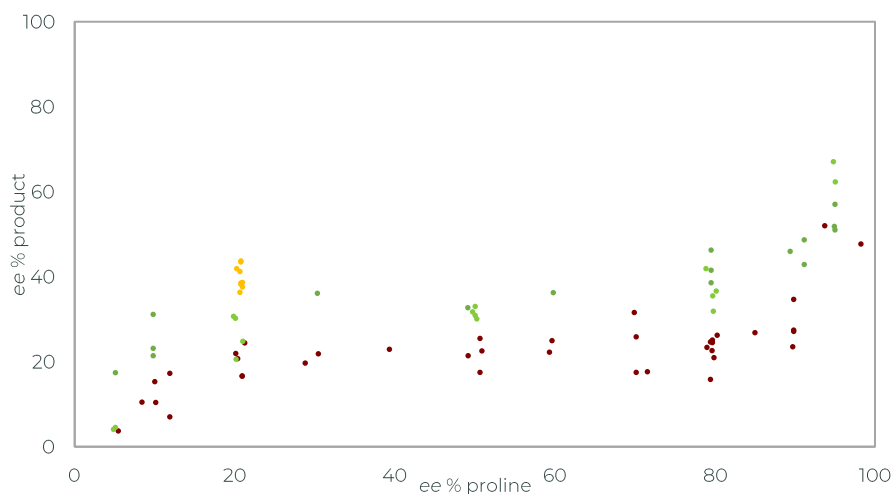


Figure 132 | Red crosses: Sigma-Aldrich 99 % (S8160866132). Green: Thermo Scientific 99 % (10215224). Yellow squares: TCI >98 % (FEMZH-GI).

To study, if any other factor besides the product supplier was impacting the outcome, we studied various other parameters using a specific material of a given supplier: 4-nitrobenzaldehyde 99 % Thermo Scientific (10215224), 4-tert-butylcyclohexanone 99 % (A0415565), L-proline Bachem 99 % (1000017110) and *rac*-proline 99 % Alfa Aesar (10184620).

The variations of the conditions are therefore to be compared with the green points on Figure 132, where the supplier of 4-nitrobenzaldehyde was Thermo Scientific 99 % (10215224), and where we used 1.1 eq of 4-tert-butylcyclohexanone (2.2 mmol), 1 eq of 4-nitrobenzaldehyde (2 mmol) and 0.2 eq of proline (0.4 mmol) with 60 x 5 mm zirconium oxide balls (+/- 30 g).

The factors studied were:

- **Balls size:** 30 g of 5 mm compared with 3 mm and 10 mm.
- **Quantity of reagent:** 4,6 mmol compared with 9,2 and 18,4 mmol.
- **Number of proline equivalents:** 0,2 eq compared with 0,4 and 0,8 eq.
- **Number of balls:** 30 g compared with 60 g.

These variations in conditions are illustrated in Figure 133. A chiral reverse HPLC was performed on each recovered solid. For the samples were first diluted using a mixture of acetonitrile and H₂O:mQ (90 : 10). Analyses were performed using the following HPLC parameters: Column: PHENOMENEX Lux Amylose, 4.6x250 mm, 5 µm; T° = 25 °C; Flow: 1 mL.min⁻¹; Mobile phase 95 % acetonitrile, 5% H₂O:mQ; Equilibrate time of 30 min; Stop time: 30 min. A table shows the different retention times and peak areas of the two enantiomers in Supporting Information p.236.

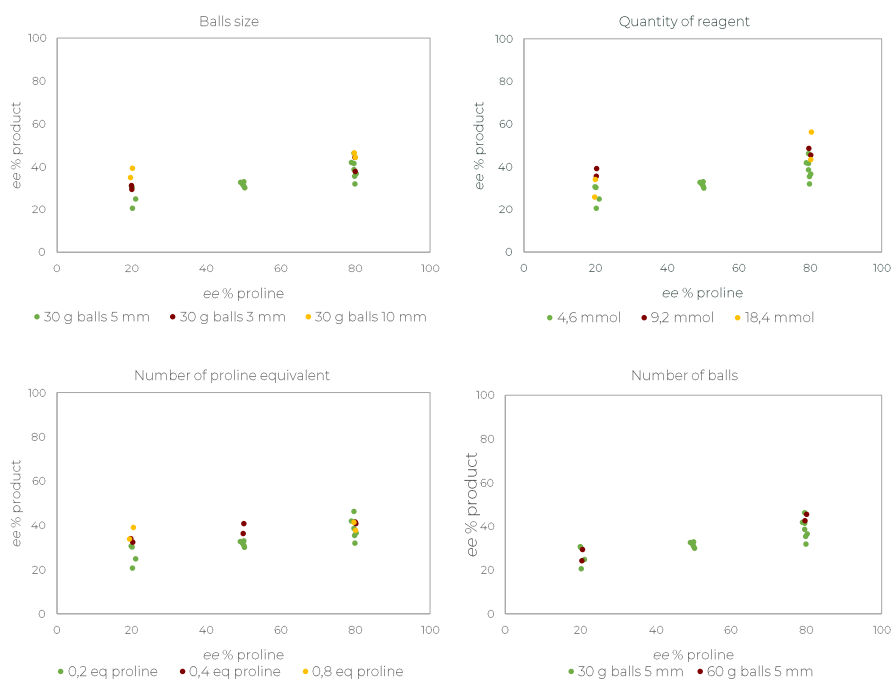


Figure 133 | Results of reaction with various parameters.

The experiment with the initial conditions (green points in Figure 133) had been repeated more than five times for each proline-ee studied. Experiments where one condition was modified were repeated only twice. In Figure 131, we could observe that the product-ee for a given proline-ee varied over a range of about 40%. According to the origin of the material used (Figure 132) this range decreased to about 20%. In Figure 133, some variability also appears to emerge (a range from 0 to 20%), but a greater repetition of experiments would have been necessary to potentially draw a conclusion about the significance of this variability. It should also be noted that there is inherent variability in mechanochemistry. During a reaction in a ball mill, different products may form at different positions within the grinding jar. This depends on the impact-to-shear ratio at each position, as studied by V. V. Boldyrev and E. V. Boldyreva. As a result, the crude product may exhibit some inhomogeneity at the end of the milling process. [110–112]

4.4 Switching to tetrahydro-4H-thiopyran-4-one to reduce experimental variability

Despite us being able to reduce the variability working with a fixed set of products, we nevertheless decided to investigate another ketone to see if we could reduce the experimental variability even further. To do so, we focused on a new solid ketone, tetrahydro-4H-thiopyran-4-one, see Figure 134. This system led to good yields by B. Rodriguez, A. Bruckmann and C. Bolm, 79% and a high enantiomeric excess of 90%. [189] However, in the literature, this system had not yet been analyzed with respect to nonlinear effects.

We made sure to always work with the same products: 4-nitrobenzaldehyde 99 % Thermo Scientific (10215224), tetrahydro-4H-thiopyran-4-one 99 % Acros Organic (A0394618), L-proline Bachem 99 % (1000017110) and *rac*-proline 99 % Alfa Aesar (10184620).

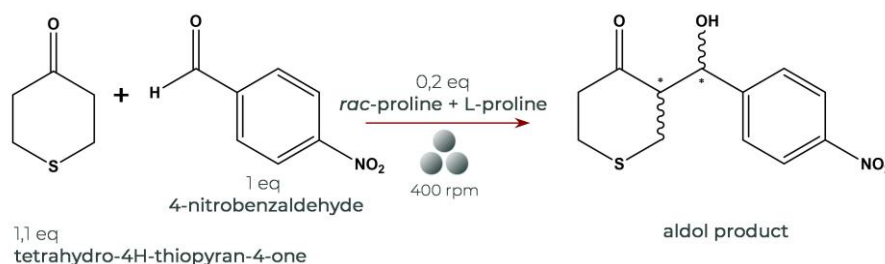


Figure 134 | Reaction using to see the impact of the proline ee with tetrahydro-4H-thiopyran-4-one.

Furthermore, with tetrahydro-4H-thiopyran-4-one, only four products can be formed as a result of the aldolization reaction, illustrated in Figure 98 (or summarized in Figure 134). We were only interested in the enantiomeric ratio of the enantiomers of the main diastereomer. The two enantiomers obtained mainly with L-proline or D-proline, respectively named OT-anti-1-(S,R) and OT-anti-2-(R,S).

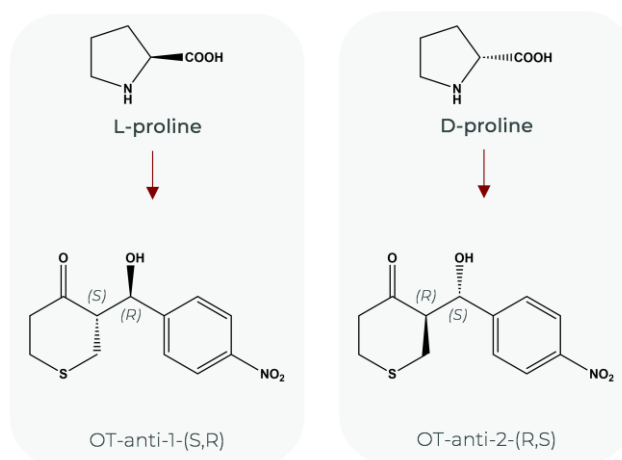


Figure 135 | Mainly enantiomers obtained with L- and D-proline.

We performed a first series of experiments to verify that the same curve pattern as B. Rodriguez, A. Bruckmann and C. Bolm (which they obtained with the solid ketone 4-tertbutylcyclohexanone) was indeed obtained. [190] For this purpose, 1 eq of tetrahydro-4H-thiopyran-4-one (2.2 mmol), 1 eq of 4-nitrobenzaldehyde (2 mmol) and 0.2 eq of proline (0.4 mmol) were weighed out and put into a 50 mL zirconium oxide bowl together with 60 x 3 mm zirconium oxide balls ($\pm$ 30 g). The ee of proline was varied by varying the amount of *rac*-proline and L-proline. The different millings were run for 48 hours at 400 rpm with intervals of 15 min of milling in one direction, 5 min of breaks, 15 min of milling in the other direction and 5 min of breaks. At the end of the 48 hours, the resulting solid in the different bowls was again not always homogeneous. The products obtained in the various bowls that were visually quite homogeneous were dissolved completely in dichloromethane and then evaporated with a rotavapor. The different sample were analyses by chiral HPLC and ^1H -NMR. Since the ^1H -NMR were carried out in DMSO, these data cannot confirm whether the reaction was complete or not. In DMSO, an aprotic polar solvent, the aldolization reaction is expected to continue to take place. [156] However, in HPLC, in acetonitrile, apolar solvent, the environment was not favorable for the reaction to continue, and it was confirmed that the reaction was not complete as there was still presence of 4-

nitrobenzaldehyde. See Supporting Information p.238 for ^1H -NMR results of this part. We decided to still carry out the experiment with an incomplete conversion because even for times longer than 48 hours, the reaction stagnated. Conversion is about 95 % based on the peaks of the two main products (red), and about 96 % based on the peaks of the two main products (red) and the two supposed products (blue) in Figure 136.

For chiral reverse HPLC, samples were first diluted using a mixture of acetonitrile and H_2OmQ (90 : 10). Analysis were performed using the following HPLC parameters: Column: PHENOMENEX Lux Amylose, 4.6x250 mm, 5 μm ; $T^\circ = 25^\circ\text{C}$; Flow: 1 $\text{mL}\cdot\text{min}^{-1}$; Mobile phase 95 % acetonitrile, 5% H_2OmQ ; Equilibrate time of 30 min; Stop time: 30 min. A table shows the different retention times and peak areas of the two enantiomers in Supporting Information p.239.

Figure 136 shows the typical pattern obtained in each chiral HPLC (this one is precisely the one obtained using a 20 % enantiomeric excess of L-proline). The variation of the enantiomeric excess of proline changed the integration of the two peaks at 9.777 min and 10.820 min, showing that the two enantiomers account for 79.25 % of the crude compound. The peak at 4.535 min can be associated with remaining starting compound tetrahydro-4H-thiopyran-4-one, the one at 3.689 min with 4-nitrobenzaldehyde. Peaks at 7.804 min and 18.417 min absorb at the same wavelength, and it could be assumed to be enantiomerically linked even though their retention times are very different. Peaks at 3.077 and 6.241 min remain unclear.

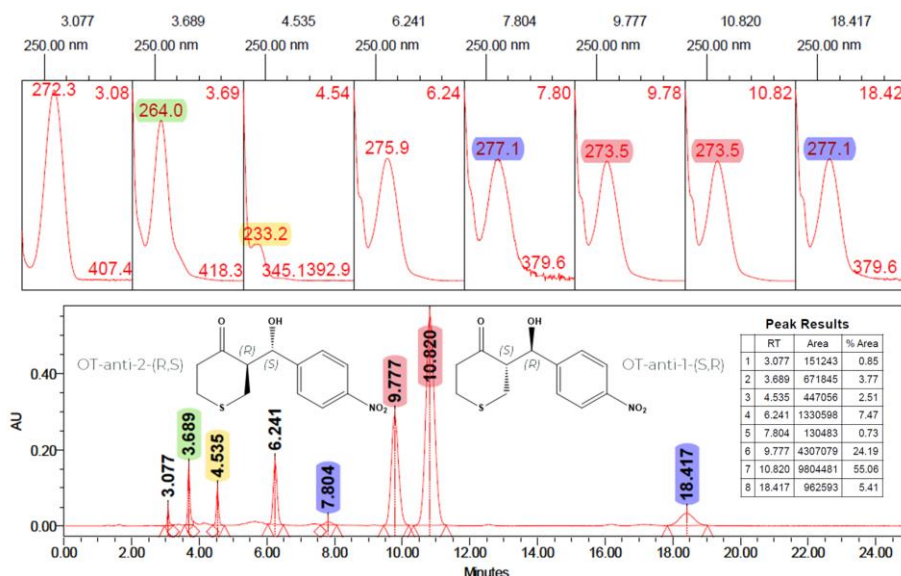


Figure 136 | Typical pattern obtained in chiral HPLC using tetrahydro-4H-thiopyran-4-one.

A single crystal was obtained by evaporation of the product in ethyl acetate under ambient conditions. This allowed its stereochemistry to be characterised by XRD, see Figure 137, and corresponding to the retention time of 10.820 min (The crystal used for the XRD was itself used for the HPLC). The crystallised product corresponds to the product expected using L-proline, OT-anti-1-(S,R). This implies the peak at 9.7 min to correspond to its enantiomer OT-anti-1-(R,S). For a given experiment, these two enantiomers are the main product, and therefore their ee will be studied for the remainder of the work.

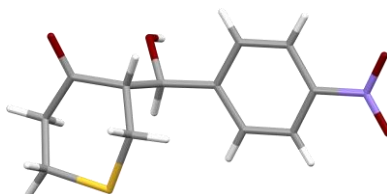


Figure 137 | OT-anti-1-(S, R) as obtained from a single crystal analysis.

A graph expressing the enantiomeric excess of the product OT-anti-1-(S,R) as a function of the enantiomeric excess of the L-proline is shown in Figure 138.

As shown by this figure, not only a similar plot is obtained as that observed in the earlier studies, there is furthermore a reduction in experimental variability of the system (a range from about 1 to 10%).

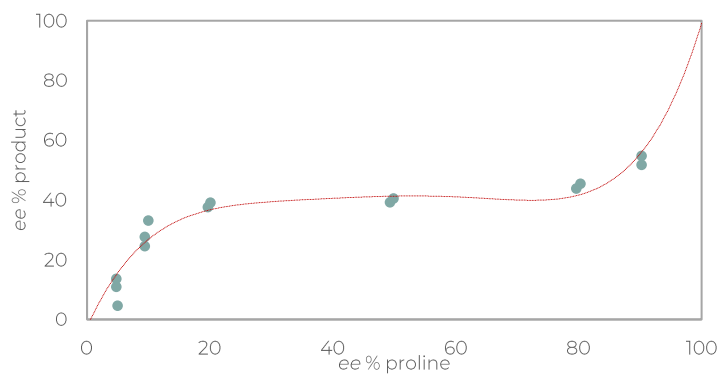


Figure 138 | Enantiomeric excess of the product OT-anti-1-(S,R) versus the enantiomeric excess of the L-proline. In red is an empirical trend curve based on the point.

4.5 Results of aldolization with tetrahydro-4H-thiopyran-4-one using proline cocrystals

Based on the results shown in Figure 138, we then switched to using two proline cocrystals as catalyst for this reaction being the 2,5-dihydroxybenzoic acid-based and the fumaric acid-based cocrystals.

To do this, we first synthesized the four cocrystals. 2,7 g of 2,5-dihydroxybenzoic acid-based cocrystals (for approximately 12 aldolization reactions) were synthesized by suspending in 15 mL of acetonitrile 1 equivalent of 2,5-dihydroxybenzoic acid (0,01 mol) with 1 equivalent of L- or DL-proline (0,01 mol) ($\eta = 5,57 \mu\text{L}.\text{mg}^{-1}$). 3,4 g of fumaric acid-based cocrystals (for approximately 25 aldolization reactions) were obtained by suspending in 15 mL ethanol 1 equivalent of fumaric acid (0,01 mol) with 2 equivalents of L- or DL-proline (0,02 mol) ($\eta = 4,33 \mu\text{L}.\text{mg}^{-1}$).

These four slurries were filtered, washed and dried. Powders were analyzed by X-ray powder diffraction to verify they corresponded with the simulated diffractogram of cocrystals (see Supporting Information p.240)

The milling experiments were then carried out using the same methodology as before, except that the proline was replaced by cocrystal, 0.4 mmol for the 1 : 1 cocrystal of 2,5-dihydroxybenzoic acid and 0.2 mmol for the 2 : 1 cocrystal of fumaric acid (so that the overall amount of proline still remains 0.4 mmol). A table shows the different retention times and peak areas of the two enantiomers in Supporting Information p.241 using 2,5-dihydroxybenzoic acid and p.242 using fumaric acid.

The results obtained are shown in the graph in Figure 139. The results obtained with 2,5-dihydroxybenzoic acid (25DHBA) are very variable and hover around the trend obtained without the cocrystal. This system therefore does not show a lot of effect on the ee. In contrast, the results obtained with fumaric acid (FUMA) show a plateau which

appears very rapidly and shows a very high enantiomeric excess, above 90% of the product, even for low overall ee of catalyst used. Moreover, for fumaric acid there is little variability among the results.

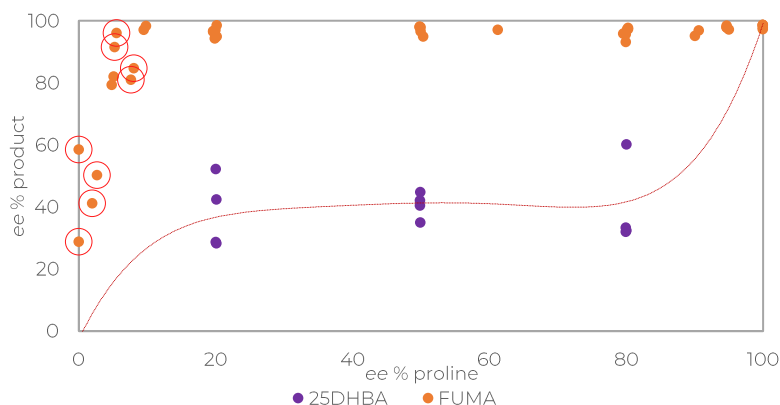


Figure 139 | Results obtain for a aldolization between 4-nitrobenzaldehyde and tetrahydro-4H-thiopyran-4-one using proline cocystal as a catalyst. In violet with 2,5-dihydroxybenzoic acid/proline cocystal (1 : 1). In orange with fumaric acid/proline cocystal (1 : 2). The red line is an empirical trend curve based on result with native proline. In red circles, viscous liquid obtained after the rotavapor step.

After rotavapor drying, some products remained in a kind of highly viscous liquid state with fumaric acid. They are marked with red circles in Figure 139 (and in green in Supporting Information p.244). For these products, a chiral HPLC analysis was performed after 4 days and after 7 days.

By chiral HPLC monitoring of the peaks corresponding to the aldehyde and the two enantiomers after 4 and 7 days, it was observed that the aldehyde peak decreased while those of the enantiomers increased, indicating that the reaction continued in this molten state. As for the enantiomeric excess, shown in Figure 140, an increase was noted, with the exception of the case using racemic proline where this excess decreased.

It is important to remember that, due to the reversibility of the aldol reaction, maintaining the products in the liquid phase is inappropriate for this experiment. The data circled in red should be interpreted with caution, due to the risk of conversion between

enantiomers in the liquid phase. This possibility of conversion has already been explored in studies by C. Rougeot *et al.* [170]. Interconversions were observed when the products were in the liquid phase. However, in conditions where the reaction medium was partially molten, the low solubility of OT-anti-1-(S,R) significantly restricted this interconversion.

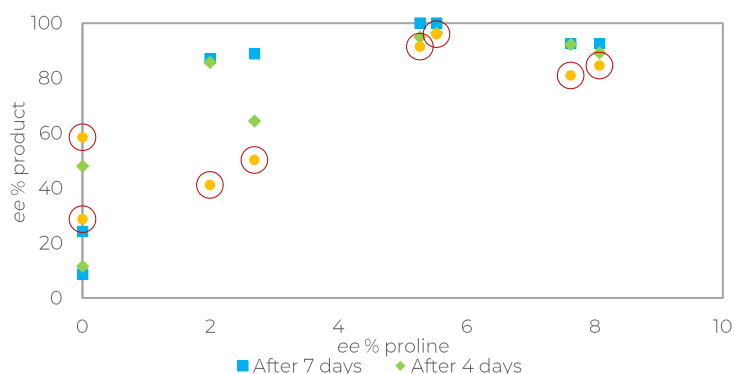


Figure 140 | Zoom on proline ee between 0 and 10 % to see variation of product ee after 4 and 7 days when viscous liquid is obtained after reaction.

To gain more insight into the cocrystal effect, the reaction was also performed starting with proline and fumaric acid in their pure solid form without prior formation of the cocrystal. The results are shown in red in Figure 141. It can be seen that the enantiomeric excess is also very high. A possible hypothesis is that the cocrystal formation occurs very rapidly (in literature cocrystal formation typically takes about 30 min or less), whereas the reaction occurs over a period of 33 hours. Identical results are therefore not so surprising.

Carrying out a series of experiments using only fumaric acid, expectedly no reaction occurred. All starting reactants were present and no product was formed.

In addition, the experiments were repeated using native proline and native maleic acid instead of fumaric acid. Maleic acid and fumaric acid are stereoisomers (see Figure 142), but maleic acid does not form a cocrystal with proline. The results are shown in blue in Figure 141. Doing this experiment, we can show that the effect observed is truly

due to the cocrystal formation and not due to the presence of an acid. The experiments confirm the enantiomeric excesses are close to those of using native proline, hence confirming the high ee is induced by the use of the cocrystal and not proline as such. This leads to the conclusion that the enantiomeric excess jump is indeed due to the proline cocrystal and not to any other effect that fumaric acid might have.

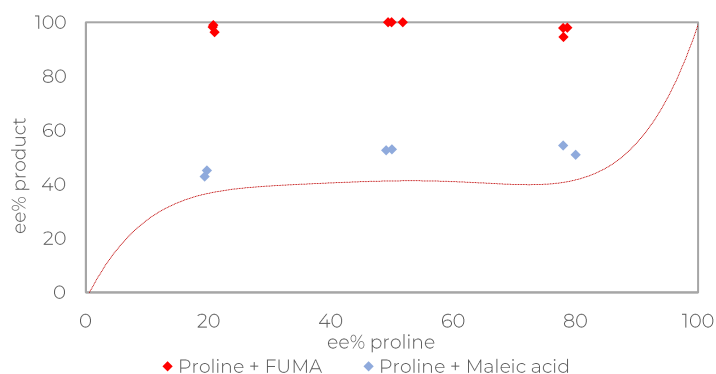


Figure 141 | Red square: Results obtained with using of proline and fumaric acid (in pure form, not in cocrystal form). Blue square: Results obtained with using of proline and maleic acid. The red line is an empirical trend curve based on result with native proline.

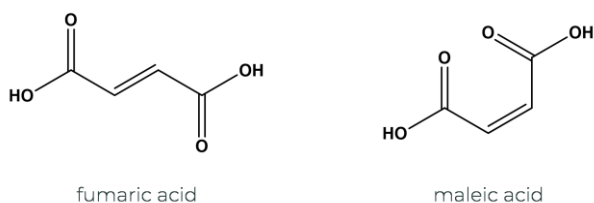


Figure 142 | Fumaric acid and maleic acid molecules.

5. Conclusion and perspectives

In this chapter, we showed that the solid-state nature of the catalyst can have a substantial impact on the selectivity of an asymmetric catalyzed aldolization reaction performed mechanochemically. This has been shown using a proline-catalyzed aldol reaction between a ketone (tetrahydro-4H-thiopyran-4-one) and an aldehyde (4-nitrobenzaldehyde), all solid at room temperature.

We were initially confronted with a great variability of the results obtained when we used 4-tert-butylcyclohexanone. In spite of several experiments we were unable to reduce or fully understand this variability. One of the plausible hypotheses remains the lack of homogenization in the grinding bowls during the reaction. We then turned to tetrahydro-4H-thiopyran-4-one with which the variability was strongly reduced.

New proline cocrystals were characterized, a cocrystal between DL-proline and 2,5-dihydroxybenzoic acid as well as two cocrystals between L-proline and succinic acid. The cocrystals between enantiopure and racemic proline with fumaric acid were already known. As a result, we had three cocrystal systems to test in organocatalyzed asymmetric aldolization reactions. However, only two were examined, the cocrystals between proline and fumaric acid and the cocrystals between proline and 2,5-dihydroxybenzoic acid. The use of the cocrystal between succinic acid and proline was not performed due to lack of time. The use of a cocrystal between proline and 2,5-dihydroxybenzoic acid as a catalyst in the aldolization reaction was not conclusive in increasing selectivity. However, the use of a cocrystal between proline and fumaric acid showed a significant increase in selectivity, sometimes reaching the pure enantiomer.

This work has demonstrated the ability to shift the enantiomeric excess (ee) plateau of the product through cocrystallization of the catalyst. The amplitude of this shift is intrinsically linked to the cocrystal and remains undeterminable at this stage. To assess this shift, it is necessary to carry out a double screening. The first screening aims to identify coformers capable of crystallizing with the catalyst, while the second assesses the reactivity of the cocrystals identified. It would also be interesting to verify how the ee of the binary melting diagram relates to displacement of the selectivity. However, making these diagrams is not always straightforward as amino acids are prone to sublimation and compound degradation often occurs upon melting. However, the realization of ternary diagrams of the cocrystals in different solvents could possibly already provide some indications as to the placement of the eutectic, while remaining cautious on the conclusions drawn.

The methodology developed in this study, consisting of an exhaustive screening of all the points using different catalytic ratios, is of limited industrial interest. First, it requires the availability of enantiopure catalyst to explore the full curve, in which case the use of a cocrystallize catalyst does not make sense. Secondly, it is extremely time consuming. However, this screening is actually unnecessary when the goal is to find out if a cocrystal improves the ee of the product compared to the catalyst. This approach can be relevant for the exploration of specific cases (working only on a single point).

This type of reactivity has a limited field of application, mainly due to the specific conditions required. In particular, it uses is possible in the context of asymmetric organocatalyzed reactions, for which obtaining enantiomerically pure catalysts is difficult. In addition, the reagents must be in solid form at room temperature and capable of forming a partial molten reactive eutectic phase. Once a reaction meets these criteria, a number of challenges remain, including the need for the coformer not to interfere with the reaction in progress and for the cocrystal to promote the enrichment of the enantiomeric

excess of the product. The methodological process relies on trial and error, involving the screening and cross-referencing of data from different analytical techniques such as high-performance liquid chromatography (HPLC), NMR spectroscopy and ternary diagrams. It also requires various experimental manipulations such as suspension preparation, grinding and extraction.

Indeed, the current understanding of the relationships between the structure of cocrystals and their properties is not sufficiently advanced to predict the behavior of such systems. Although this approach may be of theoretical interest, it encounters practical limits in terms of industrial applicability. At present, it is preferable to work differently by purifying the catalyst by chiral chromatography or by precipitation.

It would be interesting to investigate more cocrystal systems to check for example whether the effect seen using fumaric acid is common, or whether such an impact is rare. One could indeed argue that coupled with proline, fumaric acid does intervene in the reaction mechanism, e.g. by promoting retroaldolization. Or if there is possibility to establish predictive rules for the most efficient cocrystals to raise the plateau.

It would be relevant for future research to explore the sources of variability observed when using 4-tert-butylcyclohexanone. This variability can result from various factors, whether physical, such as insufficient homogenization during grinding, or chemical. These different factors will be important if one day a scale-up is launched. In this context, it would be interesting to examine the homogenization processes from one experience to another, as well as the different conditions that can influence this process. For example, even though the volume of grinding bowls is similar between grinders, their shapes can vary significantly. It is therefore plausible that homogenization differs between a long, narrow bowl and a wide, shallow bowl. Additionally, the size and number of beads used can logically affect the mixture, although our experiments on these

variables did not yield conclusive results. In this regard, another point to consider is that the aldol reaction would appear to occur in a molten phase. This aspect is of particular importance, as the aldol reaction is known to be reversible and it is not uncommon for certain stereoisomers to retransform into another, which is also what we observed when leaving the reaction environment in a liquid phase after extraction. One can assume this also occurs for the melt.

CHAPTER III

CYCLOADDITION IN THE SOLID-STATE

CYCLOADDITION IN THE SOLID-STATE

1. A brief review of the [2+2] cycloaddition in the solid-state

1.1 Pericyclic reactions

So-called **pericyclic** reactions are a class of reactions with cyclic transition states where the formation (and dissociation) of bonds is organized in a concerted manner. That is, **simultaneously** and **without** the formation of **intermediate structures**. This is in clear contrast to ionic and radical reactions, the former involving pairs of electrons moving in one direction and the latter involving the correlated movement of single electrons. Pericyclic reactions are separated into four main classes, see Figure 143 cycloadditions, electrocyclic reactions, sigmatropic rearrangements and the last and least frequently encountered class, group transfer reactions. [201]

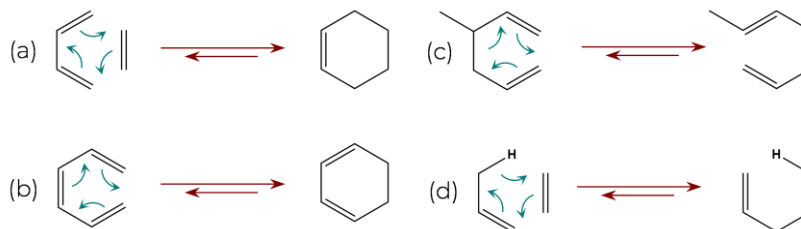


Figure 143 | (a) cycloaddition (b) electrocyclic reactions (c) sigmatropic rearrangements (d) group transfer reactions.

- Cycloadditions, usually bimolecular reactions, are characterized by the formation of a ring via the formation of two new σ -bonds. Cycloadditions are pericyclic if these two new bonds are formed at the same time (there are cycloaddition reactions that take place in several steps).
- Electrocyclic reactions, unimolecular isomerization's, are characterized by the design of a ring via the formation of a single new σ -bond.

- Sigmatropic rearrangements, unimolecular isomerization's, are characterized by the migration of a σ bond from one position to another.
- Group transfer reactions, generally bimolecular reactions without ring design, are characterized by a functional group being transferred from one molecule to another. They resemble sigmatropic rearrangements since a σ -bond is displaced, but also some cycloadditions where one of the π -bonds is replaced by a σ -bond. However, they are neither sigmatropic nor cycloadditions since the reaction is bimolecular and no ring is formed.

1.2 Stereochemistry of cycloadditions

During pericyclic cycloaddition, π orbitals approach each other frontally. The π -orbitals at the end of a conjugated system of a first compound form σ -bonds to the π -orbitals at the end of the conjugated system of a second compound, illustrated in Figure 144. Looking at the orbitals allows one to visualize the geometrical approach not visible in the 2D representations.

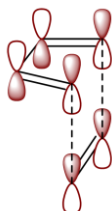


Figure 144 | Suprafacial approach in a [4+2] cycloaddition.

When the approach takes place on the same surface, it is called suprafacial. Conversely, when the approach takes place on two surfaces, the term antarafacial is used, see Figure 145. Most pericyclic cycloaddition reactions are suprafacial. If one of the components has a long-conjugated system, then it may be able to twist enough for antarafacial attack to occur. Antarafacial attacks of cycloadditions are therefore rare.

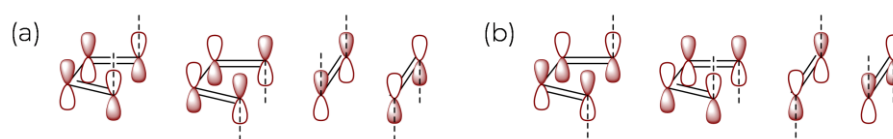


Figure 145 | (a) Suprafacial attacks. The two orbitals involved in the reaction (represented by the small dashes) are on the same side. (b) Antarafacial attacks. The two orbitals involved in the reaction are on opposite sides. (Adapted from [201])

From this suprafacial attack, it follows that the stereochemical configuration between the reactants and products are preserved. There is therefore a high level of **stereospecificity** (Figure 146).

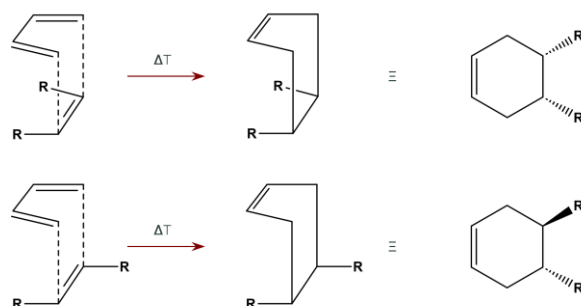


Figure 146 | stereospecific cycloaddition reactions. The first compound gives a certain product and its stereoisomer gives a stereoisomeric product.

The **regioselectivity** of cycloaddition reactions will depend on the orientation of the diene and the dienophile during the attack. This orientation can follow certain rules in solution which will not be described because they are not relevant to the goal of our project (Figure 147).

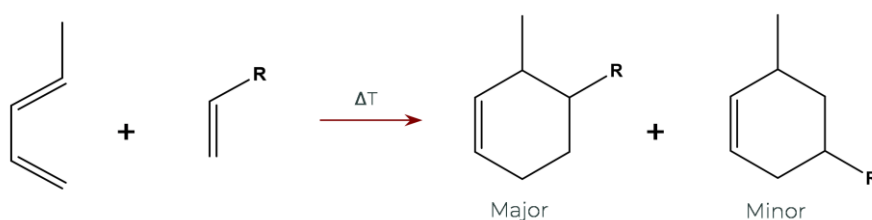


Figure 147 | Two regioisomers produced in a regioselective cycloaddition reaction.

1.3 Permitted and prohibited reactions

One of the main characteristics of pericyclic reactions is the concerted nature of the process. As a result, some reactions are allowed and others are forbidden. There are several theories to explain this.

1.3.1. Frontier orbital theory

The easiest explanation for bimolecular reactions is based on frontier orbitals (Figure 148). Frontier orbitals that need to be considered are:

- **HOMO** (Highest Occupied Molecular Orbital): which is the highest energy orbital occupied by at least one electron.
- **LUMO** (Lowest Unoccupied Molecular Orbital): which is the lowest energy orbital not occupied by an electron.

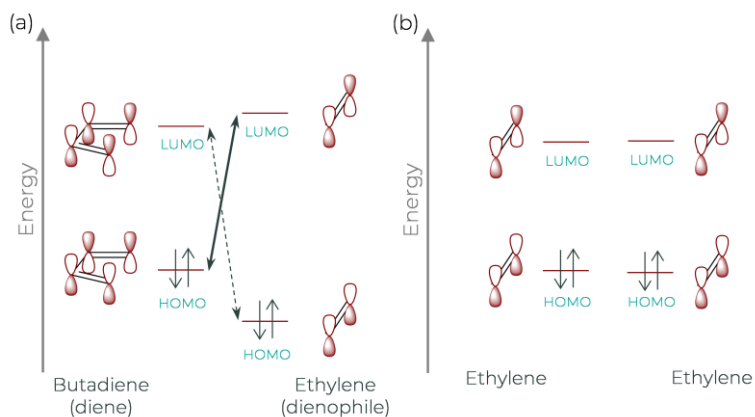


Figure 148 | Difference in energy levels of the frontier π orbitals of two partners during a thermal cycloaddition reaction. **(a)** Possible between butadiene and ethylene. **(b)** Not allowed between two ethylene molecules.

A pericyclic cycloaddition reaction takes place between the HOMO of one compound and the LUMO of the other. Figure 148 shows a [4+2] cycloaddition reaction, called a Diels-Alder reaction, between butadiene (called the diene) and ethylene (called the dienophile). The energy difference between HOMO(diene)-LUMO(dienophile) and HOMO(dienophile)-LUMO(diene) are compared. Here the smallest energy gap corresponds to HOMO of diene and LUMO of dienophile.

This is a normal electronic demand in [4+2] cycloaddition reactions. However, it is possible with the addition of a scavenger group on the diene and a donor group on the dienophile to reverse the electronic demand.

The boundary orbitals are of the same sign (indicated by an orbital color), which is a necessity for the reaction to take place. However, the [2+2] cycloaddition reaction between two ethylene molecules is not allowed due to the fact that the frontier orbitals are not of the same sign (Figure 148b).

These frontier orbitals also show why these rules change for photochemical reactions. In this type of reaction, one of the electrons is promoted from the HOMO to the LUMO, illustrated in Figure 149. The molecule is then excited and can react with a molecule in the ground state. The orbital is then called SOMO (single occupied molecular orbital).

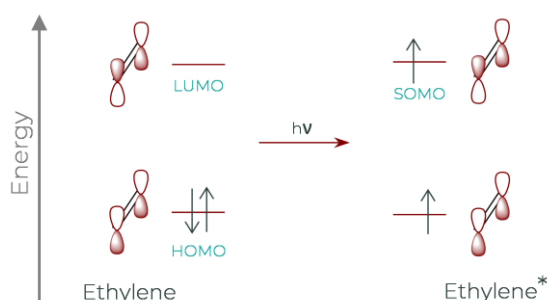


Figure 149 | Difference in energy levels of the frontier π orbitals of two partners during a photochemical cycloaddition reaction.

When they come together, the double bonds of the two compounds face each other to form an excited complex. In this configuration, cycloaddition occurs, forming two new covalent bonds simultaneously, creating a new ring.

Furthermore, it is illusory to apply the theory of frontier orbitals to unimolecular reactions such as electrocyclic reactions and sigmatropic rearrangements since the molecule should be treated as if it had separate constituents.

1.3.2. Woodward-Hoffmann rules

The most rigorous and satisfactory explanation for permissible and impermissible pericyclic reactions uses correlation diagrams. But handling these diagrams is not always easy and often time-consuming. They will not be detailed here. However, the conclusions that can be drawn from these correlation diagrams can be summarized with the Woodward-Hoffmann rules. They can be found under two statements that govern any pericyclic reaction. One is applicable to thermal reactions and the other to photochemical reactions:

Pericyclic thermal reactions: A pericyclic modification of a ground state is symmetrically permissible when the total number of components $(4q+2)_s$ and $(4r)_a$ is an odd number (q and r are integers number, s represents suprafacial acting components and a represents antarafacial acting components)

Pericyclic photochemical reactions: A pericyclic change in the first electronically excited state is allowed by symmetry when the total number of components $(4q+2)_s$ and $(4r)_a$ is an even number. (q and r are integers number, s represents suprafacial acting components and a antarafacial acting components)

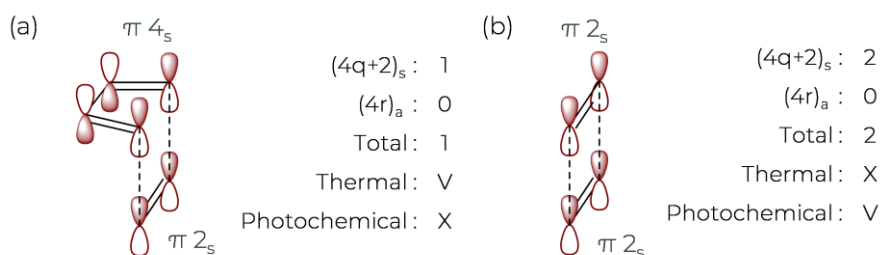


Figure 150 | (a) Thermally permitted Diels-Alder style reaction. One component of type $(4q+2)_s$ and no component of type $(4r)_a$, which forms an odd number. (b) Photochemically permitted reaction. Two components of type $(4q+2)_s$ and no component of type $(4r)_a$, which forms an even number. (Adapted from [201])

1.4 Photochemical reactions of cinnamic acid in the solid-state

Cinnamic acid presents an interesting photochemical reaction because the presence of a double bond offers the possibility of dimerization and isomerization.

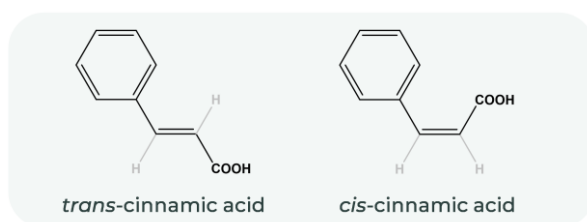


Figure 151 | *trans*-cinnamic acid and *cis*-cinnamic acid.

1.4.1. Historical perspective

The first studies of solid-state photochemical reactions of cinnamic acid date back to the 1920s and were carried out by A. W. K. De Jong, H. Stobbe, R. Stoermer, G. Ciamician and P. Silber. They were the main chemists to undertake systematic research into the behavior of cinnamic acid under light (sunlight and UV light). [202] It was reported by R. Stoermer *et al.* as well as by H. Stobbe *et al.* that *trans*-cinnamic acid produced mainly α -truxillic acid upon dry irradiation. [203, 204] While *cis*-cinnamic acid was converted into a mixture of α -truxillic and β -truxinic acid. [205, 206] See Figure 152 for α -truxillic and β -truxinic acid.

Surprisingly, A. W. K. De Jong obtained β -truxinic acid after irradiation of freshly precipitated *trans*-cinnamic acid. The longer *trans*-cinnamic acid remained before irradiation, the lower the yield of β -truxinic acid and the higher the yield of α -truxillic acid. [207]

These results can be linked to the solid-state of *trans*-cinnamic acid. Its stable form (α -polymorph) leads only to α -truxillic acid. Whereas irradiation of the metastable form (β -polymorph), leads to β -truxinic acid. These reactions are illustrated in Figure 152. The β -polymorph can however transit to the α -polymorph. If the ambient temperature

is too high, this transition occurs simultaneously with the photoreaction and leads to a mixture of α -truxillic and β -truxinic acid. [208]

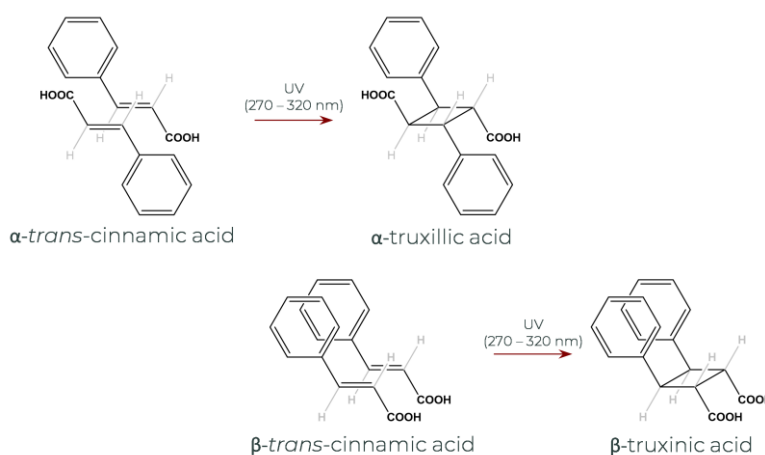


Figure 152 | Link between the solid-state of *trans*-cinnamic acid and the obtained product after irradiation. α -*trans*-cinnamic acid leads to α -truxillic acid and β -*trans*-cinnamic acid leads to β -truxinic acid.

To explain the transformation of *cis*-cinnamic acid to β -truxinic acid upon irradiation, it is assumed that dimerization is accompanied by stereoisomerization from *cis* to *trans*. [209]

In solution, cinnamic acid generally undergoes isomerization and not dimerization. [210–212] The same occurs when irradiating cinnamic acid in the melt phase. [213] The photochemical dimerization of cinnamic acid only occurs in the solid-state.

Irradiation with short ultraviolet light causes the depolymerization of truxillic and truxinic acids, giving the corresponding monomer. The optimum wavelength for dimerization is between 270 and 320 nm, below 270 nm decomposition into monomers occurs. [214]

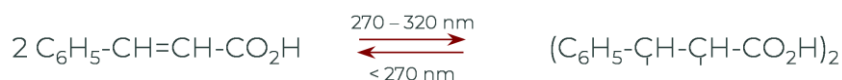


Figure 153 | Cinnamic acid dimerization occurs with UV between 270 – 320 nm. Below 270 nm truxillic and truxinic acid decomposes into monomers.

1.4.2. Links between irradiation products and crystal geometry

The links between the obtained irradiation products and the geometry of the crystal structure, called topochemical factors, have been put forward by G. M. J. Schmidt, M. D. Cohen *et al.* These topochemical relationships are based on observations related to the difference in reactivity between polymorphs of the same compound and the difference in reactivity of a compound in solid phase or in solution. Another observation led to topochemical concepts. Different but closely related chemical compounds can dimerize and give quite different products. For example, cinnamylidenemalonic acid and cinnamylideneacetic acid dimerize into two very different cyclobutanes. Similarly, irradiation of methyl α -cyanocinnamylideneacetate forms a cyclobutane while the ethyl ester forms an open chain. [215] These reactions are illustrated in Figure 154 and Figure 155.

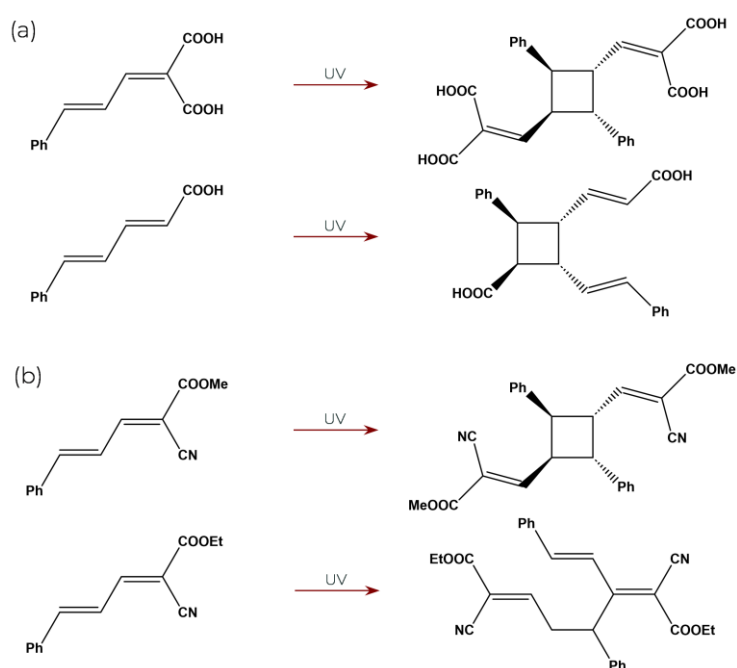


Figure 154 | (a) Dimerization of cinnamylidenemalonic acid and cinnamylideneacetic acid. (b) Dimerization of methyl α -cyanocinnamylideneacetate and ethyl α -cyanocinnamylideneacetate.

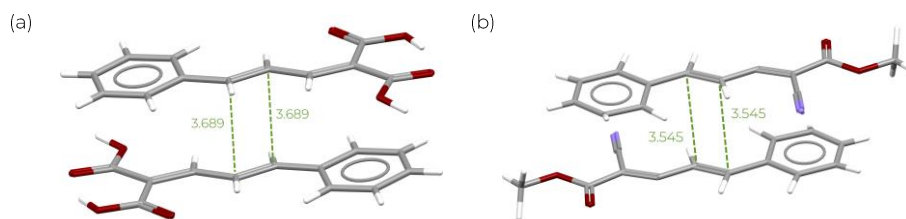


Figure 155 | (a) Dimerization of cinnamylidenemalononic acid (JIKNOJ on CSD). (b) Dimerization of methyl α -cyanocinnamylideneacetate (CANMEJ on CSD).

These observations can be formulated according to the postulate that « *reaction in the solid-state occurs with a minimum amount of atomic or molecular movement* ». [215–217] As a result of these works, topochemical concepts have emerged to explain whether or not a reaction occurs. Photodimerization [2+2] reactions require a favorable geometry to be carried out in the solid-state: the double bonds must be well aligned and spaced at a maximum of 4.2 Å in the solid. [218] It will be seen below that the topochemical factors are now considered as a practical guide and not as mandatory rules when assessing the propensity of an organic crystal to have photochemical reactivity.

Since, minimal molecular motion, good alignment and a limiting distance of 4.2 Å have been repeatedly claimed as essential features for solid-state photochemical reactions. These claims explained the stereoselectivity of the photodimerization of cinnamic acids and the non-reactivity of *trans*-stilbene. However, it was shown that some compounds could dimerize up to a distance of 4.7 Å and that some dimerization occurred even if the double bonds were not fully parallel. These exceptions should not be interpreted as violations of the basic concepts, but rather as ideas extending these concepts. [219] Since the early 2000s, various studies have revealed long-range molecular movements in solids during photoreactions. Topochemical concepts are therefore still applicable for topotactic reactions, i.e. reactions where the transformation takes place without significant disruption of the crystal structure. [220] However, many solid-state photoreactions occur in a non-topotactic manner (i.e. the crystals have disintegrated and the space groups of the products differ from

the reactants). It is also important to note that retention of the outer crystal forms is not evidence of topotaxy. [221]

1.4.3. *Regioselectivity in the solid-state*

The regioselectivity of topotactic reactions in the solid-state is determined by the molecular arrangement within the crystal and not by the rules established for solution reactivity. [222] As the bond formation is a suprafacial attack, the stereochemistry is preserved and thus the *Z*- or *E*- alkene will lead to the formation of *cis*- and *trans*-enantiomers respectively.

Figure 156 shows the different dimers accessible with a photodimerization of cinnamic acid. They can be grouped in two structurally isomeric compounds depending on the position of the substituents around the plane defined by the cyclobutane ring: truxillic acids (1,3-diphenyl-cyclobutane-2,4-dicarboxylic) and truxinic acids (1,2-diphenyl-cyclobutane-3,4-dicarboxylic). Each of these two isomers shows different stereoisomers for a total of 11 dimers (or 15 if the enantiomers are counted).

Truxillic acids are composed of five stereoisomers. These five stereoisomers are all meso compounds, so there is no enantiomeric relationship between them. Truxinic acids are composed of ten stereoisomers, two meso compounds and four pairs of enantiomers.

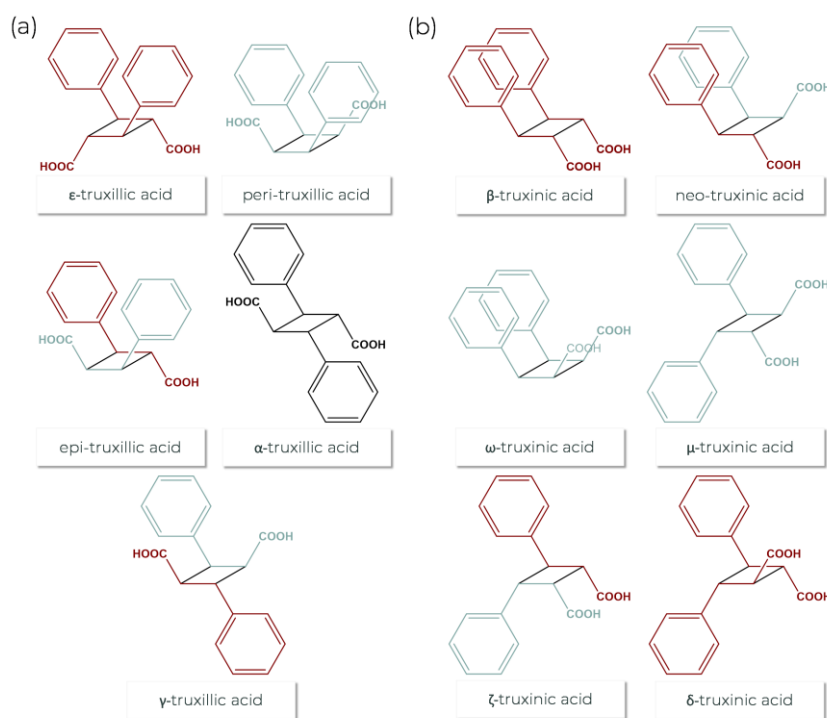


Figure 156 | In blue *cis*-cinnamic acid and in red *trans*-cinnamic acid. Enantiomers exist for neo-truxinic acid, μ -truxinic acid, ζ -truxinic acid and δ -truxinic acid. **(a)** Five stereoisomers of truxillic acid. **(b)** Six stereoisomers of truxinic acid.

G. M. J. Schmidt *et al.* classified the photochemical reactions of cinnamic acids according to the stereochemistry of the products obtained. [223] The α -class included reactions characterized by a « head-to-tail » packing arrangement (corresponding to the end product α -truxillic acids when using *trans*-cinnamic acid) while the β -class included reactions characterized by a « head-to-head » packing arrangement (corresponding to the end product β -truxinic acids when using *trans*-cinnamic acid). When the photoaddition reaction did not take place in the solid-state, then it was classified in the γ group. This classification led to some confusion as some scientists believed there to be a third polymorph of *trans*-cinnamic acid that was not reactive to light (the so called γ -polymorph). [220]

1.5 Control of dimerization

In 1995, I. Yoshikatsu *et al.* developed a first method to control the photodimerization of *trans*-cinnamic acid, via the formation of diamine salt forms. Using the diamine additive, they obtained β -truxinic acid as well as ϵ -truxillic acid. [224] Although the irradiation took place in the solid-state, the salt formation was performed in solution (Figure 157).



Figure 157 | Control of dimerization through salt formation. The synthesis process occurs in solution, while the irradiation step is conducted in the solid-state.

Their best yields were obtained with *cis*-1,2-diaminocyclohexane and *trans*-1,2-diaminocyclohexane, shown in Figure 158. As soon as the carbon number between the two amines was greater than two, the reaction was no longer possible. The crystal structure, when available, showed agreement with Schmidt's rules and seemed to explain reactivity.

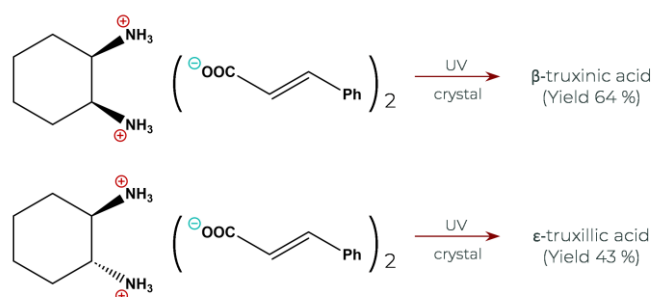


Figure 158 | Results obtained by Yoshikatsu *et al.* for a dimerization of a salt between *trans*-cinnamic acid and *cis*- or *trans*-1,2-diaminocyclohexane. (Adapted from [224])

Along the same lines, i.e. using an additional molecule with two small arms to control the photodimerization reaction, a study was published in 2021 by B. B. Yagci *et al.* in which an organic synthesis reaction was carried out to keep the cinnamic acids in the desired

position. [225] They used 1,8-dihydroxynaphthalene as a covalent control agent. This method allowed them to obtain symmetrical and especially asymmetrical β -truxinic acids in a controlled manner, which had never been reported before. [226–228] This is illustrated in Figure 159. However, once again, syntax solution step was required at a given moment.

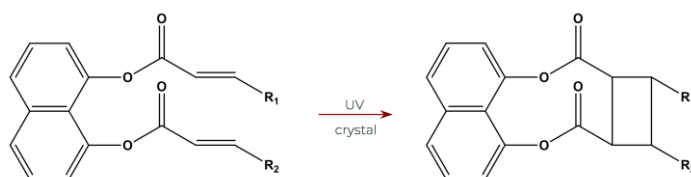


Figure 159 | Results obtained by Yagci *et al.* for a dimerization of *trans*-cinnamic acid link to 1,8-dihydroxynaphthalene. (Adapted from [225])

In addition to these covalent and ionic assemblies, which allow to direct the course of photochemical reactions in the solid-state, other control tools have been developed. For example, the use of halogen and π - π bonds [229, 230], metal ions [231], aurophilic interactions [232], coordination [233] or hydrogen bonds, as discussed in the following section. [234]

1.6 Control of dimerization with using a purely mechanochemical approach

Some molecules such as 1,2-di(4-pyridyl)ethylene do not respect Schmidt's topochemical concepts and hence do not photodimerize in the solid-state. L. R. MacGillivray *et al.* addressed this problem by cocrystallizing 1,2-di(4-pyridyl)ethylene with resorcinol derivatives, which allowed the double bonds to be directed and made photodimerization possible (Figure 160). [235–243]

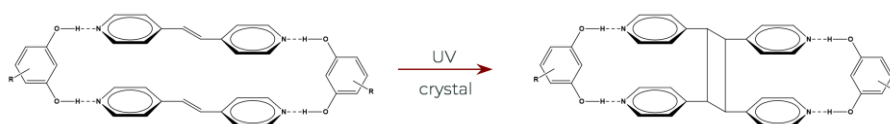


Figure 160 | Results obtained by MacGillivray *et al.* for a dimerization of 1,2-Di(4-pyridyl)ethylene cocrystallized with resorcinol derivatives. (Adapted from [235, 236])

For their first study, cocrystals were obtained by crystal growth via solvent evaporation but in their later work, this later step was replaced by a milling process allowing them to remove the solvent entirely (Figure 161). [244, 245] Of course, the separation of the control agent and the recovery of the final product still required involving some type of solvent (crystallization, chromatographic column, etc.).



Figure 161 | Control of dimerization using a pure mechanochemical approach. The synthesis process occurs in the solid-state, as does the irradiation process.

Grinding (which causes cocrystal formation) and irradiation (which causes photochemical cyclisation) were done in succession, making the method time consuming and tedious. Recently (2012) L. R. MacGillivray *et al.* conducted a new study to try to grind and irradiate at the same time (Figure 162). [246] They did this by using the 1,2-di(4-pyridyl)ethylene/4,6-dichlororesorcinol system, placing it in a borosilicate glass vessel on a vortex with two inox balls and irradiating whilst grinding. They were also able to demonstrate that the reaction could progress using a catalytic amount of 4,6-dichlororesorcinol, as the cocrystallization agents/catalyst dissociated from the product formed by irradiation and was able to form a cocrystal again allowing the cycle to repeat.

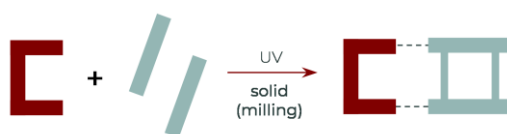


Figure 162 | Control of dimerization and irradiation in solid-state in one step. The synthesis and irradiation steps are conducted simultaneously in the solid-state.

2. Goals and methodology

2.1 Crystal engineering to control the regioselectivity upon photodimerization

Our work finds its origin in the studies of L. R. MacGillivray *et al.*, who used cocrystallization to enable solid-state photodimerization of molecules that were too far apart when considering them in the pure phase. [247] In a same mindset, we will use cocrystallization to direct the regioselectivity of a photodimerization reaction in the solid-state. Specifically, we aim to control the orientation of the molecules within the solid by adding a second component.

We hope to controlling regioselectivity using a guiding agent for cinnamic acid using a complete mechanochemical approach, hoping to come to various stereoisomer of truxillic and truxinic acid, shown in Figure 156, in a thermodynamically controlled manner. Figure 163 illustrates the control by a cocrystallization agent to reach β -truxinic acid from *trans*-cinnamic acid.

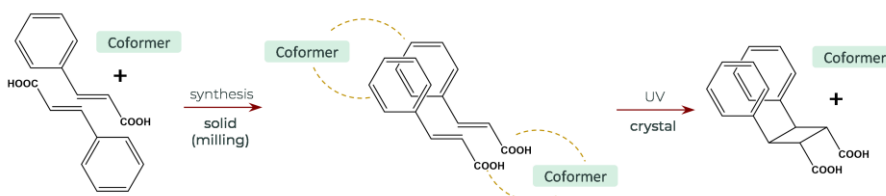


Figure 163 | Illustration of solid-state control by a cocrystallizing agent (coformer) to reach β -truxinic acid from *trans*-cinnamic acid.

Hydrogen bonds are frequently used to align molecules in crystals for photodimerization reactions because of their directional nature, which helps to control molecular arrangement. In addition to hydrogen bonds, other types of intermolecular interactions can also play a role in the alignment of molecules in crystals, such as $\pi - \pi$ stacking.

To achieve this goal, we will consider various derivatives of cinnamic acid: *trans*-cinnamic acid, 2-ethoxy-*trans*-cinnamic acid, 2-methoxy-*trans*-cinnamic acid, 2-methoxy-*cis*-cinnamic acid and 4-methoxy-*trans*-cinnamic acid, presented in Figure 164.

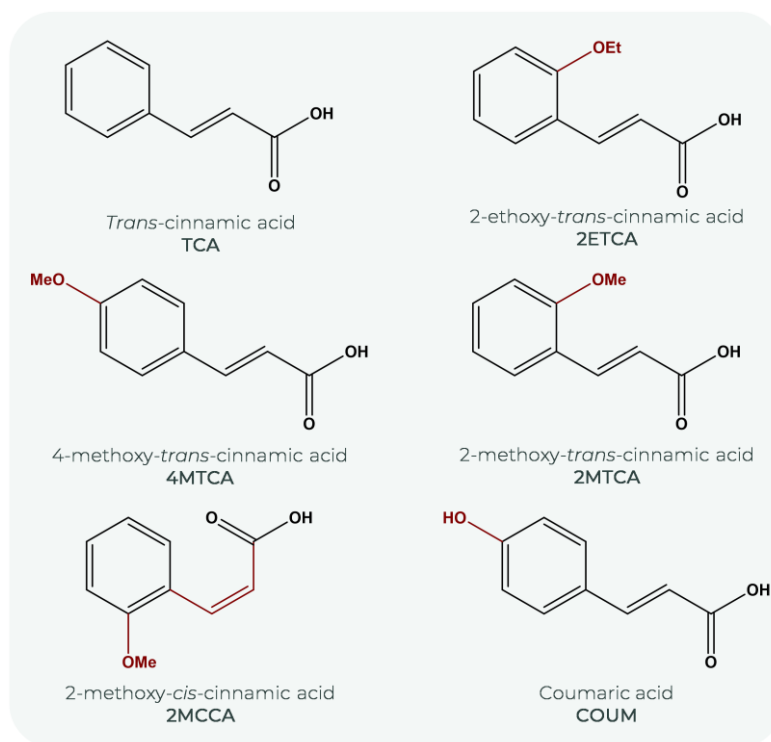


Figure 164 | Various derivatives of cinnamic acid considered in this project.

Throughout the project we will only use the terms truxillic and truxinic acid, both for *trans*-cinnamic acid irradiation products and for cinnamic acid derivatives. For these derivatives, using only the terms truxillic and truxinic acid is a nominative simplification that does not consider the chemical groups present on the phenyl. For example, α -*trans*-cinnamic acid leads to α -truxillic acid upon irradiation and coumaric acid leads to di-4-hydroxy- α -truxillic acid, however we will simply use the term « α -truxillic acid ».

2.2 Methodology

This work starts by studying the solid-state photo-reactivity of the different isolated target molecules.

Then various cocrystals of the target molecules will be sought for through a LAG cocrystal screen. The different grindings were then analyzed by X-ray powder diffraction. By comparing the diffractograms obtained for these grindings with the diffractograms of the parent compounds (target molecule and cocrystallization agent), we can estimate whether or not new solid phases have formed. When a new solid phase is assumed, it will then be photoactivated to observe whether or not photodimerization occurs.

The final product, after irradiation, will be analyzed by ^1H -NMR. Using the multiplicity of signals and their coupling constant, the different products can be identified. Figure 165 and Figure 166 shows the difference between α -truxillic acid and β -truxinic acid: two of the four isomers that can be reached with *trans*-derivatives. (See Figure 167 for the two others). Note here that the α -truxillic acid can also be formed from two molecules of *cis*-cinnamic acid.

α -truxillic acid is characterized by a doublet of doublets with $J = 10.4$ Hz et 7.2 Hz (Figure 165). Whereas β -truxinic acid is characterized by a doublet with $J = 6.2$ Hz (Figure 166). These signals are those associated with the cyclobutene hydrogens. (When protons are magnetically equivalent, they resonate at the same frequency. Coupling between them does not alter their relative resonance frequencies and therefore does not produce a multiplet structure in the ^1H -NMR spectrum. Their signals are superimposed to form a single peak. This is the case for β -truxinic acid or δ -truxinic acid).

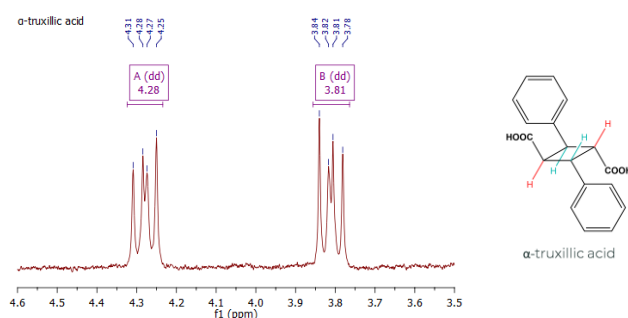


Figure 165 | ^1H -NMR identification of the α -truxillic acid. ^1H -NMR (300 MHz, DMSO) δ 4.28 (dd, $J = 10.4, 7.2$ Hz, 2H), 3.81 (dd, $J = 10.4, 7.2$ Hz, 2H). This ^1H -NMR comes from the experimental irradiation of α -*trans*-cinnamic acid.

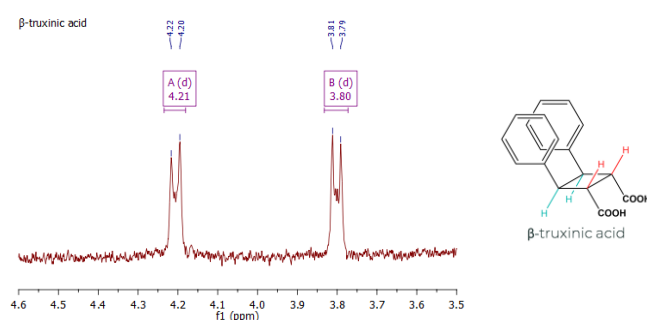


Figure 166 | ^1H -NMR identification of the β -truxinic acid. ^1H -NMR (300 MHz, DMSO) δ 4.21 (d, $J = 6.2$ Hz, 2H), 3.80 (d, $J = 6.2$ Hz, 2H). This ^1H -NMR comes from the experimental irradiation of a cocrystal between *trans*-cinnamic acid and 4,6-dichlororesorcinol.

The *trans*-derivative molecules could potentially position themselves differently in the crystal, theoretically leading to ϵ -truxillic acid and δ -truxinic acid (see Figure 167).

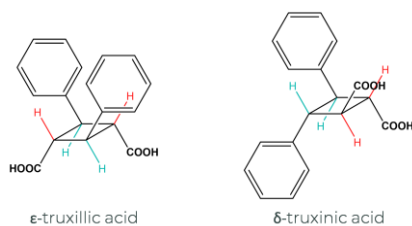


Figure 167 | Two other isomers that can be reached with *trans*-derivative.

Theoretically, for δ -truxinic acid, the ^1H -NMR follows the same style of pattern obtained with β -truxinic acid. That is to say, a pair of doublets. And for ϵ -truxillic acid, one is expecting to observe a pair of triplets.

Figure 168 is a simulation of the ^1H -NMRs that one would expect to observe for these two isomers (given here to illustrate the expected multiplicity). The small peaks present in the doublets of the δ -truxinic acid are due to additional couplings with hydrogens positioned on carbons further away than those just next to the hydrogen considered.

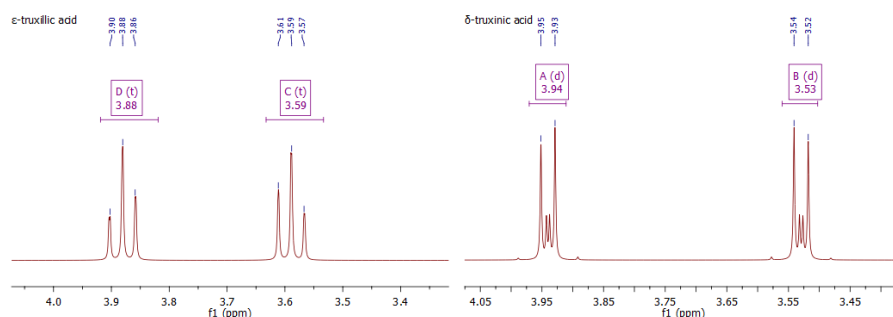


Figure 168 | Simulated ^1H -NMR for ϵ -truxillic acid and δ -truxinic acid.

Many other isomers could also be observed using *cis*-derivatives, illustrated in Figure 169. It should be noted here that mixing *cis*- and *trans*-derivatives was not considered in this project. However, Figure 156 shows the different products that could be obtained by mixing them.

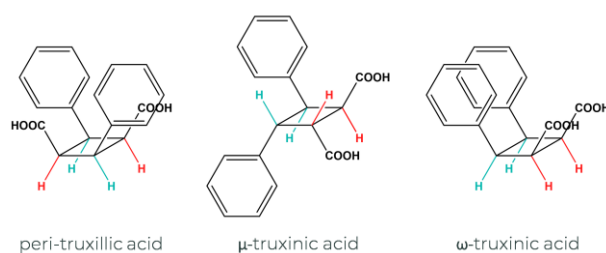


Figure 169 | Three isomers that can be reached with *cis*-derivatives.

Theoretically, for peri-truxillic acid, one would expect to observe in ^1H -NMR a pair of triplets. For μ -truxinic acid and ω -truxinic acid, one would expect to observe in ^1H -NMR a pair of doublets.

Since other isomers than α -truxillic acid and β -truxinic acid could potentially be formed and their signals could easily be confused, crystal growth of the cocrystals needs to be carried out in parallel to understand which product is formed. The crystal structure provides important 3D information on the orientation of the double bonds and allows confirmation of the regioisomer obtained after irradiation. Another way to confirm the stereochemistry of the obtained regioisomer would have been to successfully crystallize the product after irradiation. Unfortunately, due to the low yield associated with these reactions, this is not a straightforward task.

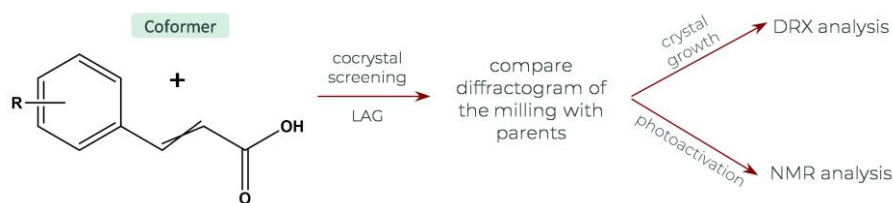


Figure 170 | Methodology for finding new cocrystals to control regioselectivity of the photodimerization of cinnamic acid.

Figure 170 provides a schematic illustration of the methodology adopted for this research project. The irradiation stage involved subjecting the sample to near-complete radiation from a 350-watt Oriel Instrument: Universal Arc Lamp Housing, excluding infrared wavelengths.

3. Results and discussion

3.1 Dimerization of parent compounds

To study the reactivity of cinnamic acid derivatives, mainly commercial powders were placed between two glass plates which were then sealed at the edges with parafilm. Except for β -*trans*-cinnamic acid which was synthesized (Unfortunately always with traces of α -*trans*-cinnamic acid) and 2-methoxy-*cis*-cinnamic acid of which crushed single crystals (α_1 -2-methoxy-*cis*-cinnamic acid and α_2 -2-methoxy-*cis*-cinnamic acid) were irradiated. The compound was then photoactivated with a UV lamp at 350 W for 48 h. It was turned over every hour (except of course during the night), trying to have an equivalent irradiation time for each side. After irradiation, the product obtained was analyzed by ^1H -NMR (300 MHz, DMSO). To facilitate the analysis of the spectra, each cinnamic acid derivative was also analyzed prior to irradiation by ^1H -NMR (300 MHz, DMSO). All of these ^1H -NMR results are presented in Supporting Information p.245.

3.1.1. *Trans*-cinnamic acid (TCA)

To date, two polymorphs of *trans*-cinnamic acid have been identified, the α and β forms. α -*trans*-cinnamic acid was characterized by D. A. Wierda *et al.* (CINMAC03). [248] The second form, β -*trans*-cinnamic acid, was characterized by I. Abdelmoty *et al.* (CINMAC06). [249] These two polymorphs are monotropically related with α -*trans*-cinnamic acid being the stable polymorph at all temperatures. β -*trans*-cinnamic acid is metastable, transiting in the solid-state to the α -form over time.

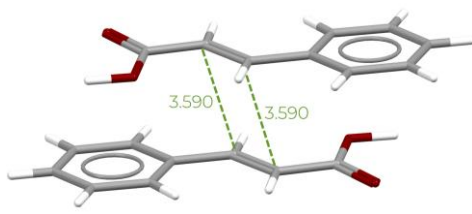


Figure 171 | Representation of α -*trans*-cinnamic acid. The interatomic distance is 3.590 Å, allowing photoreaction. (CINMAC03) Space group: $P2_1/n$.

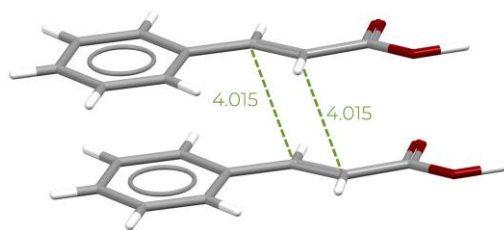


Figure 172 | Representation of β -*trans*-cinnamic acid. The interatomic distance is 4,015 Å, allowing photoreaction. (CINMAC06) Space group: P2₁/a.

As explained above, dimerization of α -*trans*-cinnamic leads to the formation of α -truxillic acid and dimerization of β -*trans*-cinnamic acid leads to the formation of β -truxinic acid. This can easily be understood looking at the crystalline arrangement of the molecules. The arrangement in α -*trans*-cinnamic acid, called « head-to-tail » packing, leads to the « head-to-tail » dimer (Figure 171). Unlike the arrangement in β -*trans*-cinnamic acid, called « head-to-head » packing, which leads to the « head-to-head » dimer (Figure 172). Obtaining α -truxillic acid in a controlled manner is straightforward as it is obtained from the stable polymorph. In contrast, the synthesis of β -truxinic acid is more difficult due to the transition of the metastable polymorph during the irradiation process, ultimately leading to a mixture of the two acids. [216]

The photodimerization of both polymorphs was verified experimentally. α -*trans*-cinnamic acid was obtained directly from the commercial powder. β -*trans*-cinnamic acid was obtained as follows: 5 g of α -*trans*-cinnamic acid was melted in an oven at 180 °C for 30 min. The melt was cooled to room temperature and then dissolved in 5 mL DMF. The solution was sonicated to aid dissolution. Then this solution was added stepwise to 250 mL of ice water under constant stirring. A precipitate form which is filtered. This solid was then analyzed by PXRD and irradiated immediately. As can be seen in Figure 173, the solid obtained contained β -*trans*-cinnamic acid but also α -*trans*-cinnamic acid.

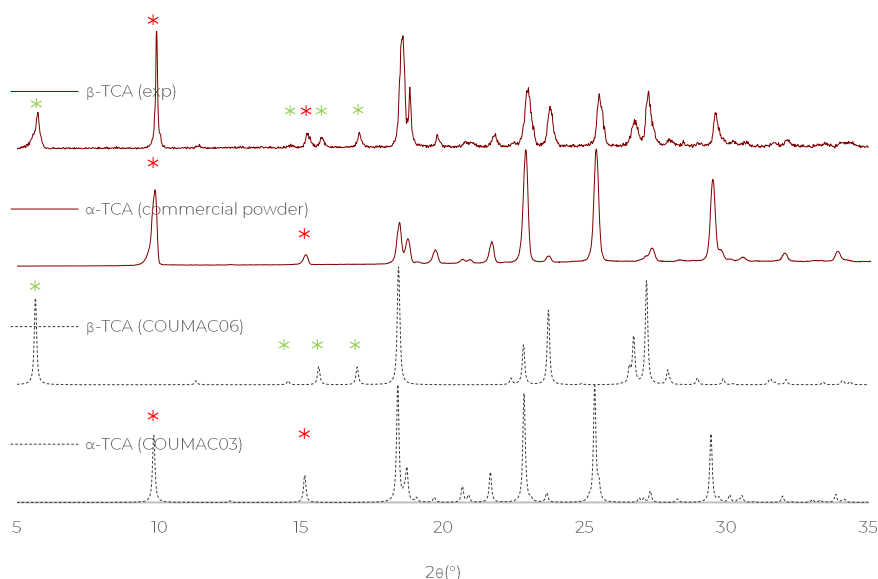


Figure 173 | Diffractograms of α -*trans*-cinnamic acid from commercial powder and β -*trans*-cinnamic acid obtained experimentally, in full line. Simulated patterns from CSD (COUMAC03 and COUMAC06) in dashed line.

The ^1H -NMR spectrum of the irradiation of both polymorphs showed traces of *trans*-cinnamic acid. The ^1H -NMR of the α -*trans*-cinnamic acid irradiation showed the formation of α -truxillic acid while the ^1H -NMR of β -*trans*-cinnamic acid showed a mixture of α -truxillic acid and β -truxinic acid. ^1H -NMR results are presented in Supporting Information p.245.

3.1.2. *Trans*-2-ethoxycinnamic acid (2ETCA)

Initially, three polymorphs of *trans*-2-ethoxycinnamic acid were identified, the α -, β - and γ -forms. [223] They were subsequently characterized by M. A. Fernandes *et al.* (ZZZNQS03, QUFHAA & ZZZNQS04). [250] It turned out that β -*trans*-2-ethoxycinnamic acid is actually a benzene solvate (1 : 6 benzene : OETCA). The benzene formed a kind of template arranging *trans*-2-ethoxycinnamic acid molecules in a « head-to-head » arrangement leading to the « head-to-head » dimer. The double bonds in this form are separated by 3.940 Å. α -*trans*-2-ethoxycinnamic acid forms a layered structure with an

antiparallel orientation linked by an inversion center. The double bonds are separated by 4.535 Å and can react to give the α -truxillic acid « head-to-tail » dimer. In contrast, the double bonds of the γ -form are separated by 5.268 Å, making the alkene photostable. [216, 251–253]

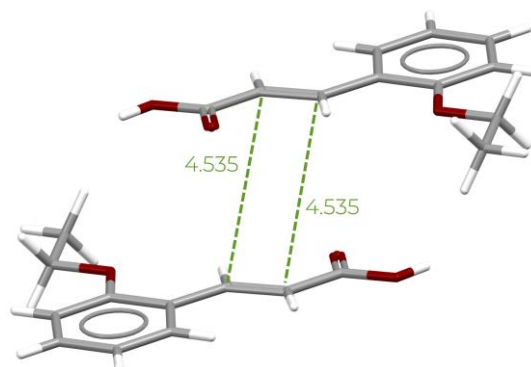


Figure 174 | Representation of α -*trans*-2-ethoxycinnamic acid. The interatomic distance is 4.535 Å, allowing photoreaction. (ZZNQSO3) Space group: *P*-1.

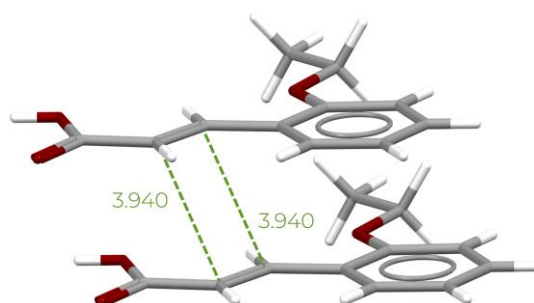


Figure 175 | Representation of β -*trans*-2-ethoxycinnamic acid (in fact a benzene solvate). The interatomic distance is 3.94 Å, allowing photoreaction. (QUFHAA) Space group: *R*-3.

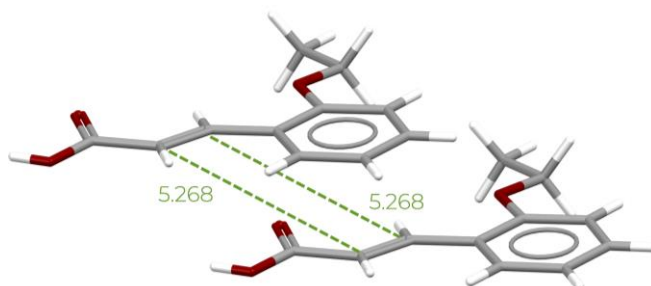


Figure 176 | Representation of γ -*trans*-2-ethoxycinnamic acid. The interatomic distance is 5.268 Å, NOT allowing photoreaction. (ZZNQS04) Space group: C2/c

Only the photodimerization of α -*trans*-2-ethoxycinnamic acid was experimentally verified. Since it is the most stable polymorph, it is also the one found in the commercial product. ^1H -NMR after irradiation confirmed the formation of the « head-to-tail » α -truxillic acid dimer. ^1H -NMR results are presented in Supporting Information p.245. The others polymorphs were not made and not reacted.

3.1.3. *Trans*-4-methoxycinnamic acid (4MTCA)

To date, only one polymorph of *trans*-4-methoxycinnamic acid is known and its crystal structure was characterized and published by Y. Cao *et al.* (MXCINN03). [223, 254]

The structure of this form is peculiar, as both « head-to-head » and « head-to-tail » arrangements are observed, with a shorter distance for the « head-to-head » arrangement.

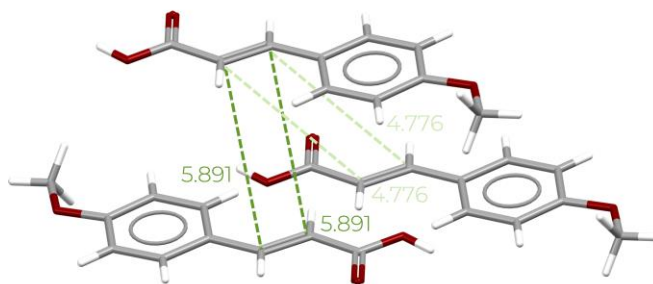


Figure 177 | Representation of *trans*-4-methoxycinnamic acid. The interatomic distance is 4.776 Å, allowing photoreaction. « Head-to-head » arrangement. And the interatomic distance is 5.891 Å, allowing photoreaction. « Head-to-tail » arrangement. (MXCINN03) Space group: P-1

Curiously, contrary to G. M. J. Schmidt's observations who reported no dimerization reaction of *trans*-4-methoxycinnamic acid, we were able to observe the formation of both isomers (« head-to-tail » and « head-to-head ») after irradiation. [216] ^1H -NMR results are presented in Supporting Information p.245. As both « head-to-tail » and « head-to-head » distances are greater than 4.2 Å, *trans*-4-methoxycinnamic acid is one example showing Schmidt's rules, are just rules and exceptions to these rules can effectively occur.

3.1.4. *Trans*-2-methoxycinnamic acid (2MTCA)

Only one polymorph of *trans*-2-methoxycinnamic acid is known. It was described by S. D. M. Atkinson *et al.* (ZZZFLLM01). [255] The distance between the double bonds is short enough to ensure the reaction and the arrangement of the molecules leads to the α -truxillic acid « head-to-tail » dimer. [216]

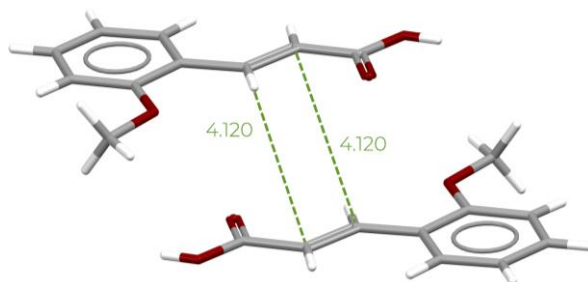


Figure 178 | Representation of *trans*-2-methoxycinnamic acid. The interatomic distance is 4.120 Å, allowing photoreaction. (ZZZFLLM01) Space group: $P2_1/a$

The photodimerization of *trans*-2-methoxycinnamic acid was verified experimentally. ^1H -NMR presented in the Supporting Information p.245, shows the formation of α -truxillic acid.

3.1.5. *Cis*-2-methoxycinnamic acid (2MCCA)

Two crystalline forms of *cis*-2-methoxycinnamic acid were discovered by J. Bregman, G. M. J. Schmidt *et al.*, α_1 et α_2 . [218] These two forms had the space group $P2_1/a$ (ZZZHXY) and $P-1$ (ZZZHXY01) respectively. But no coordinate or crystal structure was reported. These could be determined for the α_1 , thanks to the growth of crystals by evaporation at ambient temperature in dichloromethane. And for the α_2 , thanks

to the growth of crystals by slow evaporation in the fridge in dichloromethane with the presence of 3,4-dihydroxybenzoic acid (both compounds crystallized separately).

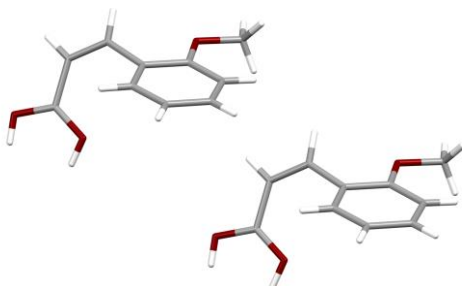


Figure 179 | Representation of α_1 -*cis*-2-methoxycinnamic acid from single crystal growth in DCM. Double bonds are not aligned correctly for the reaction to take place. Space group: $P2_1/a$

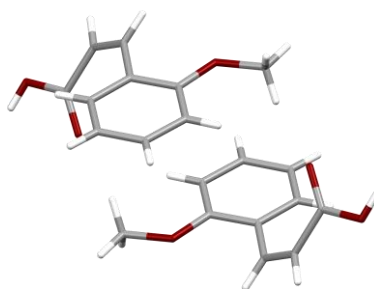


Figure 180 | Representation of α_2 -*cis*-2-methoxycinnamic acid from single crystal growth in DCM in presence of 3,5-dihydroxybenzoic acid. Double bonds are not aligned correctly for the reaction to take place. Space group: $P-1$

The distance between the olefins is too large to lead to a solid-state reaction according to Schmidt's topochemical criteria. Moreover, the olefins are not parallel. Experimentally, the two singles crystals (growth in DCM with or without presence of 3,5-dihydroxybenzoic acid) did not react upon irradiation.

Table 18 | Main crystallographic data of α_1 and α_2 -*cis*-2-methoxycinnamic acid.

Compound	α_1 -2MCCA	α_2 -2MCCA
Identification code	cb_lg_2MCCA_DCM	cb_57_2mcca_dhb_DCM
Empirical formula	C ₁₀ H ₁₀ O ₃	C ₁₀ H ₁₀ O ₃
Formula weight (g/mol)	178.18	178.18
Temperature (K)	100(2)	297(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Triclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> -1
a, b, c (Å)	a 7.1657(6) b 10.4976(9) c 11.8063(8)	a 7.500(2) b 7.783(2) c 8.864(3)
α , β , γ (°)	β 91.749(7)	α 79.77(3) β 73.63(3) γ 68.39(3)
Volume (Å ³)	887.70(12)	459.9(3)
Z	4	2
Density calculated (Mg/m ³)	1.333	1.287
Absorption coefficient (mm ⁻¹)	0.099	0.095
Crystal size (mm ³)	0.50 x 0.50 x 0.40	0.25 x 0.20 x 0.16
F(000)	376	188
Theta range for data collection (°)	2.597 to 26.116	3.007 to 26.238
Reflections collected	5837	6152
Independent reflections	1749 [R(int) = 0.0250]	1829 [R(int) = 0.0274]
Completeness to theta = 25.96°	99.4	99.2
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90004	1.00000 and 0.92214
Data / restraints / parameters	1749 / 0 / 124	1829 / 0 / 119
Goodness-of-fit on F ²	1.066	1.063
Final R indices [I > 2sigma(I)]	R1 = 0.0341, wR2 = 0.0886	R1 = 0.0450, wR2 = 0.1143
R indices (all data)	R1 = 0.0361, wR2 = 0.0900	R1 = 0.0518, wR2 = 0.1178
Largest diff. Peak and hole (e.Å ⁻³)	0.277, -0.170	0.136, -0.135

3.1.6. Coumaric acid (COUM)

Only one polymorph of coumaric acid is known. It was described by H. Utsumi *et al.* (COUMAC). [223, 256] The distance between the double bonds is short enough to ensure the reaction and the arrangement of the molecules leads to the « head-to-tail » dimer. [216]

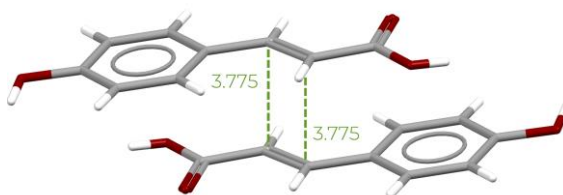


Figure 181 | Representation of the coumaric acid. The interatomic distance is 3.775 Å, allowing photoreaction. (COUMAC) Space group: P2₁/c

The photodimerization of coumaric acid was verified experimentally. ¹H-NMR presented in Supporting Information p.245 showed the formation of α-truxillic acid.

3.1.7. Summary of dimerization of cinnamic acid derivatives

Table 19 provides a concise compilation of the data previously presented, integrating the results obtained experimentally as well as those found in the literature. This summary focuses on the analysis of the different polymorphic forms of the targeted compounds when they are subjected to irradiation. This comparative approach makes it possible to assess the impact of irradiation on the different crystalline arrangements of the substances studied.

Table 19 | Comparison of the results obtained experimentally for the photodimerization of cinnamic acid derivatives with those reported in the literature.

Compound	Photoproduct (experimental)	Photoproduct (literature)
α - <i>trans</i> -cinnamic acid	α -truxillic acid	α -truxillic acid [216]
β - <i>trans</i> -cinnamic acid	β -truxinic acid	β -truxinic acid [216]
α - <i>trans</i> -2-ethoxycinnamic acid	α -truxillic acid	α -truxillic acid [216, 250]
β - <i>trans</i> -2-ethoxycinnamic acid (benzene solvate)	N/A	β -truxinic acid [216, 250]
γ - <i>trans</i> -2-ethoxycinnamic acid	N/A	No reaction [216, 250]
α - <i>trans</i> -4-methoxycinnamic acid	α -truxillic acid & β -truxinic acid	No reaction [216]
α - <i>trans</i> -2-methoxycinnamic acid	α -truxillic acid	α -truxillic acid [216]
α_1 - <i>cis</i> -2-methoxycinnamic acid	No reaction	α -truxillic acid [218]
α_2 - <i>cis</i> -2-methoxycinnamic acid	No reaction	α -truxillic acid [218]
α -coumaric acid	α -truxillic acid	α -truxillic acid [216]

Compounds from reference [216] and [218] were irradiated by exposing them to sunlight. The samples were placed in cellophane-covered Petri dishes or Pyrex cylinders, and were either rotated automatically in a continuous manner or manually once or twice a day. This irradiation process was followed by ultraviolet absorption and powder diffraction measurements until no further changes could be observed. Figure 182 shows an example of a UV absorption spectra. This is obtained with compound *m*-chloro-*trans*-cinnamic acid, which depending on the polymorph irradiated, leads to either a β -truxinic acid compound or no reactivity. Compounds from reference [250] were irradiated by exposing them to a UV lamp (No information was given about the wavelength).

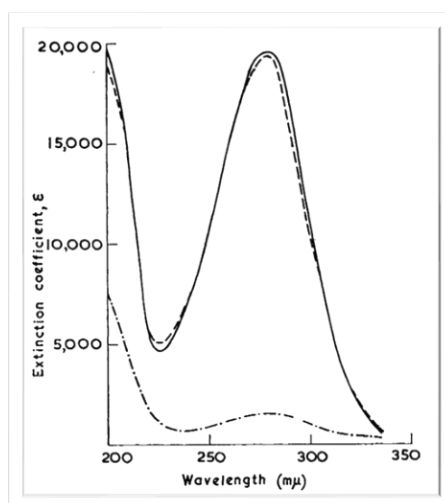


Figure 182 | Ultraviolet absorption spectra of *m*-chloro-*trans*-cinnamic acid in ethanol. Full line : unirradiated. Dots and dashed line: irradiated β -crystal modification. Dashed line: irradiated γ -crystal modification. (Reproduced from [216])

As shown in Table 19, the results we obtained experimentally show notable similarities with those reported in the literature. However, some discrepancies should be noted, particularly for α -*trans*-4-methoxycinnamic acid, which reacted in our experiments even though it was classified by G. M. J. Schmidt as a compound stable to UV radiation. Similarly, *cis*-2-methoxycinnamic acid did not react under our experimental conditions, in contrast to G. M. J. Schmidt's observations where transformation to α -truxillic acid was observed. These differences can be attributed to the specific irradiation conditions employed. With regard to α -*trans*-4-methoxycinnamic acid, its unexpected reactivity could result from exposure to a UV lamp of higher power than the daylight used in previous studies. As for *cis*-2-methoxycinnamic acid, prolonged irradiation in previous work until no observable change occurred, could have facilitated the slow isomerisation of *cis* to *trans*, allowing the reaction to α -truxillic acid. Our protocols limited irradiation to 48 hours, which could explain the lack of reaction observed.

3.2 Cocrystal screening

A total of 52 achiral cocrystallization agents (coformers) were tested by vibrational milling with the 6 cinnamic acid derivatives. This screening was carried out by liquid-assisted grinding (LAG). For this purpose, equimolar amounts of cinnamic acid derivatives (0.1 mmol) and cocrystallization agent (0.1 mmol) were put into an Eppendorf tube, then 3 stainless steel balls and 10 μL of Methanol were added ($\eta = \pm 0,22 - 0,48 \mu\text{L}.\text{mg}^{-1}$). Once the jars filled, the milling was run for 90 min at 30 Hz. A full list of the cocrystallization agents tested can be found in the Supporting Information p.248.

Based on XRPD data, 35 cocrystals were suspected out of 312 trials, with 15 of the 52 cocrystallization agents. These 15 cocrystallization agents are shown in Figure 183. This corresponds to a success rate of 11,2 %, which is in alignment with cocrystal success rates. These results are presented in Table 20. The highest number of potential cocrystals is formed with TCA (17,3 % 9/52) and COUM (17,3 % 9/52), followed by 4MTCA (13,5 % 7/52), 2MCCA (7,7 % 4/52), 2MTCA (7,7 % 4/52) and 2ETCA (3,8 % 2/52). One similarity among these 15 crystallizing agents is the presence of carboxyl and nitrogen-containing groups. These functional groups are essential because they facilitate the formation of hydrogen bonds with cinnamic acids. These interactions play a crucial role in the orientation and arrangement of the molecules within the crystal, which is essential for the efficiency of the photodimerization reactions.

Following the identification of potential cocrystals, we began growing single crystals of these entities in order to characterize them by X-ray diffraction (XRD). This crystallographic analysis is crucial, as it allows us not only to confirm the existence of the cocrystal, but also to examine the molecular arrangement within the crystal structure. The spatial organization of the molecules revealed by this method provides valuable clues as to their potential reactivity in photochemistry, offering an in-depth understanding of the cocrystal's photoreactive properties. Single crystals were grown from

solvent evaporation experiments, dissolving equimolar amounts of target molecule and cocrystallizing agent in different solvents. The different solutions were placed in the refrigerator (5°C) for slow evaporation or left to evaporate at room temperature. The different single crystals obtained were then analyzed by XRD and their simulated powder pattern was compared with the ground material, shown in Supporting Information p.263. Up to now 12 cocrystals structures could be determined. For two systems, two cocrystal polymorphs have been found: CC-12 and CC-21. Giving a total of 14 crystal structures.

All of the diffractograms can be found in the Supporting Information p.251 for suspected cocrystals and p.263 for confirmed cocrystals. The crystal structure information about confirmed cocrystals can be found in Supporting Information p.269.

Table 20 | Results of cocrystals screening: Gray cell, no potential cocrystal identified. White cell, potential cocrystals not yet characterized. Green cell, confirmed cocrystals by single crystal growth. Each potential cocrystal is named with CC-number. Two polymorphic forms were discovered for CC-21 and CC-12.

Cocrystallization agents	TCA	2ETCA	4MTCA	2MTCA	2MCCA	COUM
2-benzoylbenzoic acid	CC-1		CC-2	CC-3		CC-4
3,4-dihydroxybenzoic acid	CC-5		CC-6		CC-7	
3-nitrobenzoic acid	CC-8	CC-9	CC-10	CC-11		
4,4'-bipyridine	CC-12 I CC-12 II	CC-13	CC-14	CC-15		CC-16
4,6-dichlororesorcinol	CC-17					
4-aminobenzoic acid	CC-18		CC-19			
4-nitrobenzoic acid	CC-20		CC-21 I CC-21 II			
5-hydroxysophthalic acid			CC-22		CC-23	
Acetoacetamide	CC-24			CC-25	CC-26	CC-27
Citraconic acid						CC-28
Gallic acid						CC-29
isophthalohydrazide					CC-30	CC-31
pyromellitic acid						CC-32
Uracil						CC-33
Urea	CC-34					CC-35

Moreover, a new polymorph of one of the cocrystallization agents (2-benzoylbenzoic acid) was discovered “by chance” during the growth of cocrystals. Data for the new polymorph of 2-benzoylbenzoic acid can also be found in Supporting Information p.249.

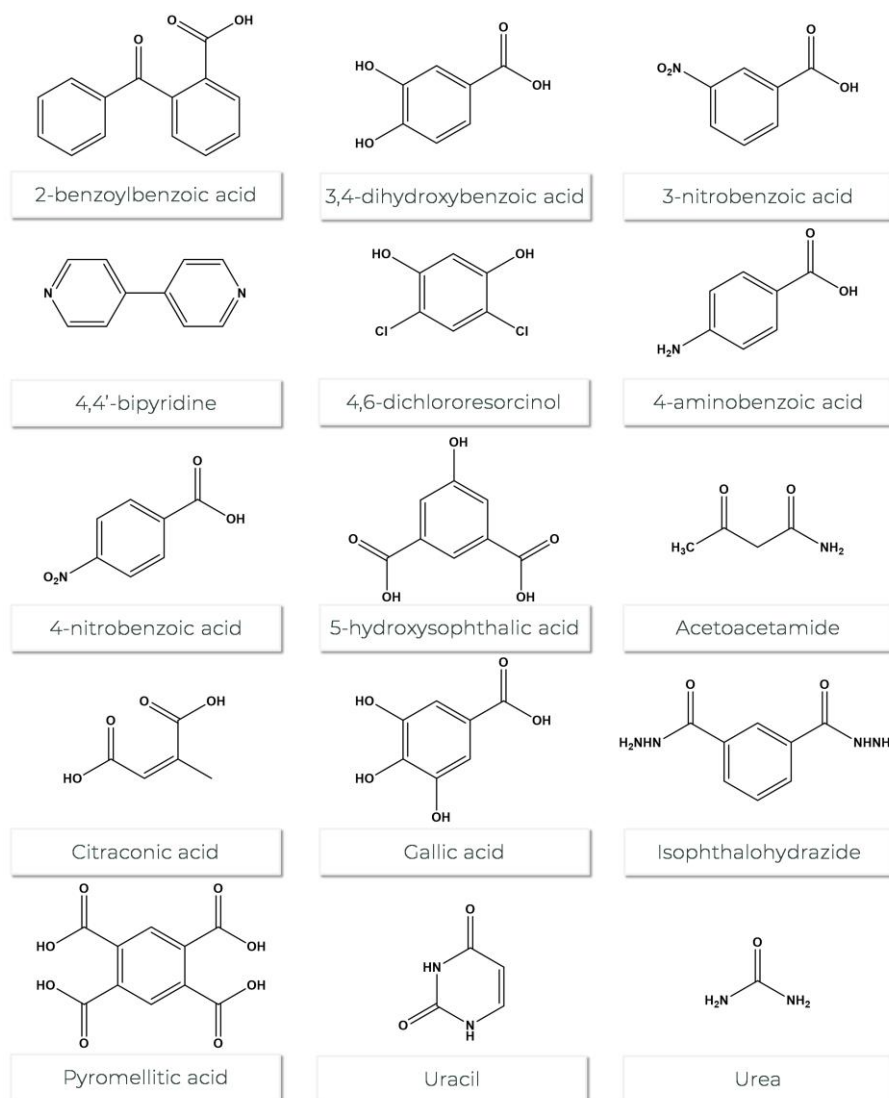


Figure 183 | Cocrystallization agents that potentially form a cocrystal with at least one cinnamic acid derivative.

3.3 Analysis of the crystalline structures of the 14 confirmed cocrystals

We have carried out a detailed study of crystal structures, focusing on the arrangement of molecules within these structures according to various criteria selected for their relevance. This analysis has enabled us to establish correlations between the molecular arrangement in the crystal and the reactivity of the molecules under irradiation, providing a better understanding for future development. One of the steps in our analysis is to measure the distances between the carbons of the double bonds in each molecule. This is clearly illustrated in Figure 184(d).

The criteria analyzed concern the relationships between two molecules and are illustrated in Figure 184. Each of these criteria is independent and should not be seen as a sequence to be followed in a specific order. Rather, they serve to evaluate molecular interactions from different angles. The following three criteria were analyzed :

The parallelism of the planes formed by the double bond and its substituents: By considering the plane in which the double bond and the ring are located, we examine whether the planes of two molecules are parallel or not. If the plane of a molecule is rotated about the y-axis, this results in the measurement of two distinct distances between the carbons of the double bonds of the two molecules. This non-parallelism is demonstrated in Figure 184(a). Another example of non-parallelism occurs when one of the molecules is rotated around the x-axis, resulting in two identical distances. The case where one molecule is rotated around the z-axis corresponds to the criterion examined next.

Alignment of the double bond in the same direction: For this second criterion, we examine whether the double bonds of the two molecules are oriented in the same direction. If this is not the case, the superimposed molecules form a cross arrangement seen from above. As a result, the distances measured between the carbons of

the double bonds of each molecule turn out to be greater than the distance separating the two molecular planes. This arrangement is illustrated in Figure 184(b).

The stacking of molecules arranged one above the other: In this analysis, we determine whether the two molecules are superimposed directly on top of each other or whether one of them is shifted. When a molecule is shifted, this results in an increase in the distance between the carbons of the double bonds of the two molecules compared with an arrangement where the molecules would be perfectly aligned one on top of the other. This criterion is illustrated in Figure 184(c).

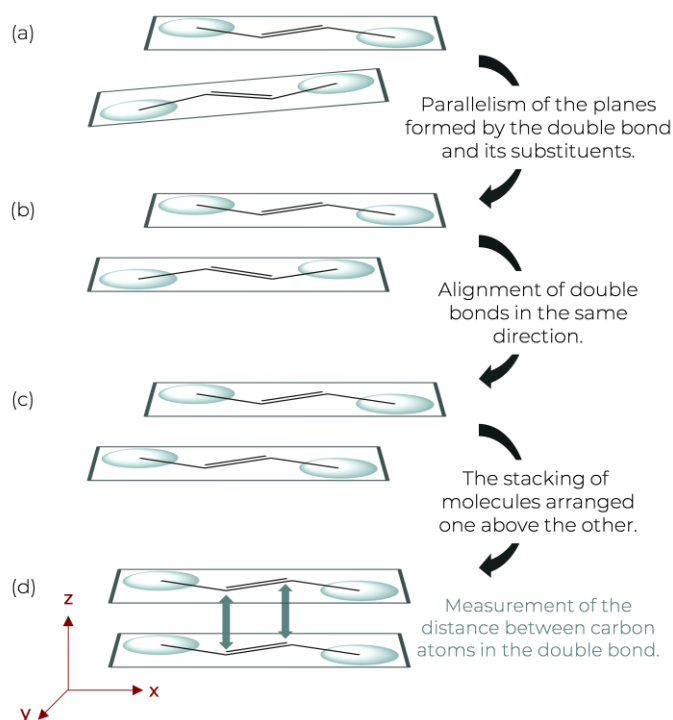


Figure 184 | Illustration of the criteria used to assess molecular arrangement within a crystal, ranging from the least favorable to the most favorable arrangements for a photochemical cycloaddition reaction.

Table 21 summarizes the results for each criterion applied to the 14 cocrystals whose crystal structures were determined. The last column of the table is dedicated to the results obtained following irradiation of the crystals. These results are determined in the next section.

Table 21 | Criteria evaluated in each crystal structure of the confirmed cocrystals as well as the results obtained after irradiation of some of these (α for cocrystals that lead to the « head-to-tail » dimer (α -truxillic acid), β for cocrystals that lead to « head-to-head » dimer (β -truxinic acid), NR for no reactivity and N/A when no irradiation was applied). Optimal conditions are marked in green, while sub-optimal conditions are marked in red.

N° of cocrystal	Parallel planes	Double bond orientation	One above the other	Distance between carbon atoms (Å)	Results of irradiation
Cocrystal with <i>trans</i> -cinnamic acid					
CC-5	Yes	Same	Almost	3.765	α
CC-8	Yes	Same	No	5.893	NR
CC-12 I	Yes	Same	No	5.603	N/A
CC-12 II	No	Same	Almost	5.104 & 5.083	N/A
CC-17	Yes	Same	Yes	3.913	β
CC-18	Yes	Same	No	8.135	NR
CC-20	Yes	Same	No	7.058	NR
CC-34	Yes	Same	No	4.601	NR
Cocrystal with 2-ethoxy- <i>trans</i> -cinnamic acid					
CC-9	Yes	Same	Yes	7.204	NR
Cocrystal with 4-methoxy- <i>trans</i> -cinnamic acid					
CC-10	Almost	Opposite	Yes	7.615 & 6.770	N/A
CC-21 I	Yes	Same	No	5.563 or 5.314	N/A
CC-21 II	Yes	Same	No	5.314	N/A
Cocrystal with coumaric acid					
CC-16	No	Opposite	No	10.028 & 9.851	N/A
CC-35	Yes	Same	Yes	3.793	α

As we predicted, a comparative analysis between the structural data and the results obtained following irradiation demonstrates the importance of a precise molecular arrangement: the planes of the molecules must be parallel, with minimal offset. It is also crucial that the double bonds are perfectly aligned and that the distance between them remains small. These specific criteria promote efficient

overlap of the π orbitals, an essential element for the success of the photochemical reaction under study. This overlap is necessary to allow adequate interaction of π electrons, thus facilitating reactions between molecules when exposed to light. These observations reinforce our understanding of the mechanism of this reaction and underline the importance of molecular arrangement in photochemical processes.

3.4 Analysis of the reactivity of the 14 confirmed cocrystals

In this section, we describe the crystal structures of the various confirmed cocrystals. We review the previously stated criteria, such as the alignment of the molecular planes, the parallelism of the double bonds and the distances between them. We also present the stereochemistry of the products resulting from the irradiation of the cocrystals.

To study the reactivity of these cocrystals, the single crystals were crushed in a mortar and placed between two glass plates which were then sealed at the edges with parafilm. The compound was then photoactivated with a UV lamp at 350 W for 48 h. It was turned over every hour (except of course during the night), trying to have an equivalent irradiation time for each side. After irradiation, the product obtained was analyzed by ^1H -NMR (300 MHz, DMSO). For unreactive cocrystals, only the parents were present in the ^1H -NMR spectra. For cocrystals that lead to the « head-to-tail » dimer (α -truxillic acid), the observed pattern in ^1H -NMR was the one presented in Figure 165 and for cocrystals that lead to « head-to-head » dimer (β -truxinic acid), the observed pattern in ^1H -NMR was the one presented in Figure 166. Knowing the crystalline structure of the cocrystal helps to confirm the isomer obtained.

Reactivity was studied for 8 of the 14 confirmed cocrystals.

3.4.1. Unreactive cocrystals

Table 22 lists five cocrystals that remained unreactive after 48 hours of irradiation. This lack of reactivity can be explained mainly by the fact that the two molecules are not stacked directly on top of each other. As a result, the distances separating them exceed $4.6 \text{ \AA}$, which is greater than the optimum distance required for effective interaction during irradiation.

Table 22 | All of the confirmed cocrystals that did not react.

N° of cocrystal	Target molecule	Coformer
CC-8	TCA	3-nitrobenzoic acid
CC-9	2ETCA	3-nitrobenzoic acid
CC-18	TCA	4-aminobenzoic acid
CC-20	TCA	4-nitrobenzoic acid
CC-34	TCA	Urea

CC-8: TCA / 3-nitrobenzoic acid

This single crystal was obtained by slow solvent evaporation (MeOH) in a fridge at 5°C .

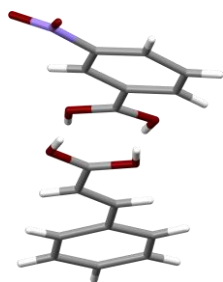


Figure 185 | Asymmetric unit of cocrystal TCA / 3-nitrobenzoic acid, view along a axis.

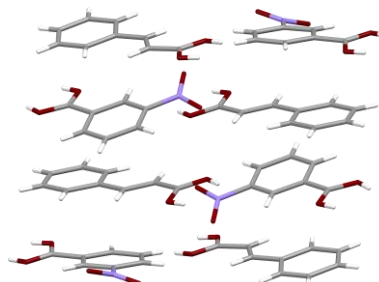


Figure 186 | Representation of cocrystal TCA / 3-nitrobenzoic acid.

As can be seen in Figure 186 (Carboxylic acids appear here with two protons because the position of these is not determined.), the TCA molecules are separated by 3-nitrobenzoic acid molecules. Moreover, if one looks at the TCA molecules one above the other, they are found in parallel planes but their double bonds are oriented in opposite

directions. The distances between the carbons of the double bonds are 7.660 Å and 7.458 Å. If one looks at the TCA molecules closest to each other, they are found in parallel planes but they are not one above the other. Their double bonds are in the same direction and are spaced by 5.893 Å. The non-reactivity of the cocrystal can therefore be easily understood.

CC-9: 2ETCA / 3-nitrobenzoic acid

This single crystal was obtained by slow solvent evaporation (ACN) in a fridge at 5°C.

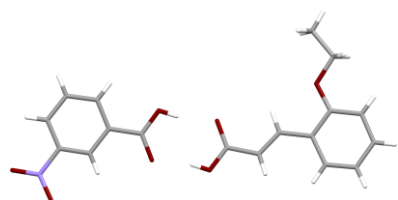


Figure 187 | Asymmetric unit of cocrystal 2ETCA / 3-nitrobenzoic acid, view along a axis.

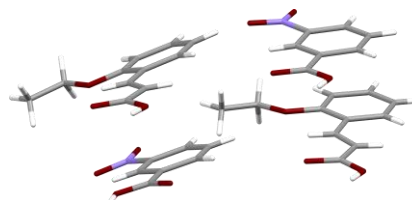


Figure 188 | Representation of cocrystal 2ETCA / 3-nitrobenzoic acid.

In the same way as for the previous cocrystal, the 2ETCA molecules are found between 3-nitrobenzoic acid molecules. This time the double bonds of the 2ETCA molecules are in the same direction and in parallel planes. Unfortunately, the distances between the carbons of these double bonds are 7.204 Å.

CC-18: TCA / 4-aminobenzoic acid

This single crystal was obtained by solvent evaporation (MeOH) at RT.

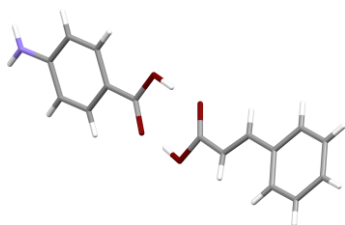


Figure 189 | Asymmetric unit of cocrystal TCA / 4-aminobenzoic acid, view along a axis.

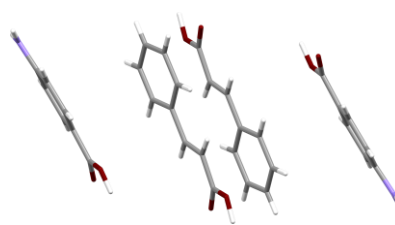


Figure 190 | Representation of cocrystal TCA / 4-aminobenzoic acid.

In this structure, the TCA molecules are found with their double bonds aligned in the same direction and in parallel planes. However, they are very far apart and contrary to what one might imagine from Figure 190, they are not on top of each other at all. The distance between the double bonds is therefore 8.135 Å.

CC-20: TCA / 4-nitrobenzoic acid

This single crystal was obtained by slow solvent evaporation (DCM) in a fridge at 5°C.

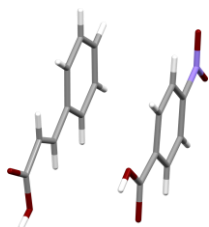


Figure 191 | Asymmetric unit of cocrystal TCA / 4-nitrobenzoic acid, view along c axis.

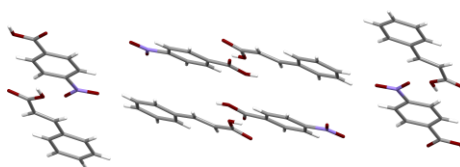


Figure 192 | Representation of cocrystal TCA / 4-nitrobenzoic acid.

In this cocrystal, the TCA molecules are each found between 4-nitrobenzoic acid molecules. If we look at the TCA molecules closest to each other, their double bonds are in parallel planes and in the same direction. However, the distance between them is 7.058 Å.

CC-34: TCA / Urea

This single crystal was obtained by solvent evaporation (DCM) at RT.

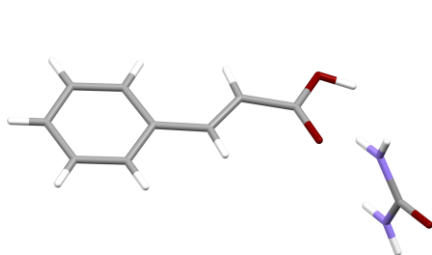


Figure 193 | Asymmetric unit of cocrystal TCA / Urea, view along c axis.

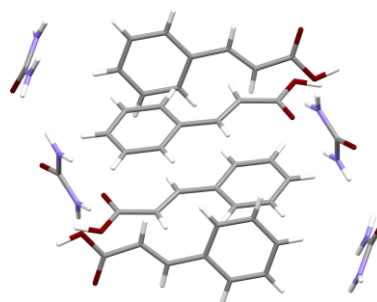


Figure 194 | Representation of cocrystal TCA / Urea.

As can be seen in Figure 194, the TCA molecules are present in two different sets of planes. Between these sets of planes, it is clear that no reaction could take place due to the orientation of the double bonds. On the other hand, within a series of planes (those where the TCA molecules are closest together), one could expect a reaction to take place. The double bonds are in the same direction and parallel and are separated by only 4.601 Å. However, these double bonds are not on top of each other, which could explain the non-reactivity. It would have been interesting here to test the photoactivation by changing the irradiation conditions, e.g. irradiation intensity and time. Given the « short » distance between the double bonds, it cannot be excluded that the dimerization reaction could take place with some molecular movement.

3.4.2. « head-to-tail » reactive cocrystals leading to α -truxillic acid

Table 23 lists the two cocrystals that have a « head-to-tail » arrangement and lead to the formation of the α -truxillic acid stereoisomer after 48 hours of irradiation. Figure 195 illustrates the products obtained from each cocrystal.

Table 23 | All of the confirmed cocrystals that lead to « head-to-tail » dimer (α -truxillic acid) under light.

N° of cocrystal	Target molecule	Coformer
CC-5	TCA	3,4-dihydroxybenzoic acid
CC-35	COUM	Urea

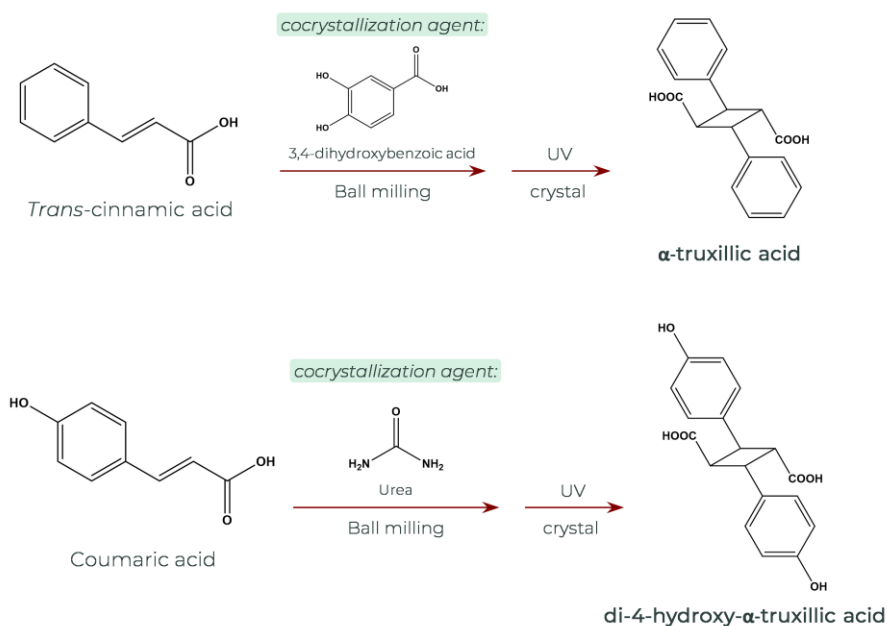


Figure 195 | Products obtained after irradiation of cocrystals *trans*-cinnamic acid/3,4-dihydroxybenzoic acid and coumaric acid/urea.

CC-5: TCA / 3,4-dihydroxybenzoic acid

This single crystal was obtained by slow solvent evaporation (EtOH) in a fridge at 5°C.

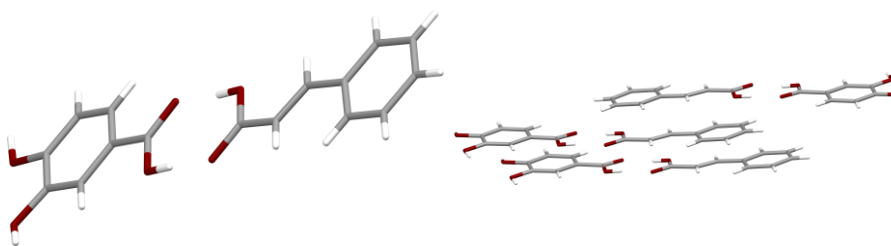


Figure 196 | Asymmetric unit of cocrystal TCA / 3,4-dihydroxybenzoic acid, view along c axis.

Figure 197 | Representation of cocrystal TCA / 3,4-dihydroxybenzoic acid.

As can be seen in Figure 197, the two bottom molecules of TCA are slightly offset. Moreover, they are not on top of each other and their double bonds are 5.603 Å apart. This assembly could have led to « head-to-head » dimer. However, when we analyze the TCA molecules

above and below, we notice that they are oriented one above the other in a parallel plane and with their double bonds in the same direction. The distance between them is 3.765 Å, which easily explains why there is a reaction and why the dimer obtained is the « head-to-tail » dimer.

CC-35: COUM / Urea

This single crystal was obtained by evaporation of solvent (MeOH) at RT.

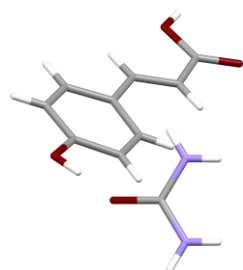


Figure 198 | Asymmetric unit of cocrystal COUM / Urea, view along a axis.

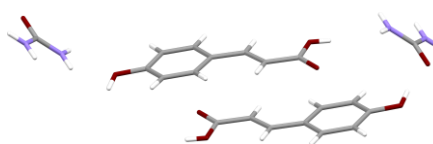


Figure 199 | Representation of cocrystal COUM / Urea.

It is quite visual here that the double bonds of COUM end up well aligned to allow photodimerization in the « head-to-tail » dimer. The double bonds are in parallel planes, are oriented in the same direction and are one above the other. The distance between them is 3.793 Å.

3.4.3. « head-to-head » reactive cocrystal leading to β -truxinic acid

Table 24 lists the cocrystal that have a « head-to-head » arrangement and lead to the formation of the β -truxinic acid stereoisomer after 48 hours of irradiation. Figure 200 illustrates the product obtained from the cocrystal.

Table 24 | All of the confirmed cocrystals that lead to "head-to-head" dimer (β -truxinic acid) under light.

N° of cocrystal	Target molecule	Coformer
CC-17	TCA	4,6-dichlororesorcinol

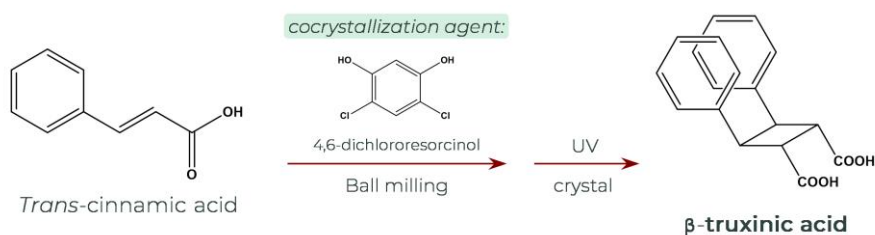


Figure 200 | Product obtained after irradiation of the cocrystal *trans*-cinnamic acid/4,6-dichlororesorcinol.

CC-17: TCA / 4,6-dichlororesorcinol

This single crystal was obtained by slow evaporation of solvent (DCM) in a fridge at 5°C.

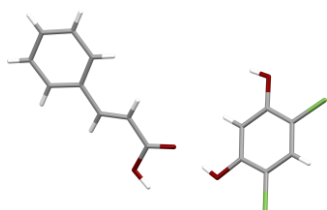


Figure 201 | Asymmetric unit of cocrystal TCA / 4,6-dichlororesorcinol, view along c axis.

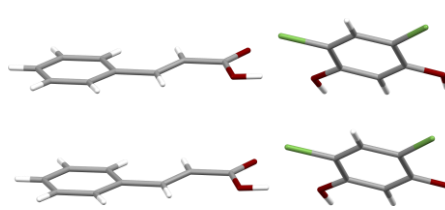


Figure 202 | Representation of cocrystal TCA / 4,6-dichlororesorcinol.

It is quite visual here that the double bonds of TCA end up well aligned to allow photodimerization in the « head-to-head » dimer. The double bonds are in parallel planes, are oriented in the same direction and are one above the other. The distance between them is 3.913 Å.

3.4.4. Confirmed cocrystals that were not tested yet towards their reactivity

In this section, we describe the six cocrystals whose structure has been characterized, but which we were unable to irradiate due to lack of time. On the basis of the results obtained with the cocrystals that were irradiated, we have estimated the chances of reactivity for each. These cocrystals are listed in Table 25.

Table 25 | List of confirmed cocrystals that were not photoactivated yet.

N° of cocrystal	Target molecule	Coformer	Expected irradiation results
CC-10	4MTCA	3-nitrobenzoic acid	NR
CC-12 Form I	TCA	4,4'-bipyridine	(α -truxillic acid)
CC-12 Form II	TCA	4,4'-bipyridine	(β -truxinic acid)
CC-16	COUM	4,4'-bipyridine	NR
CC-21 Form I	4MTCA	4-nitrobenzoic acid	NR
CC-21 Form II	4MTCA	4-nitrobenzoic acid	NR

CC-10: 4MTCA / 3-nitrobenzoic acid

This single crystal was obtained by slow solvent evaporation (MeOH) in a fridge at 5°C.

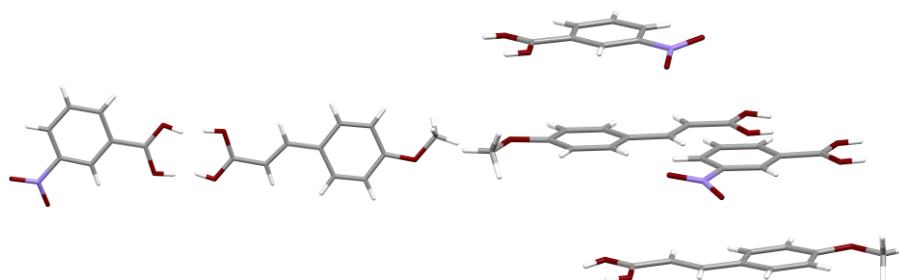


Figure 203 | Asymmetric unit of cocrystal 4MTCA / 3-nitrobenzoic acid, view along a axis.

Figure 204 | Representation of cocrystal 4MTCA / 3-nitrobenzoic acid.

By observing this structure in Figure 203 (Carboxylic acids appear here with two protons because the position of these is not determined.), it is quite easy to see that the double bonds of the 4MTCA molecules are located one above the other in quasi-parallel

planes. However, they are not in the same direction. Moreover, the distance between the carbons of these double bonds is 7.615 Å and 6.770 Å, which cannot lead to reaction.

CC-12 Form I: TCA / 4,4'-bipyridine

This single crystal was obtained by slow solvent evaporation (ACN) in a fridge at 5°C.

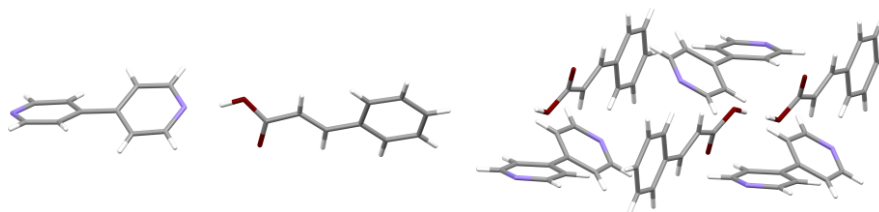


Figure 205 | Asymmetric unit of cocrystal (Form I) TCA / 4,4'-bipyridine, view along a axis.

Figure 206 | Representation of cocrystal (Form I) TCA / 4,4'-bipyridine.

The closest TCA molecules, i.e. the two on the left in Figure 206 are in parallel planes and their double bonds are in the same direction. However, they are not one above the other, and the distance between them is 5.603 Å. The dimer towards which the dimerization could lead is the « head-to-tail », which is not very interesting since it is the one obtained with the stable form of TCA.

CC-12 Form II: TCA / 4,4'-bipyridine

This single crystal was obtained by slow solvent evaporation (EtOH) in a fridge at 5°C.

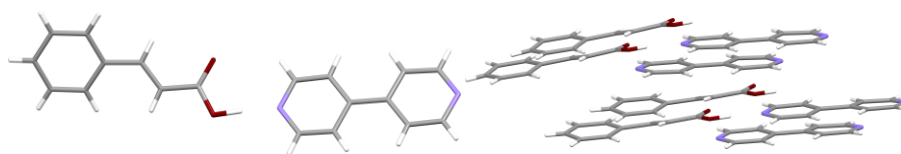


Figure 207 | Asymmetric unit of cocrystal (Form II) TCA / 4,4'-bipyridine, view along b axis.

Figure 208 | Representation of cocrystal (Form II) TCA / 4,4'-bipyridine.

In this polymorph of CC-12, the TCA molecules are nearly one above the other and oriented so as to lead to the « head-to-head » dimer. However, they are in non-parallel planes. The distance between the

carbons of the double bonds is 5.104 Å and 5.083 Å. It would be interesting to irradiate this form to see if it could lead to the « head-to-head » dimer.

CC-16: COUM / 4,4'-bipyridine

This single crystal was obtained by slow solvent evaporation (ACN) in a fridge at 5°C.

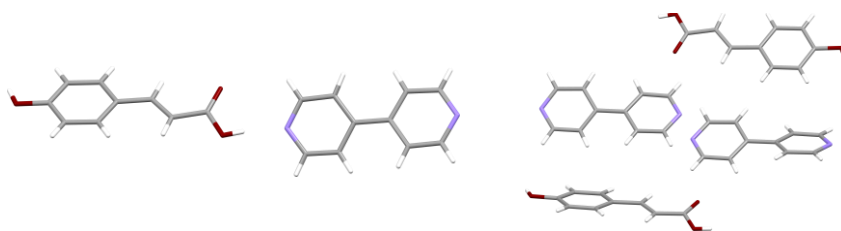


Figure 209 | Asymmetric unit of cocrystal COUM / 4,4'-bipyridine, view along b axis.

Figure 210 | Representation of cocrystal COUM / 4,4'-bipyridine.

In this structure, no dimerization reaction is expected. The COUM molecules are in non-parallel planes and not one above the other. The double bonds are in different orientations and their carbons are spaced 10.028 Å and 9.851 Å apart.

CC-21 Form I: 4MTCA / 4-nitrobenzoic acid

This single crystal was obtained by slow solvent evaporation (DCM) in a fridge at 5°C.

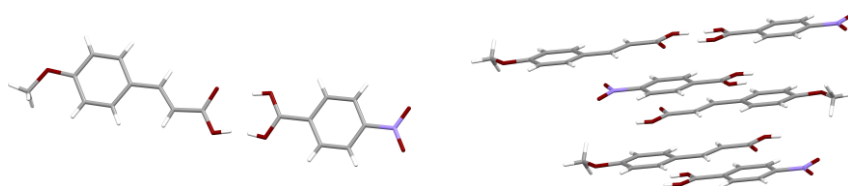


Figure 211 | Asymmetric unit of cocrystal (Form I) 4MTCA / 4-nitrobenzoic acid, view along a axis.

Figure 212 | Representation of cocrystal (Form I) 4MTCA / 4-nitrobenzoic acid.

In this structure, the dimer that could be obtained is the « head-to-tail ». If we look at the middle 4MTCA molecule with the top one in Figure 212, we see that they lie in parallel planes and are separated by 5.563 Å. (Carboxylic acids appear here with two protons because the

position of these is not determined). However, they are not at all one above the other. If we look at the middle 4MTCA molecule with the bottom one, we see that they lie in parallel planes and are separated by 5.314 Å. However, again, they are not at all one above the other.

CC-21 Form II: 4MTCA / 4-nitrobenzoic acid

This single crystal was obtained by slow evaporation of solvent (MeOH) in a fridge at 5°C.

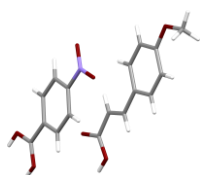


Figure 213 | Asymmetric unit of cocrystal (Form II) 4MTCA / 4-nitrobenzoic acid, view along c axis.

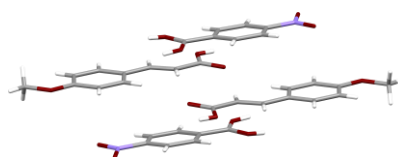


Figure 214 | Representation of cocrystal (Form I) 4MTCA / 4-nitrobenzoic acid.

In this second polymorph of CC-21, the 4MTCA molecules are in planes each time separated by planes of 4-nitrobenzoic acid, see Figure 213 (Carboxylic acids appear here with two protons because the position of these is not determined). This makes the distance between the molecules large by 7.615 Å to lead to the « head-to-head » dimer, otherwise by 5.314 Å to lead to the « head-to-tail » dimer. Unfortunately, in addition to this high distance, the molecules, although in parallel planes, are not one above the other but shifted. Here once again no reactivity is suspected.

3.5 Analysis of the reactivity of the remaining suspected cocrystals

The photoreactivity of 9 of the remaining 23 suspected cocrystals was studied (note that they were not chosen for any particular reason). In some cases, this is done on the ground material (obtained during screening) and for others on the material obtained from a slurry. The powder diffractograms of the slurries and ground materials are in the Supporting Information p.251.

The slurries were obtained in different solvents. To do this, equimolar amounts of target molecule (1 mmol) and cocrystallization agent (1 mmol) were suspended in about 1 to 2 ml of solvent (commonly used for crystal form screening and readily available in the lab) ($\eta = \pm 2,2 - 9,6 \mu\text{L.mg}^{-1}$). After 7 days of stirring (with seeding with ground material obtained during screening) the different samples were filtered, washed with the corresponding solvent and analyzed by XRPD to verify they corresponded with the forms identified by grinding.

Compounds were placed between two glass plates which were then sealed at the edges with parafilm and then photoactivated with a UV lamp at 350 W for 48 h. It was turned over every hour (except of course during the night), trying to have an equivalent irradiation time for each side. After irradiation, the product obtained was analyzed by ^1H -NMR (300 MHz, DMSO).

It is important to remember that, in ^1H -NMR, « head-to-head » arrangements generate similar patterns for β , ω , μ and δ -truxinic acids, while « head-to-tail » arrangements produce similar patterns for ϵ and peri-truxillic acids. However, the ^1H -NMR pattern for the « head-to-tail » arrangement, α -truxillic acid, is easily discernible as it is the only acid to produce a doublet of a doublet. For unreactive powders, only the parents were present in the ^1H -NMR spectra. For powders that lead to « head-to-tail » dimer (α -truxillic acid), the observed pattern in ^1H -NMR was the one presented in Figure 165 and for powders that lead to « head-to-head » dimer (β -truxinic acid), the observed pattern in ^1H -NMR was the one presented in Figure 166.

Results are summarized in Table 26. For each cocrystal, we indicate whether the irradiated compound came from a slurry (in this case, the solvent used is specified) or whether it came from the ground material obtained during screening. The last column indicates whether the compound used contained traces of the target molecule. If traces of the target molecule are detected, the specific polymorph is identified. This detail is important because the pure target molecule can be reactive to light, which means that the results

observed in ^1H -NMR could stem from its irradiation rather than from the irradiation of the cocrystal itself.

Table 26 | List of 9 suspected cocrystals that have been studied by irradiation. For ^1H -NMR results : « α » for pattern leading to « head-to-tail » dimer and « β » for pattern leading to « head-to-head » dimer. For powder traces: X-poly specifies which polymorph of the target molecule is potentially present in the irradiated powder.

N° of cocrystal	Target molecule	Coformer	^1H -NMR results	Irradiated compound	Powder traces
CC-1	TCA	2-benzoylbenzoic acid	α	Ground material	α -poly
CC-2	4MTCA	2-benzoylbenzoic acid	NR	Ground material	α -poly
CC-14	4MTCA	4,4'-bipyridine	NR	Slurry EtOAc	NT
CC-15	2MTCA	4,4'-bipyridine	NR	Slurry EtOH	α -poly
CC-19	4MTCA	4-aminobenzoic acid	NR	Ground material	NT
CC-22	4MTCA	5-hydroxysophthalic acid	β	Slurry ACN	NT
CC-23	2MCCA	5-hydroxysophthalic acid	α	Ground material	α_2 -poly
CC-24	TCA	Acetoacetamide	α	Slurry MeOH	NT
CC-26	2MCCA	Acetoacetamide	α	Ground material	α_1 -poly

For instance, for CC-1 grinding which potentially leads to α -truxillic acid, this can potentially be due to the presence of trace of α -*trans*-cinnamic acid in the powder.

Curiously for CC-2 grinding (which shows traces of α -4-methoxy-*trans*-cinnamic acid) and CC-15 slurry (which possibly shows traces of α -2-methoxy-*trans*-cinnamic acid), no reaction was observed. One would have expected, for each of these two powders, to observe the « head-to-tail » dimer (α -truxillic acid) due to the presence of the parent compound. A plausible hypothesis would be that the proportion of the initial compounds is considerably lower compared to that of the cocrystal, which itself would be non-reactive. Since irradiation is limited to a thin layer of the surface of the solid, it is possible that the starting compounds were not exposed.

CC-23 grinding potentially contains excess of α_2 -2-methoxy-*cis*-cinnamic acid, and CC-26 of α_1 -2-methoxy-*cis*-cinnamic acid. When irradiating these parent compounds, we observed no reaction. Here in both cases α -truxillic acid is observed. This can be due to the

formation of a cocrystal. It should nevertheless be mentioned that according to G. M. J. Schmidt irradiation of 2-methoxy-*cis*-cinnamic acid, can lead to isomerization into the *trans* form which could then give *the* « head-to-tail » dimer.

CC-14 slurry powder and CC-19 ground powder shows no traces of the parent derivative and no reaction was observed when the powder was irradiated, contrary to the parent compound. Likely a non-reactive cocrystal is formed here.

The CC-22 slurry is the most interesting case of this list. The diffractogram shows no trace of α -4-methoxy-*trans*-cinnamic acid and ^1H -NMR analysis shows the potential formation of only the « head-to-head » dimer, whereas for the parent compound a mixture of both α -truxillic and β -truxinic acid was found. Efforts should therefore be placed on finding the structure of this cocrystal.

Finally, the CC-24 slurry shows no trace of *trans*-cinnamic acid and ^1H -NMR analysis shows the potential formation of « head-to-tail » dimer (α -truxillic acid).

These various presumed results, based on ^1H -NMR data, can only be confirmed after analysis of the crystal structures of the cocrystals before irradiation. It is important to remember that for *cis* compounds, isomerization to the *trans* form is possible, this increases the number of possible dimers. Up to 15 different dimers can be formed from *cis* and *trans* acids, and many show very similar ^1H -NMR patterns. Another method for determining the regioisomer formed would be to successfully crystallize the compound after irradiation, which would allow more precise identification.

It would be relevant to review the irradiation parameters applied to non-reactive cocrystals to identify any variables that may influence the results. This includes the wavelength of the light used, the duration of exposure and the intensity of irradiation. Variation in these parameters could reveal new reactivity dynamics not initially observed.

4. Conclusion and perspectives

In this study, we explored the solid-state photodimérisation of *trans*-cinnamic acid and five of its derivatives, illustrating how cocrystallization can strategically be used to thermodynamically control the formation of regioisomers. We find that alignment and distance between double bonds are often major constraints on photoreactivity. However, with a suitable coformer, it is possible to control this photoreactivity. Throughout this project, 12 cocrystals were characterized. For two systems, two polymorphic cocrystals have been identified. This makes a total of 14 new cocrystal structures. Of these 14, 5 showed no photo-dimerization reaction, 2 yielded α -truxillic acid (which is predominantly obtained with pure compounds) and only 1 yielded β -truxinic acid. The other 6 were not irradiated due to time constraints. For *trans*-cinnamic acid, its cocrystallization with 4,6-dichlororesorcinol represents a thermodynamically stable route to β -truxinic acid, while the stable polymorph of the parent compound produces α -truxillic acid. However, this regioisomer can also be obtained by other methods in solution, as described in the introduction to this chapter.

A difficulty encountered in this project was the characterization of the products obtained after irradiation. In ^1H -NMR, the different regioisomers of truxillic and truxinic acids give very similar patterns. This implies that to confirm which regioisomer was obtained, we had to identify the crystal structure of each cocrystal, a not always obvious step that requires many experiments under different conditions. Through our analyses of the crystal structures of cocrystals, when available, we have observed that the « head-to-tail » molecular arrangements, leading to α -truxillic acid, and the « head-to-head » arrangement, leading to β -truxinic acid, are the most widespread. To date, we have not identified a « head-to-tail » arrangement leading to one of the other two truxillic acids (obtainable from a *cis-cis* or *trans-trans* composition: ϵ -truxillic acid or peri-truxillic acid) or a « head-to-head » arrangement leading to one of the other five truxinic acids

(obtainable from a *cis-cis* or *trans-trans* composition: ω -truxinic acid, μ -truxinic acid or its enantiomer, δ -truxinic acid or its enantiomer). It should also be remembered that, since *cis-trans* isomerizations are possible, there are six other potential dimers (epi-truxillic acid, γ -truxillic acid, neo-truxinic acid or its enantiomer, ζ -truxinic acid or its enantiomer). However, these were not observed in this study.

This study, although carried out with a limited number of coformers, effectively illustrates how cocrystal engineering can be used not only to activate or deactivate photoreactivity, but also to thermodynamically control the regioisomer of the resulting photoproduct. The use of cocrystallization to orient molecules within the crystal to control the regioisomers resulting from the reaction remains a promising approach. However, the development of this method relies heavily on an empirical approach of trial and error. At present, it is difficult to predict in advance how and with which coformer a compound of interest will cocrystallize, making coformer screenings essential to increase the chances of finding a cocrystal that will steer the molecules in the desired direction. At this stage, this project shows a high dependence on chance to find the perfect cocrystal that respects the various solid-state reaction criteria and leads to a regioisomer different from those usually obtained. Furthermore, a coformer that is beneficial for one cinnamic acid derivative is not automatically beneficial for other derivatives. This reflects one of the common difficulties in crystal engineering, namely predicting the formation of crystal structures and the arrangement of molecules within the crystal. Such a project, based on a trial-and-error methodology, could one day be optimized through the use of rapid and efficient *in silico* screening. Such an approach would make it possible to simulate interactions between the target molecule and various coformers, thus predicting possible molecular orientations before the physical synthesis of the cocrystals, significantly reducing the time and resources needed to identify favorable arrangements.

A further improvement for the coming years could be to work on the irradiation step which is found. In our set-up, a sample was placed in a double glass plate, and turned over every hour, slightly rubbing the plates to expose more powder. Optimization of solid phase irradiation remained very low. The use of all the performances and assets of the UV lamp have been little exploited and could be better controlled. The use of filters could help to increase the yield of the reactions and avoid the dissociation of the cyclobutanes towards the starting monomers. Exploiting the full power of the lamp could increase the reaction rate, while being careful not to melt the irradiated compound.

From the perspective of solvent-free reactions, this project can be incorporated without too much difficulty if we consider the formation of the cocrystal in the solid-state using ball-milling. It would be interesting to couple the grinding to the irradiation. This could be done in small quantities with PMMA (poly acrylic methyl methacrylate) or glass grinding bowls while ensuring that the desired wavelengths can pass through. PMMA could deteriorate at certain wavelengths. On the other hand, if we want to consider industrial production, there is still a certain way to go concerning the set up.

Just as it has already been shown that the use of a catalytic quantity of the coformer during dimerization reactions with a compound that is unreactive in its pure state, kinetic studies could be considered concerning the formation of the cocrystal and the reactivity under irradiation. Indeed, if the reactivity of the cocrystal is much faster than the reactivity of the pure cinnamic acid derivative, it would be possible to consider using the coformer as a catalyst. While continuously irradiating a grinding in which the cocrystal would be form, irradiation of this one and detachment of the coformer could then form another cocrystal with other molecules of the cinnamic acid derivative still available.

CONCLUSIONS

The overall conclusion of this thesis focuses on the application of crystal engineering techniques to specific solid-state based chemical reactions. The general aim of this work was to combine crystal engineering with the concepts of solid-state reactivity, more specifically to examine how the nature of the solid can be exploited to control the regio- and stereochemistry of reactions occurring in the solid-state or mechanochemically. Focusing on two model systems, aldolisation and cyclisation, we demonstrated throughout this thesis that the selectivity of reactions can indeed be controlled by fine-tuning the solid-state.

In chapter II, we focused on the solid-state reaction of proline-catalyzed asymmetric aldolisation. Our results reveal that the use of proline cocrystals as catalysts can significantly affect the enantiomeric excess (ee) of the final product. This effect, however, varies strongly depending on the type of cocrystal used. The use of a proline/fumaric acid cocrystal in an organocatalyzed aldolisation reaction can improve selectivity, sometimes reaching close to 100% ee. This study, however, highlights the difficulties encountered in terms of the reproducibility and stability of solid-phase reactions, particularly when homogenizing the reagents. Although the use of different cocrystals has led to a significant improvement in selectivity in some cases, it is constrained by practical and industrial limitations, mainly related to the time and resources needed to refine and optimize the reaction conditions. Our observations do corroborate the hypothesis that the non-linear effects observed in asymmetric solid-phase syntheses can be attributed to the phase behavior of the catalyst, the ee of the product being strongly influenced by the nature of the coformer used.

Chapter III explored the engineering of cocrystals for the photodimerization of cinnamic acids and their derivatives. This research illustrated how cocrystallization can be strategically used to

control regioisomer formation through thermodynamic control. Although this method has been successful in determining certain molecular arrangements leading to specific isomers, it is largely empiric. The chapter highlights the challenges associated with identifying crystal structures and confirming the isomers formed, requiring repeated experiments and a variety of analytical techniques.

These chapters demonstrate the strength but also the limitations of crystal engineering in the context of solid-state organic chemical synthesis. The two topics covered in this thesis are based on the identification of suitable solid phases. Predicting the structures that can form between a compound of interest and different coformers could be a way forward. Feeding structural databases with numerous co-crystal structures could feed artificial intelligence algorithms that would enable the development of predictive tools. These tools would make it possible to go beyond lengthy screening as we have been doing. Future research could benefit from the increased use of *in silico* simulations to predict molecular interactions before physical synthesis, thereby reducing the resources needed to identify favorable molecular arrangements. Innovations in this area could potentially bring this research up to industrial level, although many practical and theoretical hurdles remain to be overcome.

Although complex, this type of project represents a stimulating challenge for young researchers and contributes to advancing our understanding of the mechanisms of solid-state organic synthesis, particularly in systems involving semi-molten reactive phases (eg. aldolisation) and systems involving solid reactive phases (eg. cyclisation).

APPENDICES

1. Instruments

Vibratory ball-milling: Retsch MM 400 Mixer Mill (Haan, Allemagne) with two grinding jars in which five 2 mL Eppendorf tubes can be placed.

Planetary ball-milling: Fritsch Pulverisette 7 premium with two bowl compartments. Bowls: 45 mL stainless steel (Fristch 50.9750.00) or 45 mL tungsten carbide (Fristch 50.9740.00) or 45 mL zirconium oxide (Fristch 50.9760.00). Balls: 10 mm stainless steel (Fristch 55.0100.09) or 10 mm tungsten carbide (Fristch 55.0100.08) or 5 mm zirconium oxide (Fristch 55.0050.27).

Tencan XQM-0.4A with four bowl compartments. Bowls: 50 mL zirconium oxide. Balls: 5 mm zirconium oxide balls.

PXRD: PANalytical Bragg-Brentano diffractometer using a X'Celerator detector and a source of Ni-filtered $\text{CuK}\alpha$ ($\lambda = 1.54179 \text{ \AA}$) at 45 kV and 30 mA. Each sample was analyzed between 5 and 35 ° in 2θ angle values with a step size of ca. 0.0167° and a total scan time of 6 minutes and 42 seconds.

DRX: Oxford Diffraction Gemini R Ultra Diffractometer (Ruby CCD detector using $\text{CuK}\alpha$ radiation). Images have been integrated by «CrysAlisPRO» software. The resolution and the refinement have been done using «SHELXT» and «SHELX-2014/7» respectively. Symmetry analysis and validation were carried out using «PLATON» software. Pictures were made using the molecular visualization software «mercury 2022.3.0». CCDC were used to found crystallographic data and they were charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

^1H -NMR: Bruker Avance II 300 spectrometer operating at 300 MHz.

Bruker Avance 500 NMR spectrometer operating at 500 MHz.

HPLC: Normal HPLC Device: Waters 600; Detector: Waters 996 Photodiode Array Detector (PDA) (Max Plot)

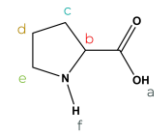
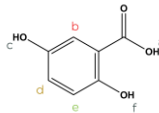
Reverse HPLC Device: Waters Alliance 2695; Detector: Waters 2998 Photodiode Array Detector (PDA) (Max Plot)

UV Lamp: Oriel Instrument: Universal Arc Lamp Housing (model: 66921; source: Hg(Xe))

2. Supporting Information to Chapter II

2.1 NMR results for cocrystal between proline and 2,5-dihydroxybenzoic acid

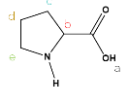
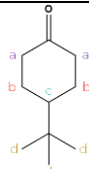
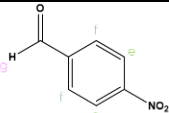
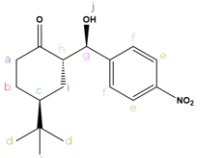
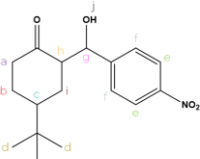
Table 27 | NMR results for slurry in DCM, ACN and MeOH with DL-proline and 2,5-dihydroxybenzoic acid. With area integration of H at δ 7.27 for 2,5-dihydroxybenzoic acid and H at δ 4.00 for proline.

NMR results		
Proline	¹ H-NMR (500 MHz, CD ₃ OD) δ 4.00 (dd, J = 8.7, 6.3 Hz, 1H), 3.41 (dt, J = 11.4, 6.9 Hz, 1H), 3.26 (dt, J = 11.4, 7.3 Hz, 1H), 2.32 (m, 1H), 2.13 (td, J = 13.4, 6.3 Hz, 1H), 1.99 (m, 2H).	
25DHBA	¹ H-NMR (500 MHz, CD ₃ OD) δ 7.27 (d, J = 3.1 Hz, 1H), 6.98 (dd, J = 8.9, 3.1 Hz, 1H), 6.79 (d, J = 8.9 Hz, 1H).	
Slurry DCM	¹ H-NMR (500 MHz, CD ₃ OD) δ 7.27 (d, J = 3.1 Hz, 1H), 6.95 (dd, J = 8.9, 3.1 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 4.05 (dd, J = 8.7, 6.4 Hz, 1H), 3.4 (dt, J = 11.4, 6.9 Hz, 1H), 3.27 (dt, J = 11.4, 7.3 Hz, 1H), 2.34 (m, 1H), 2.14 (td, J = 13.5, 6.4 Hz, 1H), 2.01 (m, 2H).	
Slurry ACN	¹ H-NMR (500 MHz, CD ₃ OD) δ 7.27 (d, J = 3.1 Hz, 1H), 6.95 (dd, J = 8.9, 3.1 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 4.04 (dd, J = 8.7, 6.4 Hz, 1H), 3.4 (dt, J = 11.4, 6.9 Hz, 1H), 3.26 (dt, J = 11.4, 7.3 Hz, 1H), 2.33 (m, 1H), 2.14 (td, J = 13.5, 6.4 Hz, 1H), 2.01 (m, 2H).	
Slurry MeOH	¹ H-NMR (500 MHz, CD ₃ OD) δ 7.27 (d, J = 3.1 Hz, 1H), 6.95 (dd, J = 8.9, 3.1 Hz, 1H), 6.77 (d, J = 8.9 Hz, 1H), 4.02 (dd, J = 8.7, 6.3 Hz, 1H), 3.4 (dt, J = 11.4, 6.9 Hz, 1H), 3.26 (dt, J = 11.4, 7.3 Hz, 1H), 2.33 (m, 1H), 2.14 (td, J = 13.5, 6.3 Hz, 1H), 2 (m, 2H).	

Slurry	25DHBA (area integration)	Proline (area integration)	Ratio (25DHBA / proline)
DCM	1.00	0.985	50.4 / 49.6
ACN	1.00	1.029	49.3 / 50.7
MeOH	1.00	1.940	34.0 / 66.0

2.2 NMR results for aldolization reaction between 4-tert-butylcyclohexanone and 4-nitrobenzaldehyde catalyzed by proline

Table 28 | NMR results of the solid compound suspended in diethyl ether as well as the part dissolved in diethyl ether.

NMR results		
Proline	¹ H-NMR (300 MHz, D ₂ O) δ 3.96 (dd, J = 8.8, 6.3 Hz, 1H), 3.26 (m, 1H), 3.16 (dt, J = 11.4, 7 Hz, 1H), 2.19 (td, J = 14.1, 6.3 Hz, 1H), 1.88 (m, 1H + 2H). ¹ H-NMR (500 MHz, CD ₃ OD) δ 4.00 (dd, J = 8.7, 6.3 Hz, 1H), 3.41 (dt, J = 11.4, 6.9 Hz, 1H), 3.26 (dt, J = 11.4, 7.3 Hz, 1H), 2.32 (m, 1H), 2.13 (td, J = 13.4, 6.3 Hz, 1H), 1.99 (m, 2H).	
4-tert-butylcyclohexanone	¹ H-NMR (300 MHz, DMSO-d ₆) δ 2.36 (m, 2H), 2.18 (m, 2H), 1.99 (m, 2H), 1.50 (m, 1H), 1.34 (m, 2H), 0.88 (s, 9H).	
4-nitrobenzaldehyde	¹ H-NMR (300 MHz, DMSO-d ₆) δ 10.15 (s, 1H), 8.39 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H).	
Found in solid suspension in diethyl ether 4tBCH-anti-1a-(S, S, R) 4tBCH-anti-2a-(R, R, S)	¹ H-NMR (300 MHz, DMSO-d ₆) δ 8.22 (d, J = 8.8 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 5.74 (d, J = 4.9 Hz, 1H), 5.19 (dd, J = 9.8, 4.9 Hz, 1H), 2.72 (m, 1H), 2.17 (m, 1H), 2.03 (m, 1H), 1.88 (m, 1H), 1.32 (m, 3H), 0.77 (s, 9H).	
Found dissolved in diethyl ether (with also anti-1a and anti-2a) 4tBCH enantiomers 1 4tBCH enantiomers 2	¹ H-NMR (300 MHz, DMSO-d ₆) δ 8.16 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 5.47 (d, J = 4.7 Hz, 1H), 5.05 (m, 1H), 2.71 (m, 1H), 2.14 (m, 1H), 2.03 (m, 1H), 1.92 (m, 1H), 1.30 (m, 3H), 0.81 (s, 9H).	

2.3 Chiral reverse HPLC results for 4-tert-butylcyclohexanone with various supplier of 4-nitrobenzaldehyde

Table 29 | Chiral reverse HPLC result for 4-tert-butylcyclohexanone and different supplier of 4-nitrobenzaldehyde.

ee L-proline	4tBCH-anti-a2-(R, R, S)		4tBCH-anti-a1-(S, S, R)		ee (S, S, R)
	Retention time (min)	Area	Retention time (min)	Area	
Using 4-nitrobenzaldehyde from TCI (FEMZH-GI)					
20,23	4,240	7944837	5,122	19455681	42,01
20,92	4,257	1868340	5,218	4230567	38,73
20,59	4,255	2025647	5,206	4871641	41,26
20,71	4,253	1586207	5,200	3556588	38,31
20,74	4,252	1437794	5,194	3678555	43,80
20,92	4,245	634788	5,153	1402269	37,68
20,59	4,246	2205042	5,147	4727611	36,39
20,71	4,243	1961989	5,144	4431288	38,62
20,74	4,243	1433691	5,146	3647026	43,56
Using 4-nitrobenzaldehyde from Thermo Scientific (10215224)					
50,22	4,337	5090686	5,346	9485808	30,15
49,67	4,334	3225256	5,343	6238854	31,84
50,00	4,333	1353881	5,344	2691580	33,07
50,00	4,336	1288335	5,341	2445013	30,98
79,78	4,342	2277088	5,337	4417943	31,98
79,70	4,346	1075549	5,340	2261946	35,55
19,83	4,334	2460227	5,327	4645358	30,75
20,13	4,334	4434063	5,322	6747672	20,69
95,01	4,333	821050	5,321	3544158	62,38
94,77	4,342	26523	5,322	134974	67,15
4,81	4,332	17817	5,330	19358	4,15
5,03	4,327	2122898	5,310	2327730	4,60
20,99	4,329	9312	5,324	15489	24,91
20,04	4,324	2099429	5,302	3927851	30,34
80,13	4,325	3959227	5,295	8551853	36,71
78,83	4,326	957442	5,301	2342944	41,98
5,06	4,243	4466901	5,177	6359454	17,48

9,76	4,247	1939630	5,182	3696674	31,17
30,31	4,244	3237152	5,173	6903898	36,16
49,09	4,244	2930273	5,172	5787905	32,78
59,77	4,241	6454422	5,160	13818884	36,33
79,51	4,242	4941463	5,164	11176597	38,68
89,38	4,244	1700863	5,174	4601505	46,02
94,90	4,241	3522086	5,159	11136135	51,94
79,50	4,247	2921293	5,183	7078039	41,57
9,78	4,247	2550974	5,187	4095356	23,24
91,15	4,244	11295826	5,155	28294791	42,94
94,95	4,249	2117396	5,181	6542168	51,10
79,50	4,222	2041057	5,126	5562933	46,32
9,78	4,218	5302249	5,124	8202730	21,48
91,15	4,221	4477832	5,111	13005495	48,78
94,95	4,225	2046370	5,151	7504876	57,15
Using 4-nitrobenzaldehyde from Sigma-Aldrich (S8160866132)					
10,11	4,214	783786	5,122	968214	10,53
30,39	4,235	1357175	5,146	2118798	21,91
59,61	4,233	3739101	5,136	6236095	25,03
89,82	4,265	1496508	5,144	2614279	27,19
9,98	4,236	1335085	5,149	1821871	15,42
28,77	4,236	1199607	5,149	1790916	19,77
59,30	4,238	1044115	5,150	1643121	22,29
89,69	4,237	1033310	5,148	1670626	23,57
5,41	4,236	1102583	5,151	1189951	3,81
39,27	4,234	2625386	5,141	4196324	23,03
69,91	4,226	1432714	5,136	2757819	31,62
93,68	4,189	503555	4,649	1598048	52,08
8,39	4,219	1061022	5,128	1312729	10,60
84,95	4,218	557615	5,131	968177	26,91
98,20	4,221	815643	5,125	2309144	47,80
71,54	4,224	917494	5,134	1313574	17,75
20,88	4,243	2596214	5,145	3634580	16,67
20,91	4,243	2666213	5,142	3740614	16,77
20,09	4,244	1640842	5,149	2565600	21,98
20,33	4,243	2767960	5,145	4221747	20,80
21,21	4,243	2193989	5,146	3616872	24,49
49,11	4,241	3477697	5,141	5382347	21,50
50,86	4,242	2725580	5,144	4318753	22,62

79,42	4,245	1693148	5,147	2333381	15,90
79,62	4,240	2855184	5,140	4533102	22,71
79,85	4,244	1832074	5,148	2809770	21,06
79,40	4,244	1901050	5,148	3151829	24,75
79,63	4,243	1256889	5,149	2077274	24,61
79,66	4,244	1504102	5,148	2516271	25,18
78,96	4,242	2315831	5,143	3736064	23,47
80,25	4,239	1424689	5,145	2440108	26,27
70,11	4,220	646198	5,135	1099565	25,97
11,86	4,224	1218449	5,139	1730535	17,36
89,82	4,223	656489	5,136	1355733	34,75
50,60	4,220	3576524	5,126	6032372	25,56
70,11	4,250	5017373	5,199	7159218	17,59
11,86	4,249	5020828	5,197	5789873	7,11
89,82	4,250	1142534	5,198	2010874	27,54
50,60	4,248	3643762	5,192	5193606	17,54

2.4 Chiral reverse HPLC result for 4-tert-butylcyclohexanone and various parameters

Table 30 | Chiral reverse HPLC result for 4-tert-butylcyclohexanone and various parameters

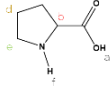
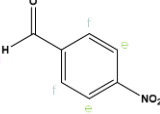
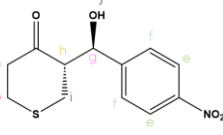
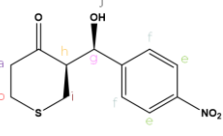
ee L-proline	4tBCH-anti-a2-(R, R, S)		4tBCH-anti-a1-(S, S, R)		ee (S, S, R)
	Retention time (min)	Area	Retention time (min)	Area	
Using 10 mm zirconium oxide balls					
20,13	4,304	1349049	5,265	3098042	39,33
19,57	4,305	1733821	5,265	3599007	34,98
79,57	4,305	2326558	5,260	6364853	46,46
79,83	4,305	3207907	5,258	8324377	44,37
Using 3 mm zirconium oxide balls					
19,96	4,305	3506620	5,260	6434344	29,45
19,83	4,308	1609730	5,265	3070114	31,21
79,87	4,304	3316427	5,254	7350550	37,82
79,78	4,306	1975146	5,257	5122671	44,34
Using 2 eq of reagent					
20,20	4,324	983165	5,299	2255153	39,28
20,15	4,321	1074809	5,296	2264629	35,63
80,11	4,323	1023328	5,294	2740132	45,62
79,59	4,321	1271056	5,288	3687639	48,73
Using 4 eq of reagent					
19,84	4,315	3004479	5,28	6128844	34,21
19,71	4,315	114098	5,288	193487	25,81
80,24	4,313	52451	5,286	187598	56,30
80,12	4,312	1853581	5,275	4709847	43,52
Using 0,4 eq of proline					
20,26	4,303	1710930	5,259	3355673	32,46
19,74	4,303	2508541	5,255	5095292	34,02
49,84	4,301	3981027	5,25	8543353	36,43
50,00	4,302	956842	5,259	2276424	40,81
80,02	4,302	2833105	5,251	6761031	40,94
79,89	4,3	1561207	5,251	3781026	41,55
Using 0,8 eq of proline					
20,42	4,31	984189	5,261	2245983	39,06

Appendices

19,42	4,315	2509645	5,257	5094124	33,99
79,96	4,311	3316472	5,264	7355418	37,85
79,49	4,312	1564965	5,259	3784521	41,49
Using 60 g balls of 5 mm					
20,31	4,311	2501697	5,276	4115901	24,39
20,43	4,305	4824333	5,262	8861680	29,50
79,96	4,306	1698286	5,267	4555239	45,69
79,56	4,304	1411051	5,264	3507145	42,62

2.5 NMR results for aldolization reaction between tetrahydro-4H-thiopyran-4-one and 4-nitrobenzaldehyde catalyzed by proline

Table 31 | NMR results for aldolization reaction between tetrahydro-4H-thiopyran-4-one and 4-nitrobenzaldehyde catalyzed by proline.

NMR results		
Proline	¹ H-NMR (300 MHz, D ₂ O) δ 3.96 (dd, J = 8.8, 6.3 Hz, 1H), 3.26 (m, 1H), 3.16 (dt, J = 11.4, 7 Hz, 1H), 2.19 (td, J = 14.1, 6.3 Hz, 1H), 1.88 (m, 1H + 2H). ¹ H-NMR (500 MHz, CD ₃ OD) δ 4.00 (dd, J = 8.7, 6.3 Hz, 1H), 3.41 (dt, J = 11.4, 6.9 Hz, 1H), 3.26 (dt, J = 11.4, 7.3 Hz, 1H), 2.32 (m, 1H), 2.13 (td, J = 13.4, 6.3 Hz, 1H), 1.99 (m, 2H).	
tetrahydro-4H-thiopyran-4-one	¹ H-NMR (300 MHz, DMSO-d) δ 2.93 (m, 4H), 2.57 (m, 4H).	
4-nitrobenzaldehyde	¹ H-NMR (300 MHz, DMSO-d) δ 10.15 (s, 1H), 8.39 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 8.8 Hz, 2H).	
OT-anti-1-(S,R) OT-anti-2-(R,S)	¹ H-NMR (300 MHz, DMSO-d) δ 8.23 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 5.82 (d, J = 4.9 Hz, 1H), 5.37 (dd, J = 7.8, 4.9 Hz, 1H), 2.86 (m, 4H), 2.63 (m, 1H), 2.37 (m, 1H).	
OT-anti-1-(S,R) OT-anti-2-(R,S) With traces of another enantiomer couple (OT-syn-1-(R,R) and OT-syn-2-(S,S))	¹ H-NMR (300 MHz, DMSO-d) δ 8.28 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 5.72 (d, J = 4.8 Hz, 1H), 5.15 (dt, J = 10.1, 4.8 Hz, 1H).	

2.6 Chiral reverse HPLC results for tetrahydro-4H-thiopyran-4-one with native proline

Table 32 | Chiral reverse HPLC results for tetrahydro-4H-thiopyran-4-one with native proline.

ee L-proline	OT-anti-2-(R, S)		OT-anti-1-(S, R)		ee (S, R)
	Retention time (min)	Area	Retention time (min)	Area	
19,70	9,769	3512446	10,758	7726840	37,50
20,13	9,777	4307079	10,82	9804481	38,96
49,89	9,784	4408120	10,866	10382377	40,39
49,35	9,808	800372	10,938	1827181	39,08
79,65	9,799	2884412	10,952	7367463	43,73
80,31	9,817	1435184	11,003	3813777	45,32
10,02	9,671	7217040	10,067	14340298	33,04
9,41	9,671	18767511	10,271	33017126	27,52
9,41	9,772	26884352	11,366	44291277	24,46
4,98	9,739	9075634	10,49	9920495	4,45
4,77	9,772	5944157	10,623	7790171	13,44
4,77	9,838	9789624	11,5	12164715	10,82
90,28	9,795	5022587	10,764	17122893	54,64
90,28	9,834	12130165	11,453	38064376	51,67

2.7 Slurry diffractograms of proline cocrystals

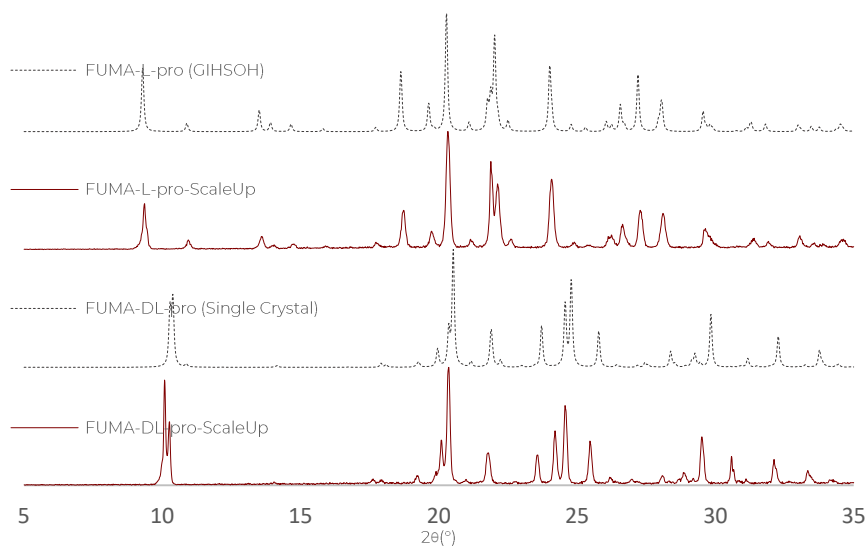


Figure 215 | Experimental diffraction patterns of slurry between proline and fumaric acid in ethanol. (full red lines). Simulated diffraction patterns of cocrystals (dashed black lines).

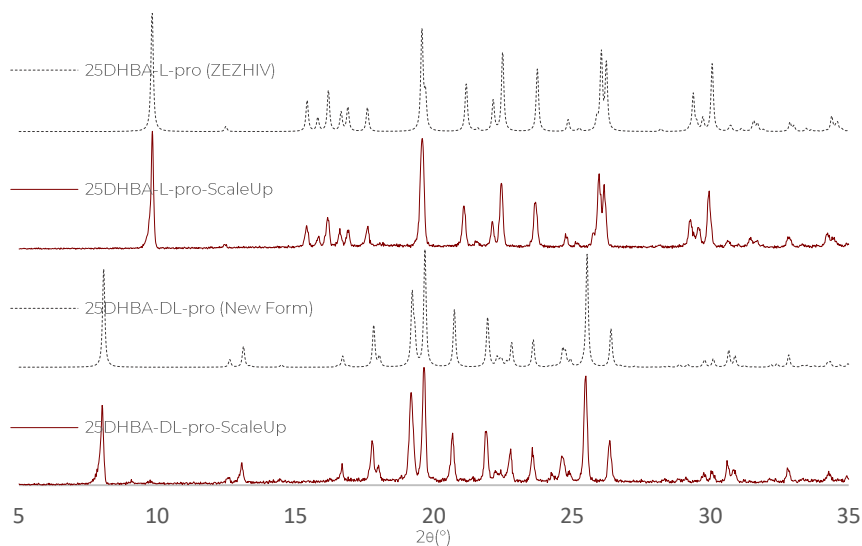


Figure 216 | Experimental diffraction patterns of slurry between proline and 2,5-dihydroxybenzoic acid in acetonitrile. (full red lines). Simulated diffraction patterns of cocrystals (dashed black lines).

2.8 Chiral reverse HPLC results for tetrahydro-4H-thiopyran-4-one using 2,5-dihydroxybenzoic acid – proline cocrystal

Table 33 | Chiral reverse HPLC results for tetrahydro-4H-thiopyran-4-one using 2,5-dihydroxybenzoic acid – proline cocrystal.

ee L-proline	OT-anti-2-(R, S)		OT-anti-1-(S, R)		ee (S, R)
	Retention time (min)	Area	Retention time (min)	Area	
2,5-dihydroxybenzoic acid – proline cocrystal					
20,06	9,861	16561081	11,846	52631574	52,13
20,11	9,833	22376971	11,822	55185776	42,30
49,95	9,825	24961481	11,809	65280730	44,68
49,91	9,786	31784471	11,743	77845695	42,02
79,94	9,873	12365127	11,882	24687202	33,26
80,04	9,886	7859902	11,879	31493050	60,05
20,06	9,679	1838572	10,371	3313785	28,63
20,11	9,721	2669106	10,622	4761039	28,15
49,95	9,734	5341816	10,827	11070354	34,90
49,91	9,771	2950524	10,975	6935946	40,31
79,94	9,747	16871569	11,083	32658121	31,87
80,04	9,8	7067227	11,23	13811231	32,30

2.9 Chiral reverse HPLC results for tetrahydro-4H-thiopyran-4-one using fumaric acid

Table 34 | Chiral reverse HPLC results for tetrahydro-4H-thiopyran-4-one using 2,5-dihydroxybenzoic acid – proline cocrystal.

ee L-proline	OT-anti-2-(R, S)		OT-anti-1-(S, R)		ee (S, R)
	Retention time (min)	Area	Retention time (min)	Area	
Fumaric acid – proline cocrystal					
20,17	9,92	785421	11,942	25702911	94,07
19,68	9,909	1212894	11,704	69692689	96,58
50,00	9,914	510711	11,775	45203552	97,77
49,86	9,909	709072	11,703	64608537	97,83
80,29	9,91	375832	11,842	26367359	97,19
79,97	9,917	809501	11,864	22502911	93,06
9,85	9,63	162866	10,144	18156296	98,22
9,53	9,68	197124	10,34	12825929	96,97
19,98	9,701	295436	10,468	18534286	96,86
19,89	9,719	311064	10,598	10426968	94,21
50,37	9,754	289232	10,69	10848272	94,81
61,24	9,759	181183	10,767	12029300	97,03
80,17	9,762	95008	10,856	6326517	97,04
79,57	9,775	306323	10,89	14146604	95,76
90,62	9,791	214836	10,951	13023538	96,75
90,06	9,802	448922	10,978	17485828	94,99
4,84	9,439	915462	11,103	8147911	79,80
5,11	9,85	3782838	11,173	37969131	81,88
5,53	9,675	110264	10,451	5315661	95,94
5,27	9,698	929987	10,629	20679012	91,39
0,00	9,729	1309915	10,823	2363384	28,68
0,00	9,742	2360285	10,911	8998106	58,44
7,62	9,753	2108734	10,958	20023577	80,94
8,07	9,766	1673566	11,033	20041321	84,59
2,69	9,773	3127593	11,125	9423527	50,16
1,99	9,771	4527181	11,161	10852941	41,13
100,00	9,804	245394	11,176	17018643	97,16
100,00	9,809	136048	11,229	11873930	97,73
94,71	9,811	155499	11,282	13211922	97,67

95,02	9,82	331042	11,296	22307524	97,08
100,00	9,814	92593	11,254	12976376	98,58
94,71	9,817	176405	11,277	20593004	98,30
100,00	9,893	130946	11,6	17605185	98,52
100,00	9,88	159902	11,614	21398978	98,52
94,71	9,881	427353	11,581	39003259	97,83
20,17	9,841	921171	11,327	99894130	98,17
19,68	9,837	634909	11,264	34589126	96,40
50,00	9,853	732481	11,282	40411956	96,44
49,86	9,861	475419	11,278	47772193	98,03
80,29	9,869	399271	11,356	33497582	97,64
79,97	9,834	1511171	11,392	63294130	95,34

Table 35 | Chiral reverse HPLC results after 4 days for viscous product.

Fumaric acid – proline cocrystal after 4 days					
5,53	9,835	178502	11,218	10007111	96,50
5,27	9,855	403662	11,314	15452266	94,91
0,00	9,863	773228	11,433	975498	11,57
0,00	9,868	772983	11,474	2200374	48,01
7,62	9,879	347693	11,513	8583453	92,21
8,07	9,878	879184	11,529	15464007	89,24
2,69	9,868	2359999	11,581	10916038	64,45
1,99	9,879	523116	11,613	6794572	85,70

Table 36 | Chiral reverse HPLC results after 7 days for viscous product.

Fumaric acid – proline cocrystal after 7 days					
5,53	0	0	10,689	3675192	100,00
5,27	0	0	10,911	3441502	100,00
0,00	9,759	1444613	11,062	1716545	8,60
0,00	9,773	2217099	11,158	3632893	24,20
7,62	9,804	221888	11,236	5729688	92,54
8,07	9,812	264775	11,29	6919727	92,63
2,69	9,814	298439	11,368	5055719	88,85
1,99	9,816	126537	11,42	1844980	87,16

2.10 Further insight into fumaric acid - proline cocrystal as a catalyst

Table 37 | Further insight into fumaric acid - proline cocrystal as a catalyst.

ee L-proline	OT-anti-2-(R, S)		OT-anti-1-(S, R)		ee (S, R)
	Retention time (min)	Area	Retention time (min)	Area	
proline + fumaric acid					
49,36	0	0	11,43	2632932	100,00
49,92	0	0	11,456	286214	100,00
51,78	0	0	11,484	314625	100,00
78,62	9,731	151360	10,668	15468801	98,06
78,01	9,753	375269	10,913	13474471	94,58
77,94	9,793	64801	11,086	6136668	97,91
20,72	9,791	89482	11,172	10357582	98,29
20,81	9,819	65713	11,245	12983895	98,99
21,02	9,821	450229	11,268	24544471	96,40
proline + maleic acid					
77,94	9,806	4487699	11,35	15226384	54,47
79,99	9,828	2365403	11,424	7275907	50,93
19,42	9,836	2299604	11,47	5750401	42,87
19,77	9,83	4108782	11,486	10864477	45,12
49,06	9,846	1356588	11,534	4376981	52,68
49,99	9,842	3201553	11,541	10435232	53,05

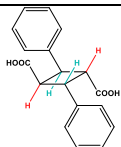
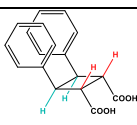
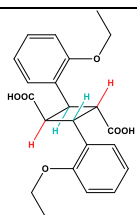
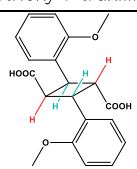
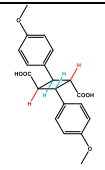
3. Supporting Information to Chapter III

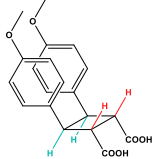
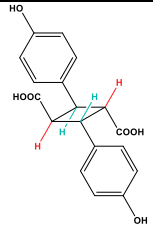
3.1 NMR results for cinnamic acid derivatives irradiation

Table 38 | Reference NMR results for cinnamic acid derivatives.

NMR results for cinnamic acid derivatives		
TCA	¹ H-NMR (300 MHz, DMSOd) δ 12.41 (s, 1H), 7.68 (m, 2H), 7.60 (d, J = 16.0 Hz, 1H), 7.41 (m, 2H + 1H), 6.53 (d, J = 16.0 Hz, 1H).	
2ETCA	¹ H-NMR (300 MHz, DMSOd) δ 12.32 (s, 1H), 7.85 (d, J = 16.2 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.37 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.96 (m, 1H), 6.53 (d, J = 16.2 Hz, 1H), 4.10 (q, J = 7.0 Hz, 1H), 1.38 (t, J = 7.0, 3H).	
2MTCA	¹ H-NMR (300 MHz, DMSOd) δ 12.33 (s, 1H), 7.84 (d, J = 16.2 Hz, 1H), 7.67 (d, J = 7.7, 1H), 7.4 (m, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.98 (m, 1H), 6.51 (d, J = 16.2 Hz, 1H), 3.86 (s, 3H).	
4MTCA	¹ H-NMR (300 MHz, DMSOd) δ 12.23 (s, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 16.0 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 6.38 (d, J = 16.0 Hz, 1H), 3.78 (s, 3H).	
2MCCA	¹ H-NMR (300 MHz, DMSOd) δ 12.31 (s, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.31 (m, 1H), 7.03 (d, J = 4.8 Hz, 1H), 6.99 (s, 1H), 6.90 (m, 1H), 5.94 (d, J = 12.5 Hz, 1H), 3.79 (s, 3H).	
COUM	¹ H-NMR (300 MHz, DMSOd) δ 12.11 (s, 1H), 10.01 (s, 1H), 7.51 (d, J = 16 Hz, 1H), 7.51 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 6.30 (d, J = 16.0 Hz, 1H).	

Table 39 | NMR results for cinnamic acid derivatives after irradiation.

NMR results for cinnamic acid derivatives after irradiation		
Irradiated compound	NMR shift	Identified molecules
α -TCA	$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆) δ 12.11 (s, 2H), 7.29 (m, 10H), 4.28 (dd, J = 10.4, 7.2 Hz, 2H), 3.81 (dd, J = 10.4, 7.2 Hz, 2H).	 α -truxillic acid
β -TCA	$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆) δ 12.41 (s, 2H), 7.04 (m, 10H), 4.20 (d, J = 6.2 Hz, 2H), 3.80 (dd, J = 6.2 Hz, 2H).	 β -truxinic acid (56,2 %)
	$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆) δ 4.28 (dd, J = 10.6, 2H).	+ α -truxillic acid (14,2 %)
	$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆) δ 7.69 (m, 2H), 7.59 (d, J = 16.0 Hz, 1H), 7.42 (m, 3H), 6.53 (d, J = 16.0 Hz, 1H).	+ TCA (29,6 %)
α -2ETCA	$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆) δ 11.86 (s, 2H), 7.20 (m, 4H), 6.91 (m, 4H), 4.41 (dd, J = 10.3, 7.5 Hz, 2H), 4.01 (m, 4H), 3.78 (dd, J = 10.3, 7.5 Hz, 2H), 1.38 (t, J = 6,9 Hz, 6H).	 di-2-ethoxy- α -truxillic acid
2MTCA	$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆) δ 12.13 (s, 2H), 7.10 (m, 4H), 6.81 (m, 4H), 4.39 (dd, J = 10.3, 7.5 Hz, 2H), 3.76 (dd, J = 10.3, 7.5 Hz, 2H), 3.86 (s, 6H).	 di-2-methoxy- α -truxillic acid
4MTCA	$^1\text{H-NMR}$ (300 MHz, DMSO-d ₆) δ 7.26 (d, J = 8.6 Hz, 4H), 6.66 (d, J = 8.6 Hz, 4H), 4.20 (dd, J = 10, 7.7 Hz, 2H), 3.74 (s, 6H).	 di-4-methoxy- α -truxillic acid (26,5 %)

	¹ H-NMR (300 MHz, DMSO-d ₆) δ 6.95 (d, J = 8.7, 4H), 6.88 (d, J = 8.7 Hz, 4H), 4.09 (d, J = 6.4 Hz, 2H), 3.63 (s, 6H).	 + di-4-methoxy-β-truxinic acid (17,6 %)
	¹ H-NMR (300 MHz, DMSO-d ₆) δ 12.21 (s, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 16.0 Hz, 1H), 6.97 (d, J = 8.7 Hz, 2H), 6.37 (d, J = 16.0 Hz, 1H), 3.79 (s, 3H).	+ 4MTCA (55,9 %)
α ₁ -2MCCA	No reaction	N/A
α ₂ -2MCCA	No reaction	N/A
COUM	¹ H-NMR (300 MHz, DMSO-d ₆) δ 11.98 (s, 2H), 9.26 (s, 2H), 7.12 (d, J = 8.5 Hz, 4H), 6.69 (d, J = 8.5 Hz, 4H), 4.12 (dd, J = 10.4, 7.2 Hz, 2H), 3.64 (dd, J = 10.4, 7.2 Hz, 2H).	 di-4-hydroxy-α-truxillic acid (96,6 %)
	¹ H-NMR (300 MHz, DMSO-d ₆) δ 9.96 (s, 1H), 7.50 (d, J = 15.9 Hz, 1H), 7.50 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.29 (d, J = 15.9 Hz, 1H).	+ coumaric acid (3,4 %)

3.2 Coformer tested with cinnamic acid derivatives

Table 40 | List of all cocrystallization agent (coformer) tested with the six cinnamic acid derivatives. In green, those that potentially form a cocrystal with at least one derivative.

Coformers screened in vibratory mill		
1,3-dimethylurea	5-hydroxysophthalic acid	Malonamide
1-hydroxy-2-naphthoic acid	5-tert-butylisophthalic acid	Malonic acid
2,2-dimethylsuccinic acid	Acetoacetamide	Orcinol
2,3-dihydroxybenzoic acid	Anthranilic acid	Oxamide
2,4-dihydroxybenzoic acid	Benzoic acid	Phloroglucinol
2,5-dihydroxybenzoic acid	Bisurea	Phthalic acid
2-benzoylbenzoic acid	Citraconic acid	Pyrogallol
3,4-dihydroxybenzoic acid	Citric acid	Pyromellitic acid
3,5-dihydroxybenzoic acid	Ethyl-gallate	Resorcinol
3-hydroxybenzoic acid	Ethylvanillin	Saccharin
3-nitrobenzoic acid	Ferulic acid	Succinic acid
4,4'-bipyridine	Fumaramide	Terephthalic acid
4,6-dichlororesorcinol	Fumaric acid	Trimesic acid
4-aminobenzoic acid	Gallic acid	Uracil
4-dimethylaminobenzoic acid	Indole	Urea
4-hydroxybenzoic acid	Indole-3-acetic acid	Vanillin
4-nitrobenzoic acid	Isophthalic acid	
5-aminoisophthalic acid	Isophthalohydrazide	

3.3 Crystal structures information of new polymorph of 2-benzoylbenzoic acid

Table 41 | Main crystallographic data of new polymorph of 2-benzoylbenzoic acid.

Compound	2-benzoylbenzoic acid polymorph
Identification code	cb_20_mtca_bba_acn
Empirical formula	C ₁₄ H ₁₀ O ₃
Formula weight (g/mol)	226.22
Temperature (K)	297(2)
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	Pca2 ₁
a,b,c (Å)	a = 26.6927(6) b = 7.17894(15) c = 24.4329(6)
α, β, γ (°)	a = 90 b = 90 g = 90
Volume (Å ³)	4681.95(19)
Z	16
Density calculated (Mg/m ³)	1.284
Absorption coefficient (mm ⁻¹)	0.090
Crystal size (mm ³)	0.17x 0.07 x 0.03
F(000)	1888
Theta range for data collection (°)	2.260 to 25.685
Reflections collected	30947
Independent reflections	8611 [R(int) = 0.0436]
Completeness to theta = 25.96°	99.8
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.99035
Data / restraints / parameters	8611 / 109 / 668
Goodness-of-fit on F ²	1.040
Final R indices [I>2sigma(I)]	R1 = 0.0433, wR2 = 0.1010
R indices (all data)	R1 = 0.0720, wR2 = 0.1128
Largest diff. Peak and hole (eÅ ⁻³)	0.151, -0.149

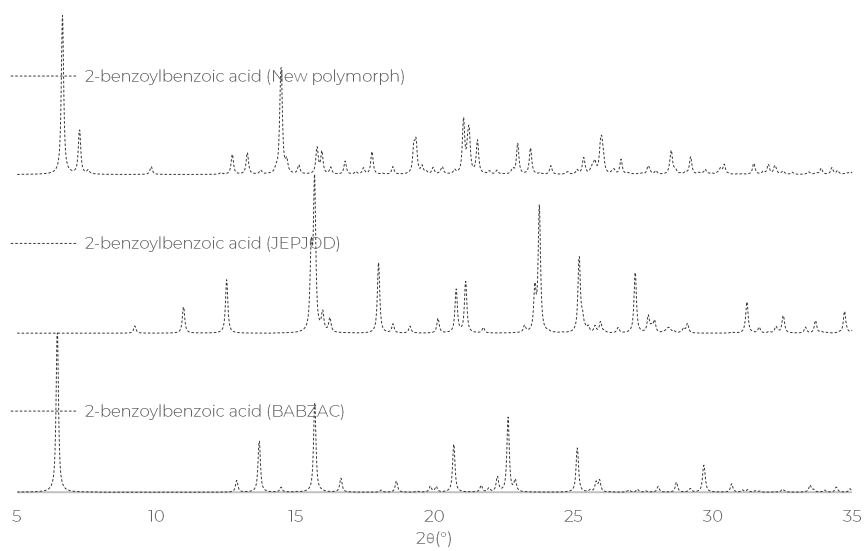


Figure 217 | Simulated powder pattern of 2-benzoylbenzoic acid polymorphs.

3.4 Diffractograms of screening on cinnamic acid derivatives (suspected cocrystals)

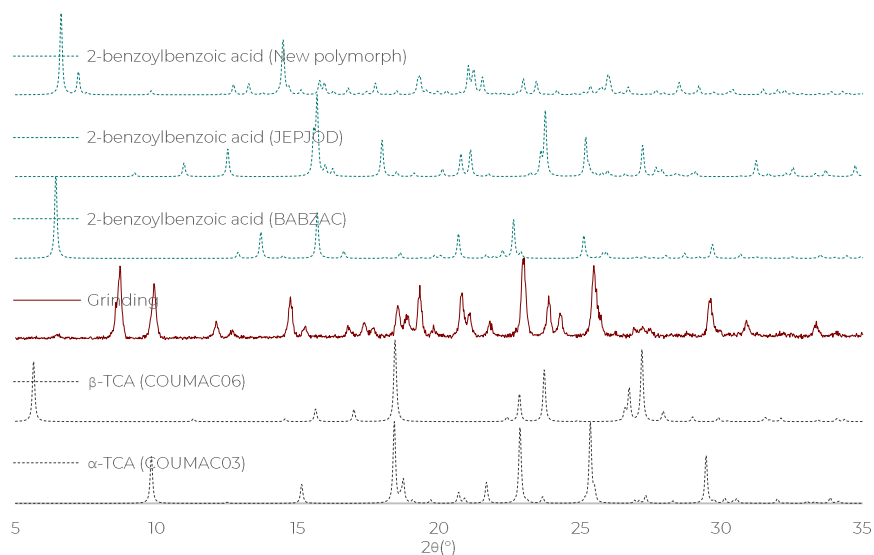


Figure 218 | CC-1) Experimental diffraction patterns of grinding between TCA and 2-benzoylbenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

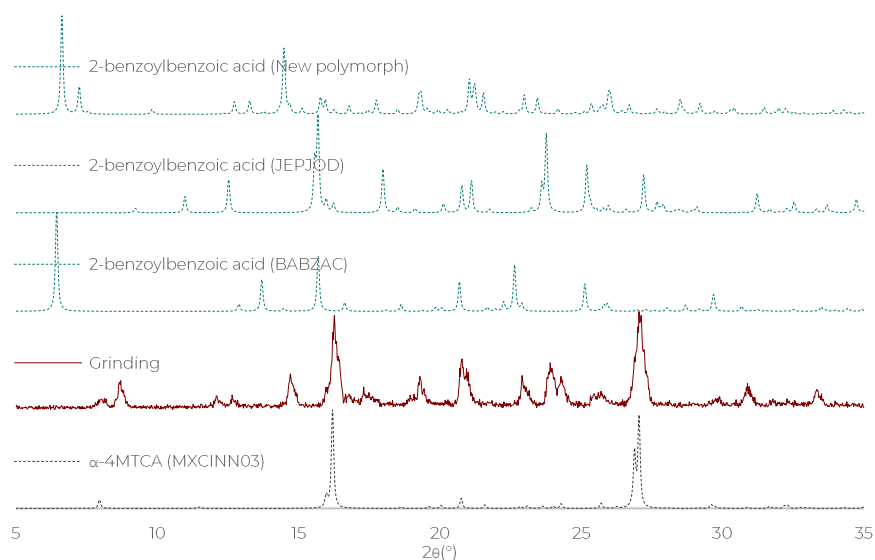


Figure 219 | CC-2) Experimental diffraction patterns of grinding between 4MTCA and 2-benzoylbenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

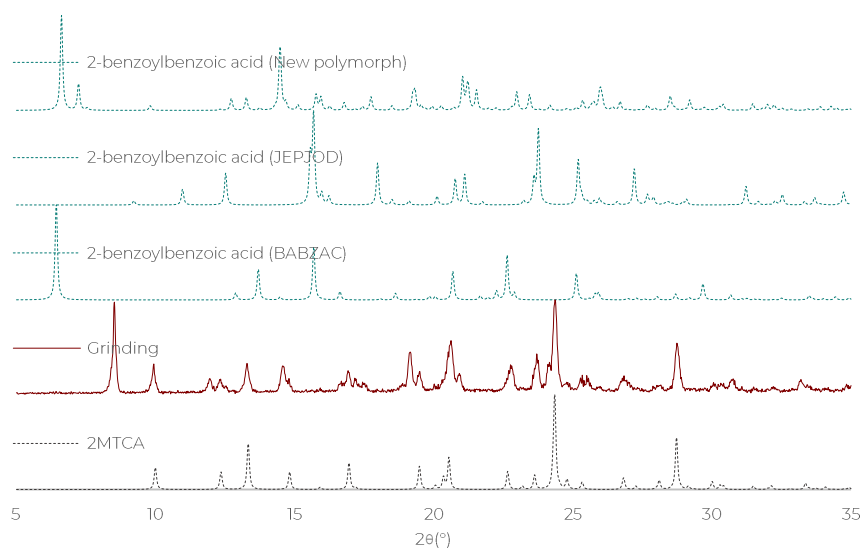


Figure 220 | CC-3) Experimental diffraction patterns of grinding between 2MTCA and 2-benzoylbenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

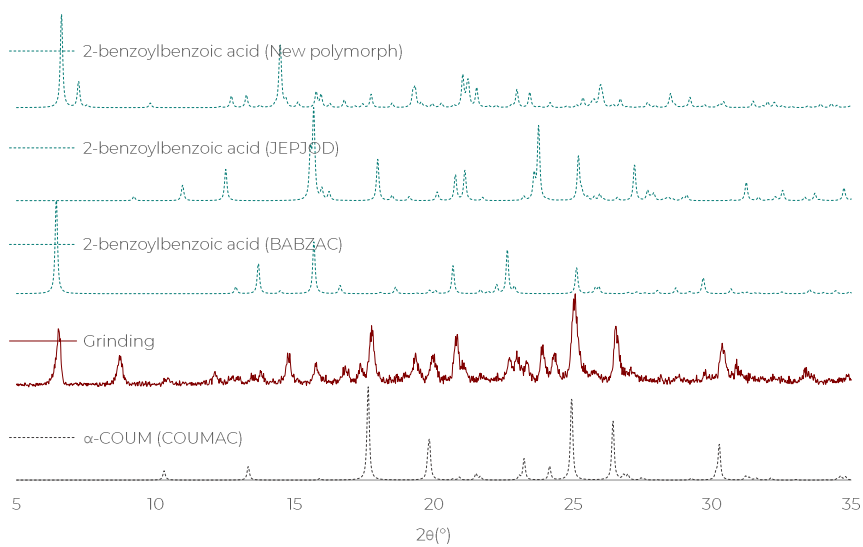


Figure 221 | CC-4) Experimental diffraction patterns of grinding between COUM and 2-benzoylbenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

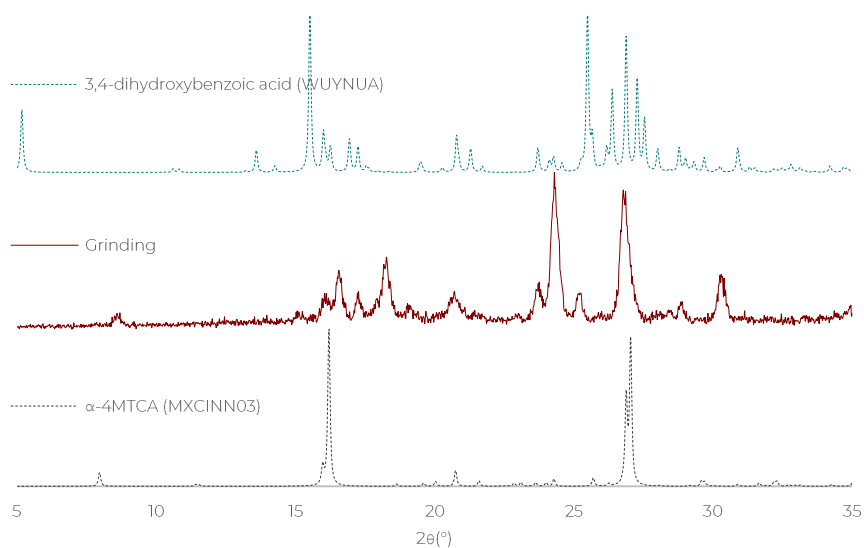


Figure 222 | CC-6) Experimental diffraction patterns of grinding between 4MTCA and 3,4-dihydroxybenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

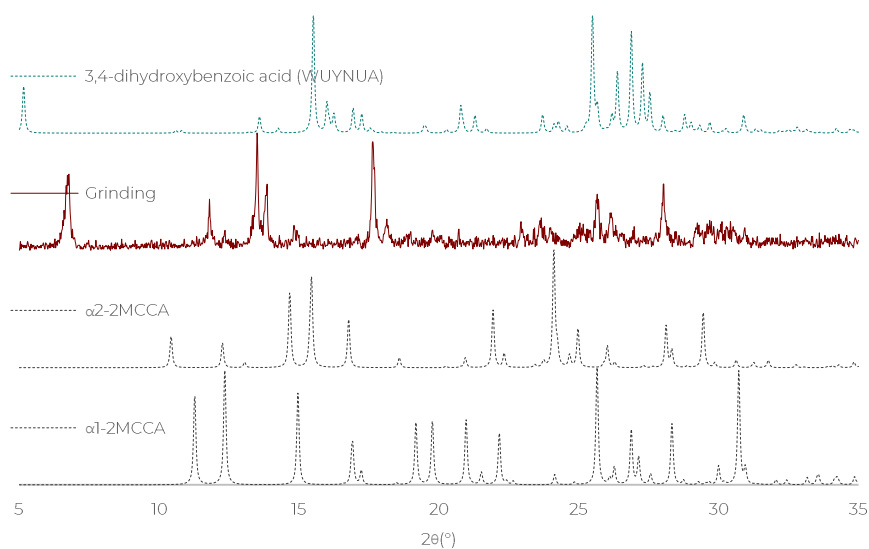


Figure 223 | CC-7) Experimental diffraction patterns of grinding between 2MCCA and 3,4-dihydroxybenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

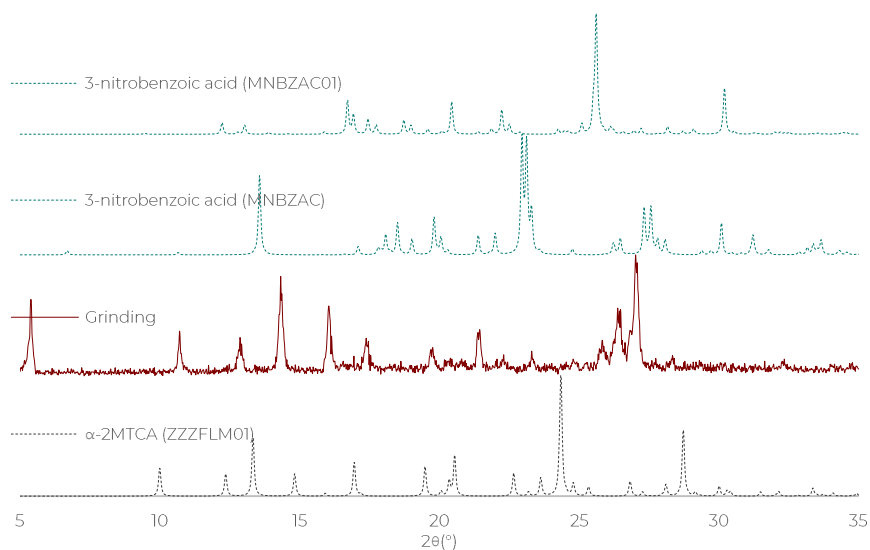


Figure 224 | CC-11) Experimental diffraction patterns of grinding between 2MTCA and 3-nitrobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

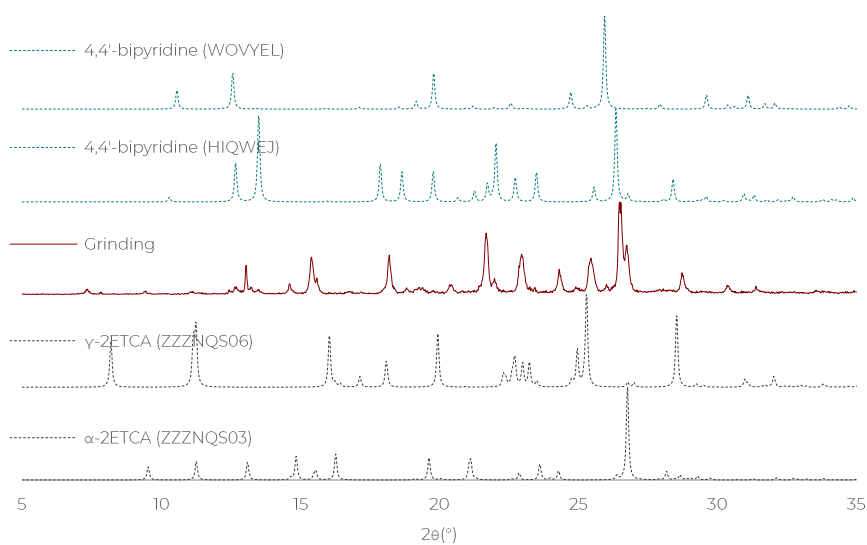


Figure 225 | CC-13) Experimental diffraction patterns of grinding between 2ETCA and 4,4'-bipyridine (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

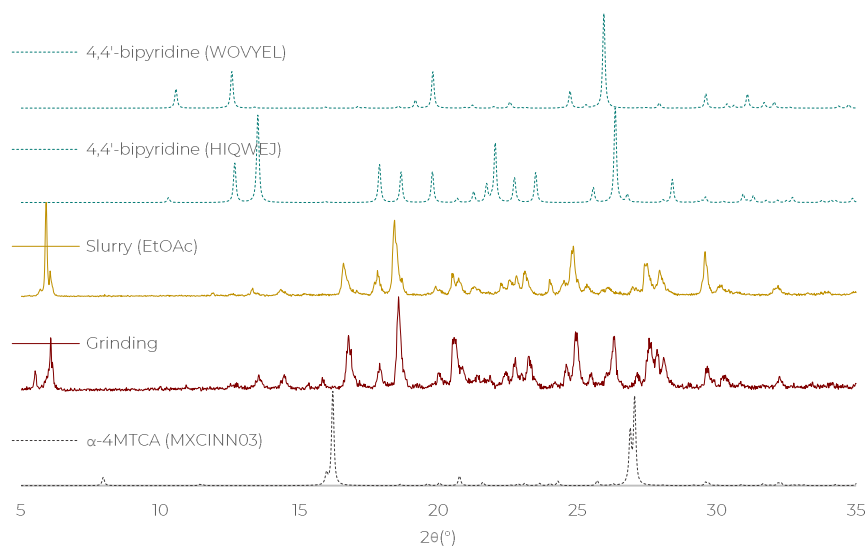


Figure 226 | CC-14) Experimental diffraction patterns of grinding between **4MTCA** and **4,4'-bipyridine** (red). Experimental diffraction patterns of slurry in EtOAc (yellow). Simulated diffraction patterns of the parents (dashed lines blue and black).

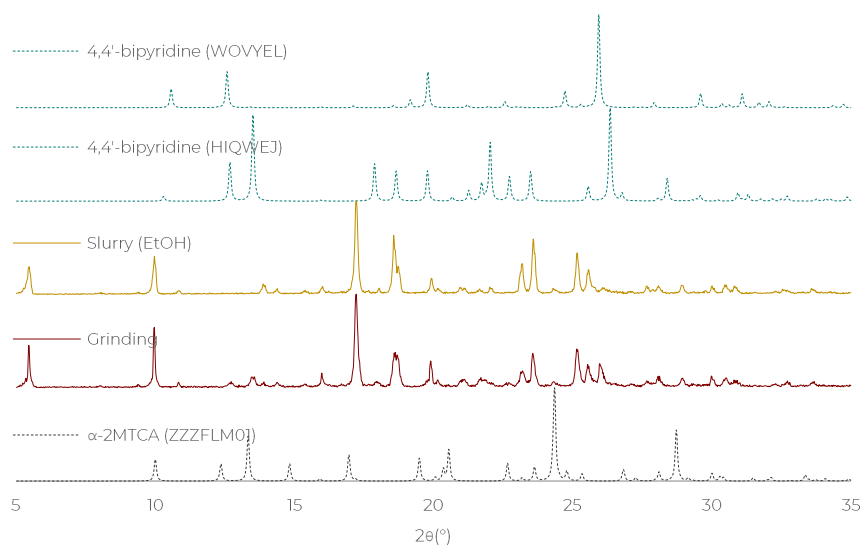


Figure 227 | CC-15) Experimental diffraction patterns of grinding between **2MTCA** and **4,4'-bipyridine** (red). Experimental diffraction patterns of slurry in EtOH (yellow). Simulated diffraction patterns of the parents (dashed lines blue and black).

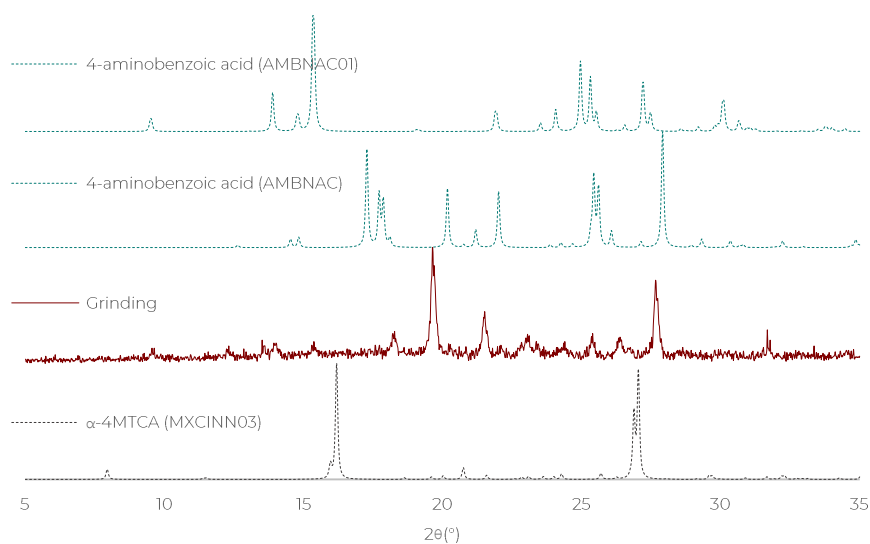


Figure 228 | CC-19) Experimental diffraction patterns of grinding between 4MTCA and 4-aminobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

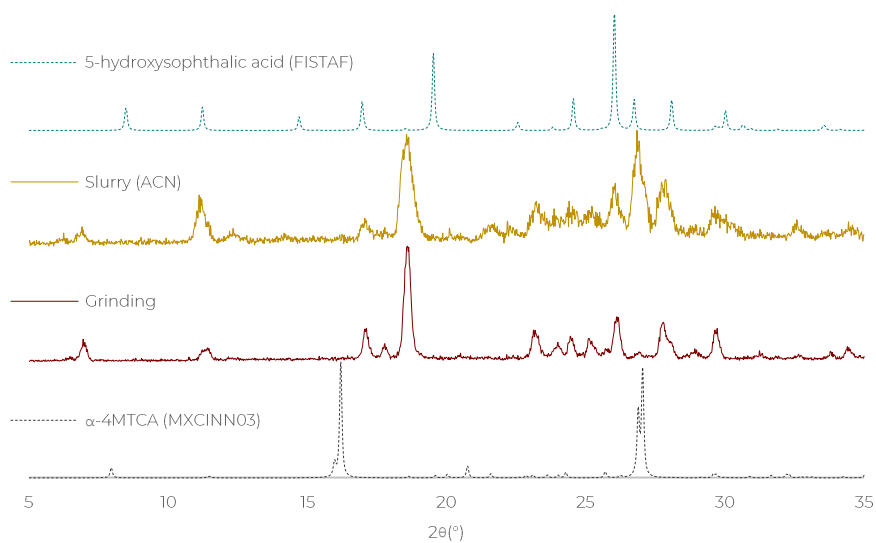


Figure 229 | CC-22) Experimental diffraction patterns of grinding between 4MTCA and 5-hydroxysophthalic acid (red). Experimental diffraction patterns of slurry in ACN (yellow). Simulated diffraction patterns of the parents (dashed lines blue and black).

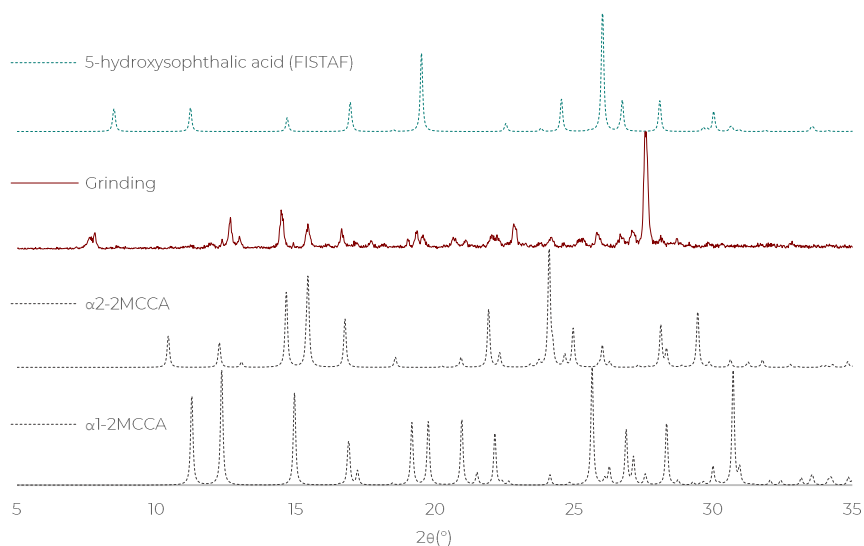


Figure 230 | CC-23) Experimental diffraction patterns of grinding between 2MCCA and 5-hydroxysophthalic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

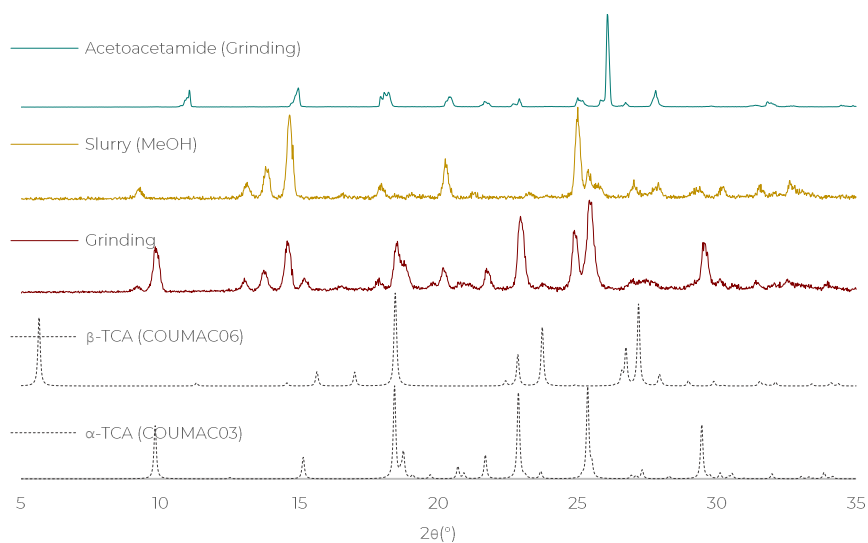


Figure 231 | CC-24) Experimental diffraction patterns of grinding between TCA and Acetoacetamide (red). Experimental diffraction patterns of slurry in MeOH (yellow). Simulated diffraction patterns of the TCA (dashed lines black). Experimental diffraction patterns of grinding of Acetoacetamide (blue).

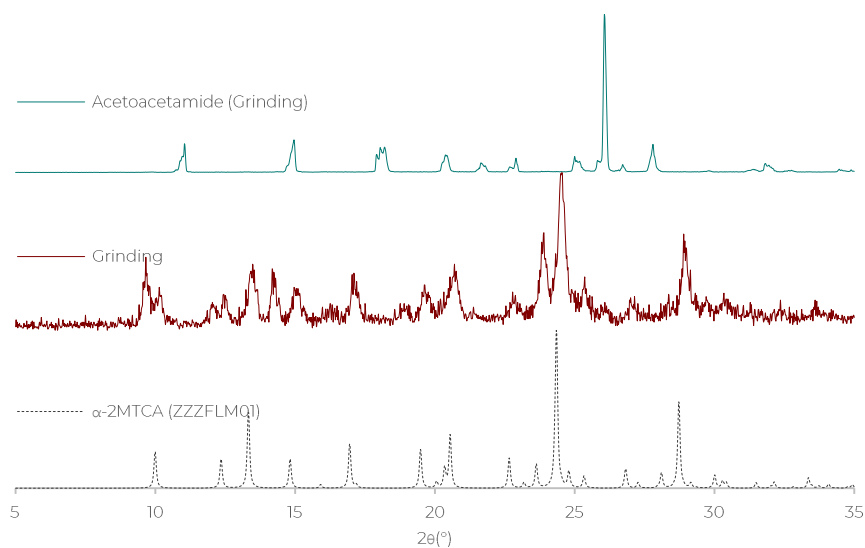


Figure 232 | CC-25) Experimental diffraction patterns of grinding between **2MTCA** and **Acetoacetamide** (red). Simulated diffraction patterns of the 2MTCA (dashed lines black). Experimental diffraction patterns of grinding of Acetoacetamide (blue).

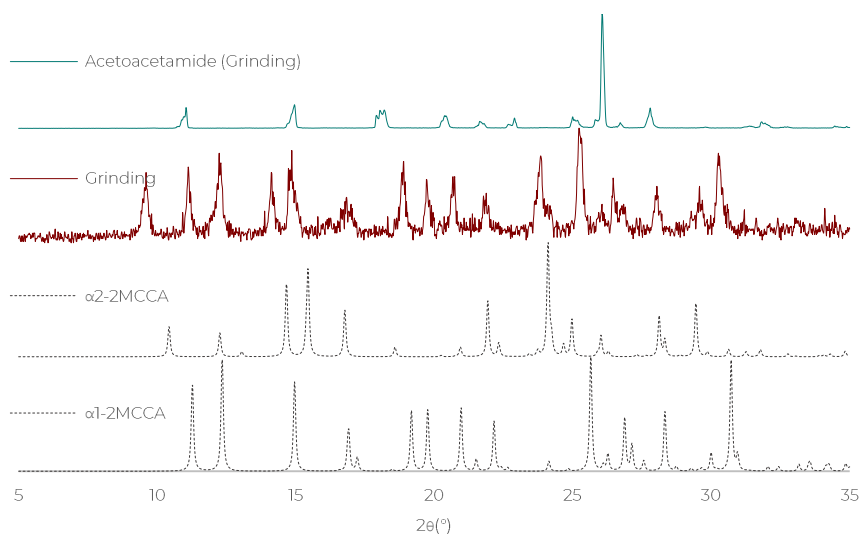


Figure 233 | CC-26) Experimental diffraction patterns of grinding between **2MCCA** and **Acetoacetamide** (red). Simulated diffraction patterns of the 2MCCA (dashed lines black). Experimental diffraction patterns of grinding of Acetoacetamide (blue).

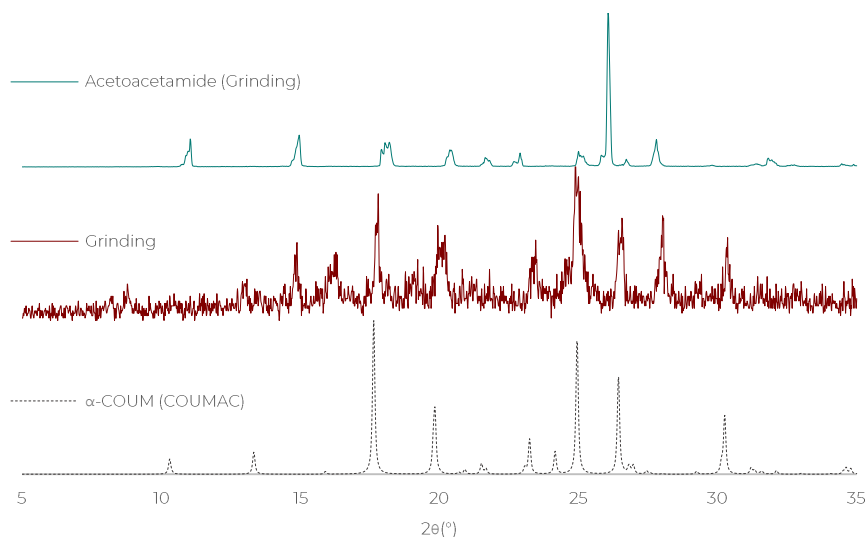


Figure 234 | CC-27) Experimental diffraction patterns of grinding between COUM and Acetoacetamide (red). Simulated diffraction patterns of the COUM (dashed lines black). Experimental diffraction patterns of grinding of Acetoacetamide (blue).

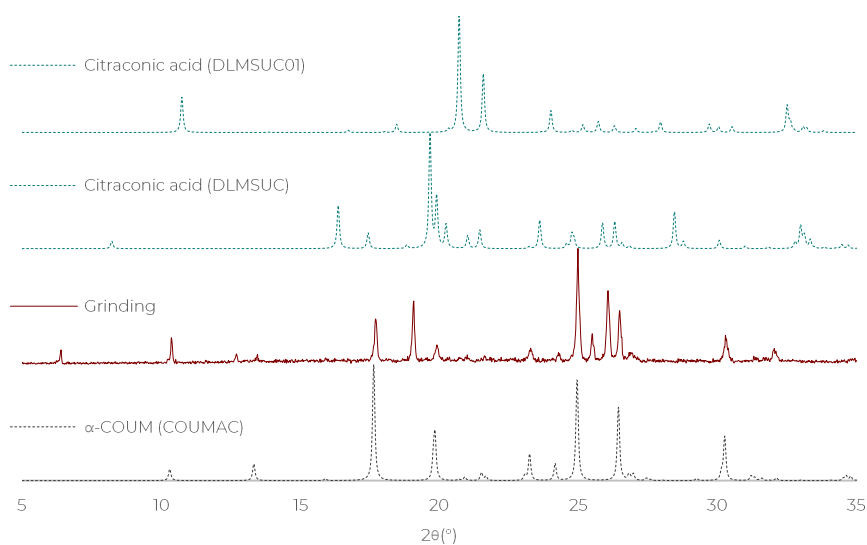


Figure 235 | CC-28) Experimental diffraction patterns of grinding between COUM and Citraconic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

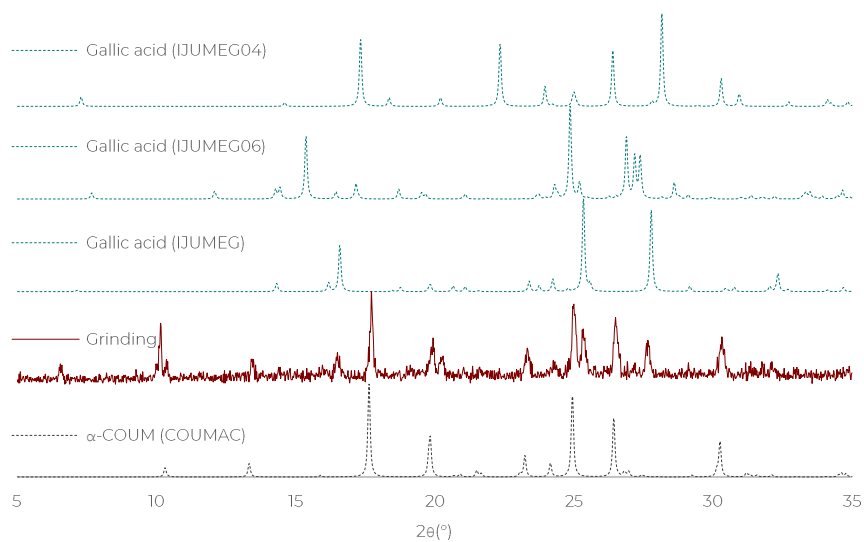


Figure 236 | CC-29 Experimental diffraction patterns of grinding between COUM and Gallic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

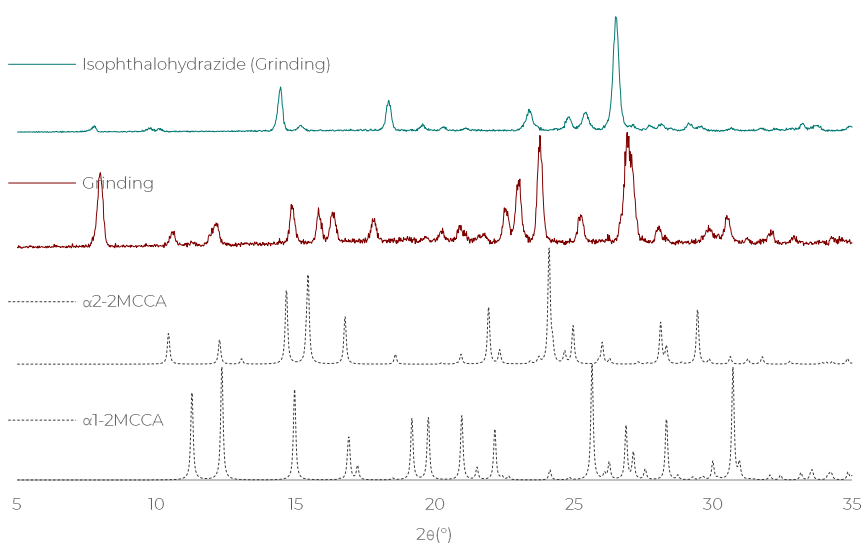


Figure 237 | CC-30 Experimental diffraction patterns of grinding between 2MCCA and Isophthalohydrazide (red). Simulated diffraction patterns of the 2MCCA (dashed lines black). Experimental diffraction patterns of grinding of Isophthalohydrazide (blue).

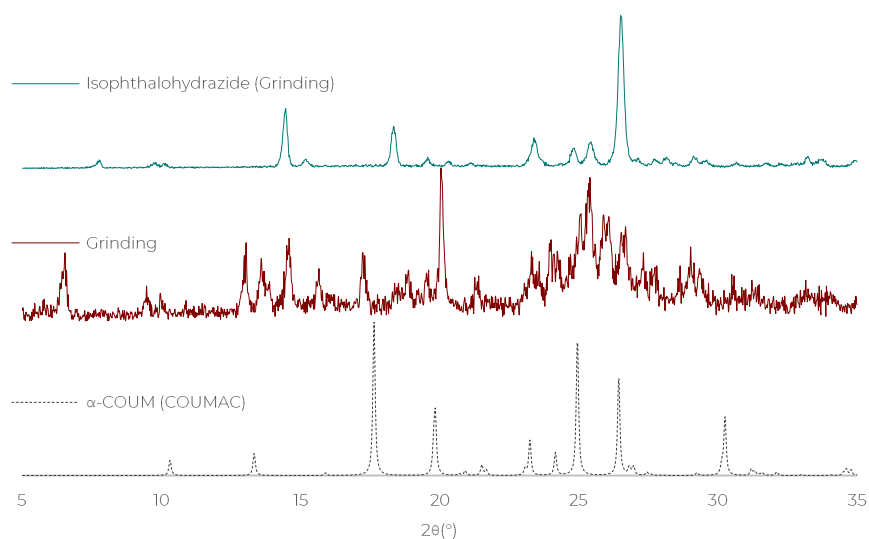


Figure 238 | CC-31) Experimental diffraction patterns of grinding between COUM and Isophthalohydrazide (red). Simulated diffraction patterns of the COUM (dashed lines black). Experimental diffraction patterns of grinding of Isophthalohydrazide (blue).

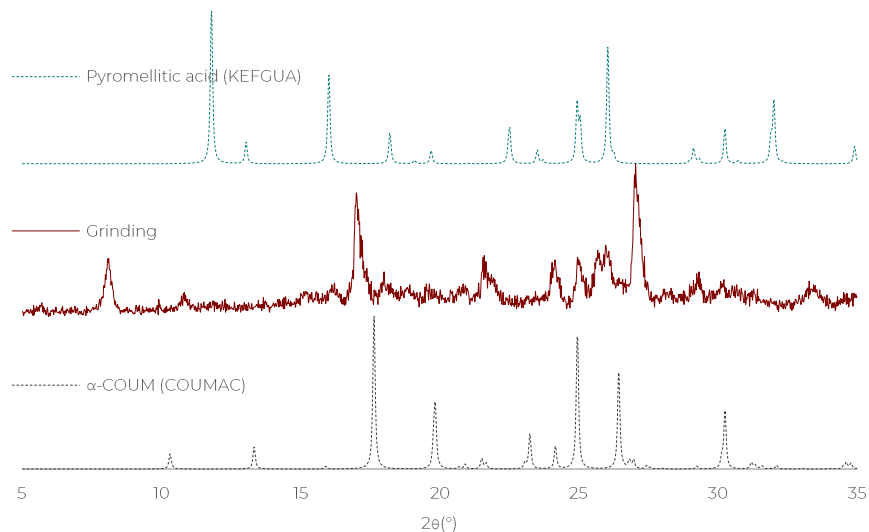


Figure 239 | CC-32) Experimental diffraction patterns of grinding between COUM and Pyromellitic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

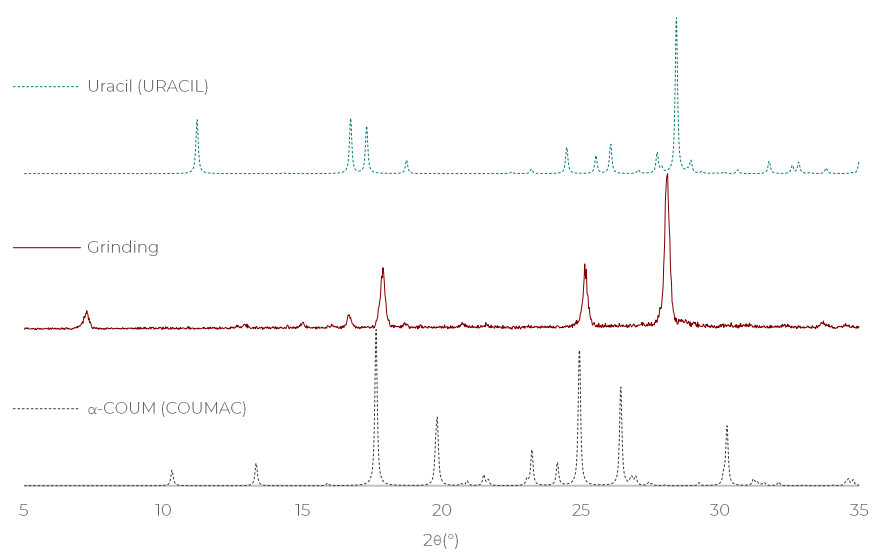


Figure 240 | CC-33) Experimental diffraction patterns of grinding between COUM and Uracil (red). Simulated diffraction patterns of the parents (dashed lines blue and black).

3.5 Diffractograms of screening on cinnamic acid derivatives (confirmed cocrystals)

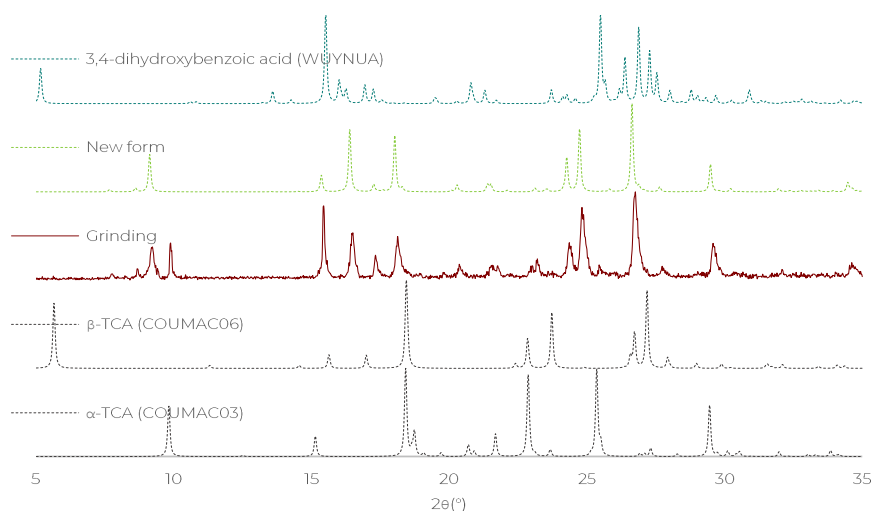


Figure 241 | CC-5) Experimental diffraction patterns of grinding between TCA and 3,4-dihydroxybenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1 : 1 TCA-3,4-dihydroxybenzoic acid (dashed line green).

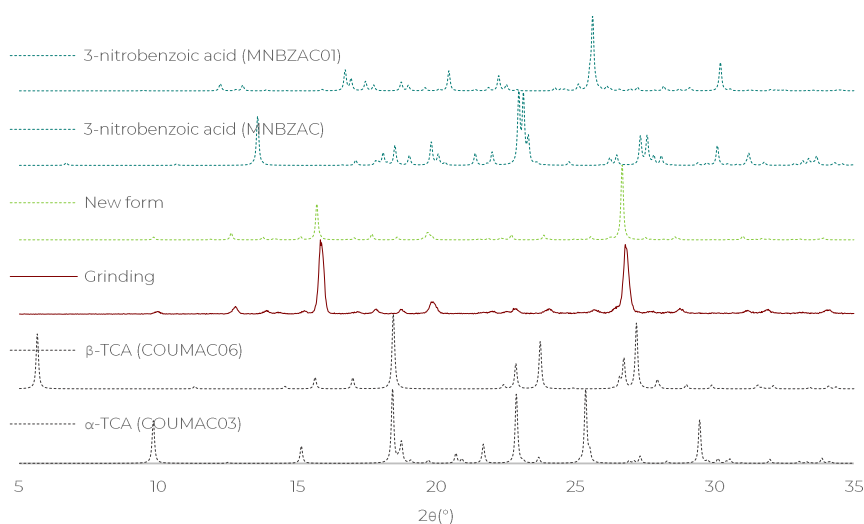


Figure 242 | CC-8) Experimental diffraction patterns of grinding between TCA and 3-nitrobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1 : 1 TCA-3nitrobenzoic acid (dashed line green).

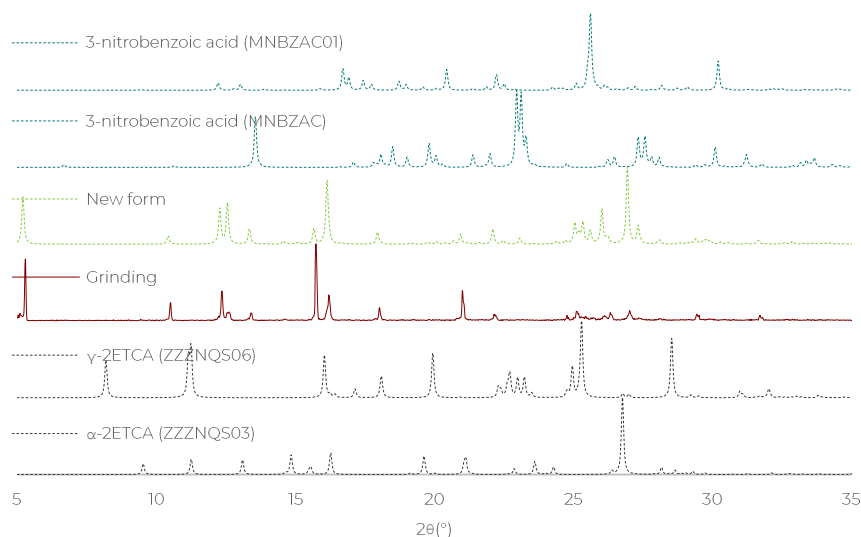


Figure 243 | CC-9) Experimental diffraction patterns of grinding between 2ETCA and 3-nitrobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1:1 2ETCA-3nitrobenzoic acid (dashed line green).

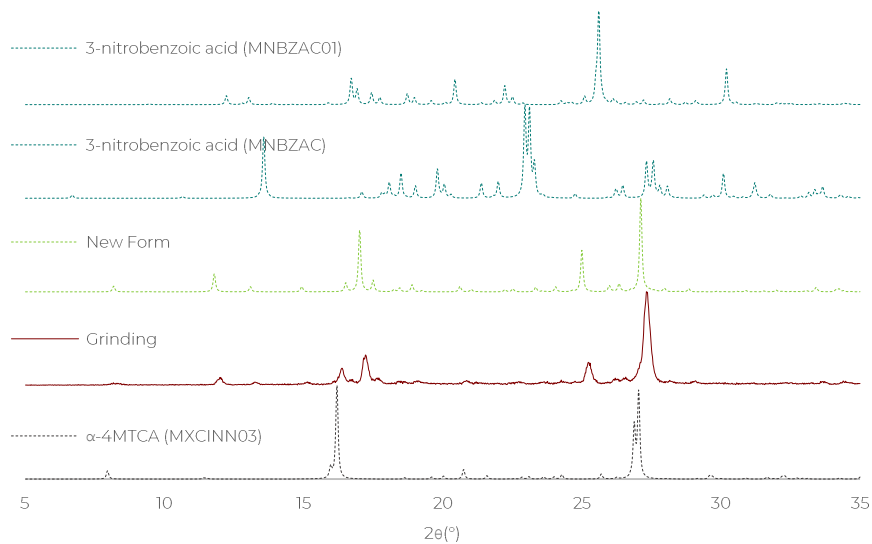


Figure 244 | CC-10) Experimental diffraction patterns of grinding between 4MTCA and 3-nitrobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1:1 4MTCA-3nitrobenzoic acid (dashed line green).

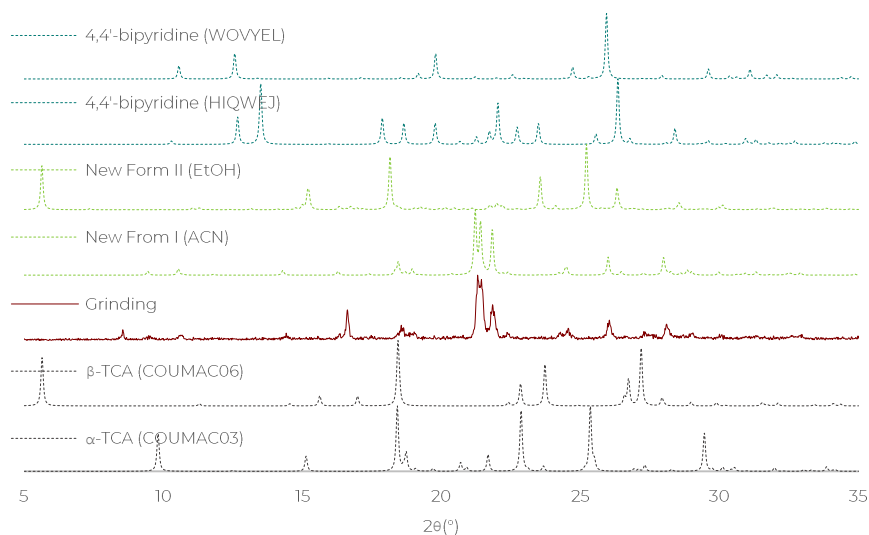


Figure 245 | CC-12) Experimental diffraction patterns of grinding between TCA and 4,4'-bipyridine (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the two cocrystals 1:1 TCA-4,4'-bipyridine (dashed line green).

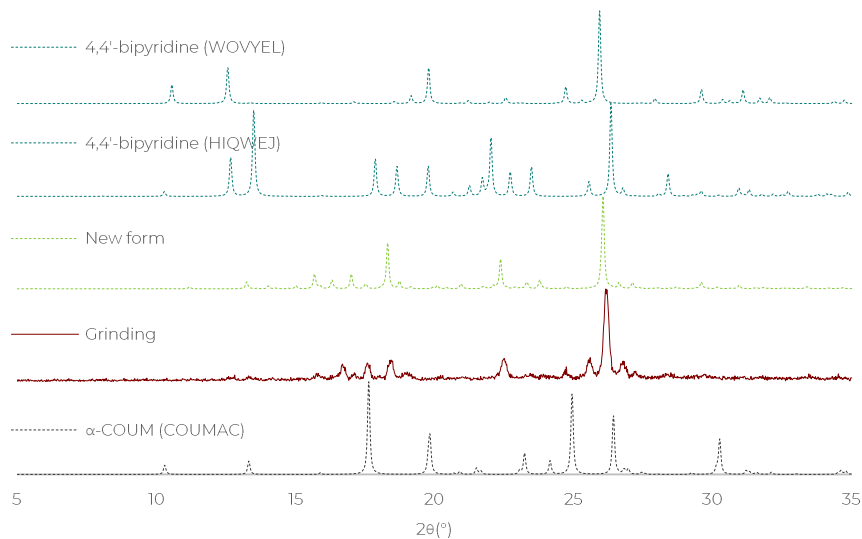


Figure 246 | CC-16) Experimental diffraction patterns of grinding between COUM and 4,4'-bipyridine (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1:1 COUM-4,4'-bipyridine (dashed line green).

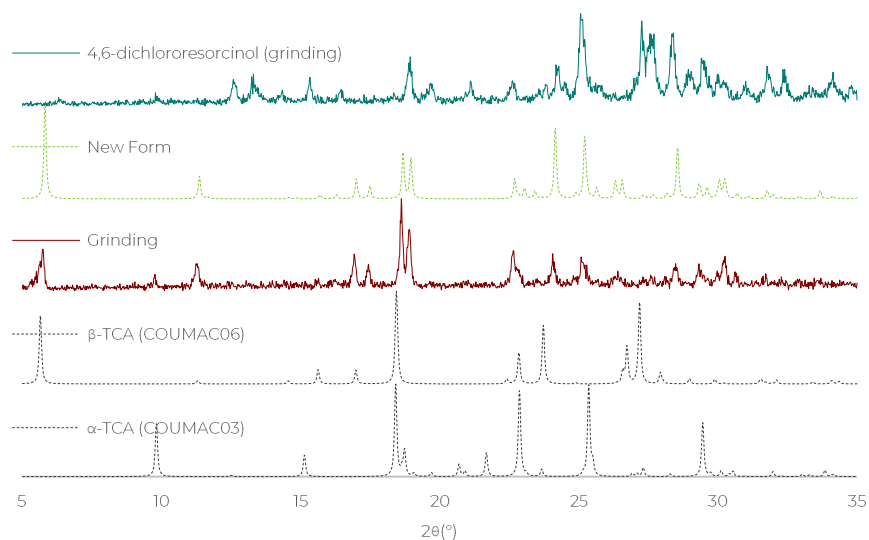


Figure 247 | CC-17) Experimental diffraction patterns of grinding between TCA and 4,6-dichlororesorcinol (red). Simulated diffraction patterns of the TCA (dashed lines black). Experimental diffraction patterns of grinding of 4,6-dichlororesorcinol (blue). Simulated diffraction pattern of the cocrystal 1 : 1 TCA-4,6-dichlororesorcinol (dashed line green).

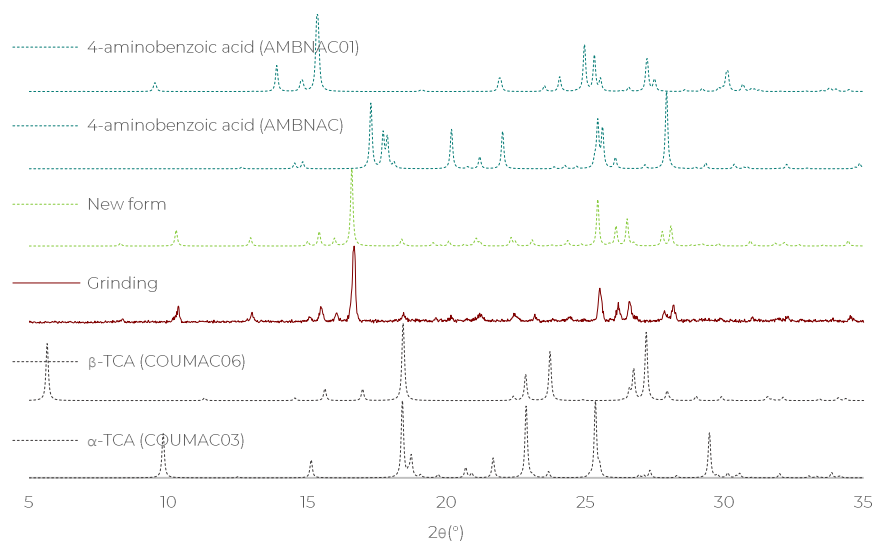


Figure 248 | CC-18) Experimental diffraction patterns of grinding between TCA and 4-aminobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1 : 1 TCA-4-aminobenzoic acid (dashed line green).

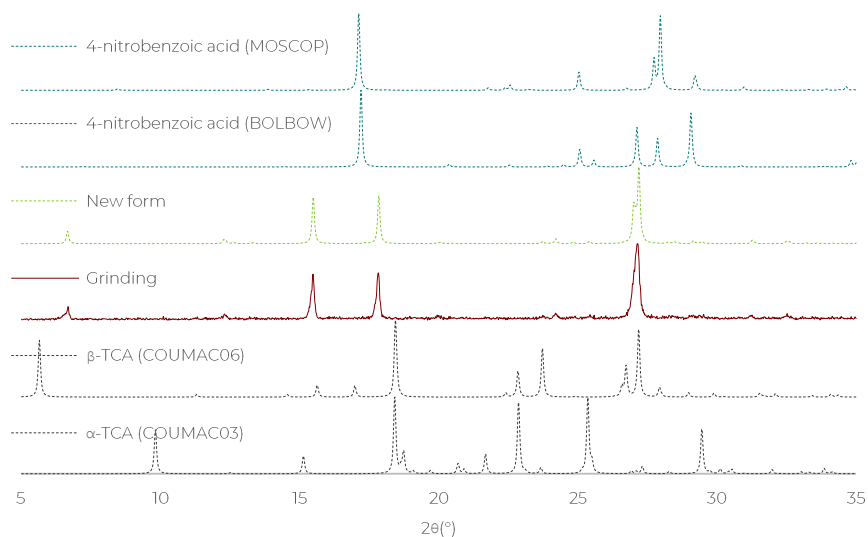


Figure 249 | CC-20) Experimental diffraction patterns of grinding between TCA and 4-nitrobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1:1 TCA-4-nitrobenzoic acid (dashed line green).

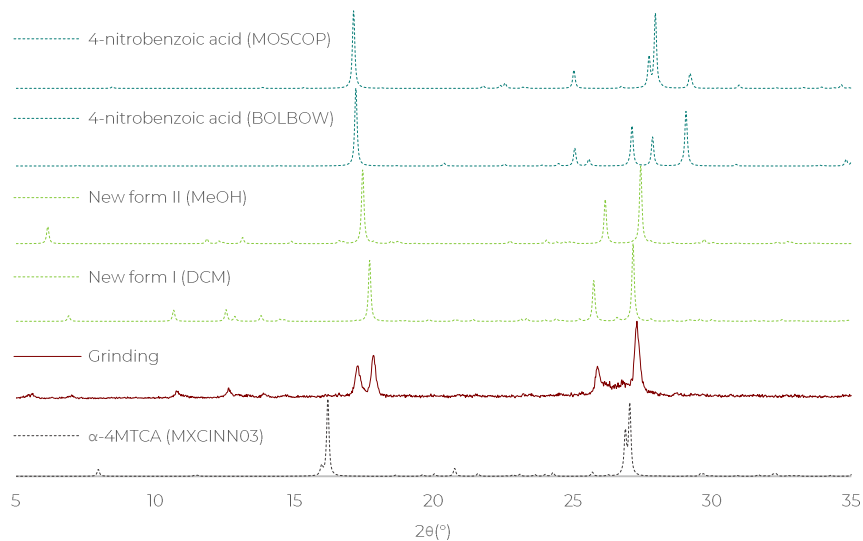


Figure 250 | CC-21) Experimental diffraction patterns of grinding between 4MTCA and 4-nitrobenzoic acid (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the two cocrystals 1:1 4MTCA-4-nitrobenzoic acid (dashed line green).

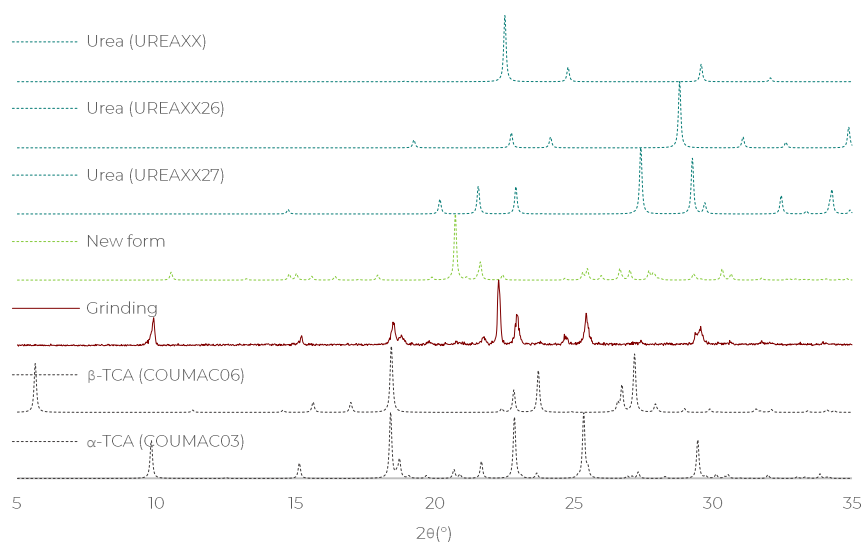


Figure 251 | CC-34) Experimental diffraction patterns of grinding between **TCA** and **Urea** (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1:1 TCA-Urea (dashed line green).

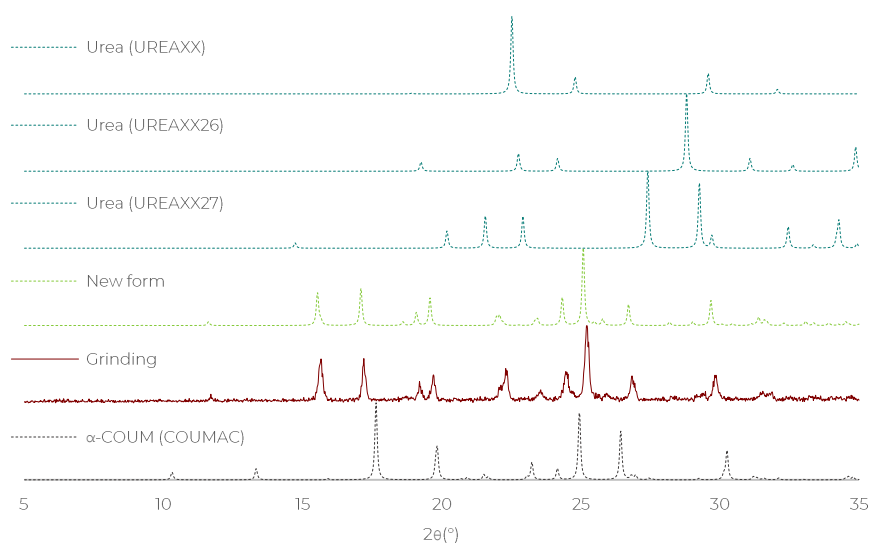


Figure 252 | CC-35) Experimental diffraction patterns of grinding between **COUM** and **Urea** (red). Simulated diffraction patterns of the parents (dashed lines blue and black). Simulated diffraction pattern of the cocrystal 1:1 COUM-Urea (dashed line green).

3.6 Crystal structure information of confirmed cocrystals

Table 42 | Main crystallographic data of new cocrystal forms between TCA and 3,4-dihydroxybenzoic acid and between TCA and 3-nitrobenzoic acid.

Compound	CC-5: TCA – 3,4-dihydroxybenzoic acid	CC-8: TCA – 3-nitrobenzoic acid
Identification code	cb_g_56_DHBA	cb_16_tCIN_3no2benz
Empirical formula	C ₁₆ H ₁₄ O ₆	C ₁₆ H ₁₃ N O ₆
Formula weight (g/mol)	302.27	315.27
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁ /n	P2 ₁ /c
a,b,c (Å)	a 12.4459(7) b 5.6025(3) c 20.9470(12)	a 8.9569(4) b 11.2851(6) c 14.9130(9)
α, β, γ (°)	α 90 β 101.311(6) γ 90	α 90 β 92.664(5) γ 90
Volume (Å ³)	1432.22(14)	1505.77(14)
Z	4	4
Density calculated (Mg/m ³)	1.402	1.391
Absorption coefficient (mm ⁻¹)	0.108	0.108
Crystal size (mm ³)	0.22x 0.05 x 0.02	0.20x 0.15 x 0.10
F(000)	632	656
Theta range for data collection (°)	3.113 to 25.236	3.166 to 25.693
Reflections collected	9026	8471
Independent reflections	2585 [R(int) = 0.0489]	2842 [R(int) = 0.0387]
Completeness to theta = 25.96°	99.7	99.7
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.89782	1.00000 and 0.63066
Data / restraints / parameters	2585 / 0 / 203	2842 / 0 / 208
Goodness-of-fit on F ²	1.059	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0488, wR2 = 0.1211	R1 = 0.0464, wR2 = 0.1257
R indices (all data)	R1 = 0.0776, wR2 = 0.1344	R1 = 0.0786, wR2 = 0.1427
Largest diff. Peak and hole (e.Å ⁻³)	0.163, -0.164	0.128, -0.130

Table 43 | Main crystallographic data of new cocrystal forms between 2ETCA and 3-nitrobenzoic acid and between 4MTCA and 3-nitrobenzoic acid.

Compound	CC-9: 2ETCA – 3-nitrobenzoic acid	CC-10: 4MTCA – 3-nitrobenzoic acid
Identification code	cb_etca_nia_acn9	cb_46_mtcaNIAMeOH
Empirical formula	C ₁₈ H ₁₇ N O ₇	C ₁₇ H ₁₅ N O ₇
Formula weight (g/mol)	359.32	345.30
Temperature (K)	297(2)	297(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁ /c	P2 ₁ /n
a,b,c (Å)	a 7.2042(4) b 33.9088(13) c 14.6024(6)	a 7.2873(5) b 21.6263(9) c 10.6648(5)
α, β, γ (°)	α 90 β 99.539(5) γ 90	α 90 β 102.409(6) γ 90
Volume (Å ³)	3517.8(3)	1641.48(15)
Z	8	4
Density calculated (Mg/m ³)	1.357	1.397
Absorption coefficient (mm ⁻¹)	0.106	0.110
Crystal size (mm ³)	0.28x 0.05 x 0.02	0.50x 0.15 x 0.12
F(000)	1504	720
Theta range for data collection (°)	2.929 to 22.464	3.013 to 26.259
Reflections collected	18597	11625
Independent reflections	4567 [R(int) = 0.0828]	3289 [R(int) = 0.0305]
Completeness to theta = 25.96°	99.6	99.6
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.74208	1.00000 and 0.85921
Data / restraints / parameters	4567 / 0 / 471	3289 / 0 / 228
Goodness-of-fit on F ²	1.067	1.064
Final R indices [I>2sigma(I)]	R1 = 0.0527, wR2 = 0.1287	R1 = 0.0466, wR2 = 0.1179
R indices (all data)	R1 = 0.1040, wR2 = 0.1517	R1 = 0.0655, wR2 = 0.1298
Largest diff. Peak and hole (e.Å ⁻³)	0.156, -0.157	0.219, -0.159

Table 44 | Main crystallographic data of new cocrystal forms between TCA and 4,4'-bipyridine.

Compound	CC-12: TCA – 4,4'-bipyridine Form I (ACN)	CC-12': TCA – 4,4'-bipyridine Form II (EtOH)
Identification code	cb_6_tca_bip_acn	cb_6_tca_bip_etOH
Empirical formula	C ₁₉ H ₁₆ N ₂ O ₂	C ₂₈ H ₂₄ N ₂ O ₄
Formula weight (g/mol)	304.34	452.49
Temperature (K)	297(2)	297(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
a,b,c (Å)	a 9.6750(15) b 9.790(3) c 10.008(3)	a 6.3265(6) b 15.8477(18) c 24.439(2)
α, β, γ (°)	α 100.98(2) β 100.73(2) γ 115.83(2)	α 98.385(9) β 97.034(8) γ 90.895(9)
Volume (Å ³)	797.8(4)	2404.4(4)
Z	2	4
Density calculated (Mg/m ³)	1.267	1.250
Absorption coefficient (mm ⁻¹)	0.083	0.084
Crystal size (mm ³)	0.50x 0.30 x 0.12	0.50x 0.05 x 0.02
F(000)	320	952
Theta range for data collection (°)	2.718 to 26.313	2.886 to 25.241
Reflections collected	10990	28997
Independent reflections	3170 [R(int) = 0.0280]	8619 [R(int) = 0.0742]
Completeness to theta = 25.96°	99.4	98.8
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.86425	1.00000 and 0.61483
Data / restraints / parameters	3170 / 0 / 210	8619 / 114 / 719
Goodness-of-fit on F ²	1.054	1.049
Final R indices [I>2sigma(I)]	R1 = 0.0484, wR2 = 0.1251	R1 = 0.0700, wR2 = 0.1493
R indices (all data)	R1 = 0.0588, wR2 = 0.1324	R1 = 0.1386, wR2 = 0.1809
Largest diff. Peak and hole (e.Å ⁻³)	0.147, -0.166	0.143, -0.154

Table 45 | Main crystallographic data of new cocrystal forms between COUM and 4,4'-bipyridine and between TCA and 4,6-dichlororesorcinol.

Compound	CC-16: COUM – 4,4'-bipyridine	CC-17: TCA – 4,6-dichlororesorcinol
Identification code	cb_35_coum_bip_acn	cb_tca_dcr_tol
Empirical formula	C ₁₉ H ₁₆ N ₂ O ₃	C ₁₅ H ₁₂ Cl ₂ O ₄
Formula weight (g/mol)	320.34	327.15
Temperature (K)	297(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Orthorhombic
Space group	P2 ₁ /n	Fdd2
a,b,c (Å)	a 16.9799(4) b 11.9990(2) c 32.0806(6)	a 60.793(4) b 24.306(3) c 3.9127(3)
α, β, γ (°)	α 90 β 101.206(2) γ 90	α 90 β 90 γ 90
Volume (Å ³)	6411.5(2)	5781.7(9)
Z	16	16
Density calculated (Mg/m ³)	1.327	1.503
Absorption coefficient (mm ⁻¹)	0.091	0.461
Crystal size (mm ³)	0.38x 0.30 x 0.20	0.30x 0.06 x 0.04
F(000)	2688	2688
Theta range for data collection (°)	2.944 to 25.680	3.162 to 25.242
Reflections collected	42948	5596
Independent reflections	12142 [R(int) = 0.0403]	2573 [R(int) = 0.0400]
Completeness to theta = 25.96°	99.7	98.9
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.79921	1.00000 and 0.74387
Data / restraints / parameters	12142 / 0 / 865	2573 / 1 / 194
Goodness-of-fit on F ²	1.095	1.077
Final R indices [I>2sigma(I)]	R1 = 0.0672, wR2 = 0.1627	R1 = 0.0470, wR2 = 0.1170
R indices (all data)	R1 = 0.1032, wR2 = 0.1848	R1 = 0.0547, wR2 = 0.1220
Largest diff. Peak and hole (e.Å ⁻³)	0.435, -0.227	0.54(13)

Table 46 | Main crystallographic data of new cocrystal forms between TCA and 4-aminobenzoic acid and between TCA and 4-nitrobenzoic acid.

Compound	CC-18: TCA – 4-aminobenzoic acid	CC-20: TCA – 4-nitrobenzoic acid
Identification code	cb_g_35_NbenzA	cb_16_tCIN_4no2benz
Empirical formula	C ₁₆ H ₁₅ N O ₄	C ₁₆ H ₁₃ N O ₆
Formula weight (g/mol)	285.29	315.27
Temperature (K)	297(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁ /n	P2 ₁ /n
a,b,c (Å)	a 4.8743(2) b 25.1207(12) c 11.7930(5)	a 7.3572(7) b 7.4910(5) c 26.566(5)
α, β, γ (°)	α 90 β 90.645(4) γ 90	α 90 β 92.529(12) γ 90
Volume (Å ³)	1443.93(11)	1462.7(3)
Z	4	4
Density calculated (Mg/m ³)	1.312	1.432
Absorption coefficient (mm ⁻¹)	0.095	0.111
Crystal size (mm ³)	0.20x 0.15 x 0.12	0.40x 0.10 x 0.10
F(000)	600	656
Theta range for data collection (°)	2.369 to 25.257	3.070 to 25.389
Reflections collected	5256	8893
Independent reflections	5256 [R(int) = ?]	2650 [R(int) = 0.0874]
Completeness to theta = 25.96°	94.8	99.1
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.81211	1.00000 and 0.62125
Data / restraints / parameters	5256 / 0 / 196	2650 / 0 / 208
Goodness-of-fit on F ²	1.055	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0462, wR2 = 0.1403	R1 = 0.0539, wR2 = 0.1255
R indices (all data)	R1 = 0.0614, wR2 = 0.1468	R1 = 0.0812, wR2 = 0.1390
Largest diff. Peak and hole (e.Å ⁻³)	0.203, -0.138	0.211, -0.203

Table 47 | Main crystallographic data of new cocrystal forms between 4MTCA and 4-nitrobenzoic acid.

Compound	CC-21: 4MTCA – 4-nitrobenzoic acid Form I (DCM)	CC-21': 4MTCA – 4-nitrobenzoic acid Form II (MeOH)
	cb43_4mtcanbadcmf2_tw	cb_43_4MTCA_NBAmeOH
Identification code	cb43_4mtcanbadcmf2_tw	cb_43_4MTCA_NBAmeOH
Empirical formula	C ₁₇ H ₁₅ N O ₇	C ₁₇ H ₁₅ N O ₇
Formula weight (g/mol)	345.30	345.30
Temperature (K)	297(2)	297(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Triclinic	Triclinic
Space group	P-1	P-1
a,b,c (Å)	a 7.6149(11) b 9.121(2) c 12.830(2)	a 7.4129(13) b 7.4812(14) c 14.781(4)
α, β, γ (°)	α 88.473(16) β 89.741(15) γ 65.453(18)	α 86.917(18) β 77.087(18) γ 86.259(15)
Volume (Å ³)	810.3(3)	796.6(3)
Z	2	2
Density calculated (Mg/m ³)	1.415	1.440
Absorption coefficient (mm ⁻¹)	0.112	0.113
Crystal size (mm ³)	0.50x 0.25 x 0.04	0.26x 0.20 x 0.03
F(000)	360	360
Theta range for data collection (°)	2.941 to 26.300	3.126 to 25.252
Reflections collected	3247	10463
Independent reflections	3247 [R(int) = ?]	2805 [R(int) = 0.0393]
Completeness to theta = 25.96°	99.5	97.7
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.51348	1.00000 and 0.57688
Data / restraints / parameters	3247 / 136 / 347	2805 / 0 / 228
Goodness-of-fit on F ²	1.076	1.075
Final R indices [I>2sigma(I)]	R1 = 0.0523, wR2 = 0.1473	R1 = 0.0619, wR2 = 0.1424
R indices (all data)	R1 = 0.0638, wR2 = 0.1549	R1 = 0.0829, wR2 = 0.1536
Largest diff. Peak and hole (eÅ ⁻³)	0.156, -0.138	0.155, -0.195

Table 48 | Main crystallographic data of new cocrystal forms between TCA and Urea and between COUM and Urea.

Compound	CC-34: TCA – Urea	CC-35: COUM – Urea
Identification code	cb_g_tCin_urea	cb_coum_ure_meoh
Empirical formula	C ₁₀ H ₁₂ N ₂ O ₃	C ₁₉ H ₂₀ N ₂ O ₇
Formula weight (g/mol)	208.22	388.37
Temperature (K)	297(2)	296(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Monoclinic	Monoclinic
Space group	P2 ₁ /c	C2/c
a,b,c (Å)	a 13.7046(17) b 10.7811(12) c 7.3880(10)	a 16.133(3) b 6.1474(12) c 20.195(4)
α, β, γ (°)	α 90 β 102.791(12) γ 90	α 90 β 109.29(2) γ 90
Volume (Å ³)	1064.5(2)	1890.4(7)
Z	4	4
Density calculated (Mg/m ³)	1.299	1.365
Absorption coefficient (mm ⁻¹)	0.097	0.105
Crystal size (mm ³)	0.50x 0.38 x 0.02	0.30x 0.20 x 0.05
F(000)	440	816
Theta range for data collection (°)	3.048 to 25.254	3.602 to 26.194
Reflections collected	10073	5961
Independent reflections	1886 [R(int) = 0.0347]	1873 [R(int) = 0.0636]
Completeness to theta = 25.96°	98.0	99.3
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90690	1.00000 and 0.83118
Data / restraints / parameters	1886 / 0 / 138	1873 / 0 / 130
Goodness-of-fit on F ²	1.147	1.060
Final R indices [I>2sigma(I)]	R1 = 0.0420, wR2 = 0.1077	R1 = 0.0616, wR2 = 0.1770
R indices (all data)	R1 = 0.0484, wR2 = 0.1117	R1 = 0.0685, wR2 = 0.1860
Largest diff. Peak and hole (eÅ ⁻³)	0.114, -0.127	0.266, -0.281

BIBLIOGRAPHY

- [1] L. Gubbels. *Crystal Engineering to Control the Regioselectivity in the Dimerisation of Trans-Cinnamic Acid Derivatives*; Master Thesis; UCLouvain: Louvain-la-Neuve, 2022.
- [2] P. M. Nowak. What Does It Mean That “Something Is Green”? The Fundamentals of a Unified Greenness Theory. *Green Chem.* 2023, **25** (12), 4625–4640.
- [3] P. T. Anastas, J. C. Warner. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.
- [4] R. A. Sheldon. The E Factor 25 Years on: The Rise of Green Chemistry and Sustainability. *Green Chem.* 2017, **19** (1), 18–43.
- [5] J. Pinto, T. Barroso, J. Capitão-Mor, A. Aguiar-Ricardo. Towards a New, Green and Dynamic Scoring Tool, G2, to Evaluate Products and Processes. *Journal of Cleaner Production* 2020, **276**, 123079.
- [6] G. W. V. Cave, C. L. Raston, J. L. Scott. Recent Advances in Solventless Organic Reactions: Towards Benign Synthesis with Remarkable Versatility. *Chem. Commun.* 2001, 2159–2169.
- [7] P. Sharma, E. Ponnusamy, S. Ghorai, T. J. Colacot. DOZNTM 2.0: A Quantitative Green Chemistry Evaluator for a Sustainable Future. *Journal of Organometallic Chemistry* 2022, **970–971**, 122367.
- [8] P. Sharma, C. Vetter, E. Ponnusamy, E. Colacino. Assessing the Greenness of Mechanochemical Processes with the DOZN 2.0 Tool. *ACS Sustainable Chem. Eng.* 2022, **10** (16), 5110–5116.
- [9] L. Pasteur. *Recherches Sur Les Relations Qui Peuvent Exister Entre La Forme Cristalline, La Composition Chimique et Les Sens de La Polarisation Rotatoire*; Paris, 1848.
- [10] G. Vantomme, J. Crassous. Pasteur and Chirality: A Story of How Serendipity Favors the Prepared Minds. *Chirality* 2021, **33** (10), 597–601.
- [11] P. Y. Bruice. *Chimie Organique*, 2nd ed.; Pearson: France, 2012.
- [12] J. Clayden, N. Greeves, S. Warren, P. Wothers. *Organic Chemistry*, 2nd ed.; Oxford University Press, 2000.
- [13] C. Viedma, G. Coquerel, P. Cintas. Chapter 22 - Crystallization of Chiral Molecules. In *Handbook of Crystal Growth*; Elsevier, 2015; pp 951–1002.
- [14] C. Policar. Louis Pasteur dans l’œil du microscope. *Reflets phys.* 2022, **73**, 32–34.
- [15] H. Lorenz, A. Seidel-Morgenstern. Processes To Separate Enantiomers. *Angew. Chem. Int. Ed.* 2014, **53** (5), 1218–1250.
- [16] L. A. Nguyen, H. He, C. Pham-Huy. Chiral Drugs: An Overview. *International Journal of Biomedical Science* 2006, **2** (2), 85–100.
- [17] A. Calcaterra, I. D’Acquarica. The Market of Chiral Drugs: Chiral Switches versus de Novo Enantiomerically Pure Compounds. *Journal of Pharmaceutical and Biomedical Analysis* 2018, **147**, 323–340.
- [18] G. Hancu, A. Modroiu. Chiral Switch: Between Therapeutical Benefit and Marketing Strategy. *Pharmaceuticals* 2022, **15** (2), 240.

- [19] A. Ault. Selectivity and Specificity in Organic Reactions. *J. Chem. Educ.* 1977, **54** (10), 614.
- [20] A. Mattei, T. Li. Chapter 4 - Intermolecular Interactions and Computational Modeling. In *Pharmaceutical Crystals Sciences and Engineering*; John Wiley & Sons, Inc., 2018.
- [21] T. W. Martin, Z. S. Derewenda. The Name Is Bond - H Bond. *Nat. Struct. Biol.* 1999, **6** (5), 403–406.
- [22] G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo. The Halogen Bond. *Chem. Rev.* 2016, **116** (4), 2478–2601.
- [23] K. Roy, M. Zeghal, J. M. Thomas, K.-S. Focsaneanu. *General chemistry for Gee-Gees*. ecampusontario. <https://ecampusontario.pressbooks.pub/genchemforgeegees/> (accessed 2022-10-09).
- [24] *National Institute of Standards and Technology*. <https://www.nist.gov/> (accessed 2024-03-14).
- [25] *Courbe DSC, Calorimétrie Différentielle de Balayage. Analyse Amorphe et Semicrystalline Polymère.*; 2020. <https://www.istockphoto.com/> (accessed 2022-12-05).
- [26] L. C. Williams, S. M. Underwood, M. W. Klymkowsky, M. M. Cooper. Are Noncovalent Interactions an Achilles Heel in Chemistry Education? A Comparison of Instructional Approaches. *J. Chem. Educ.* 2015, **92** (12), 1979–1987.
- [27] B. L. Baldock, J. D. Blanchard, A. L. Fernandez. Student Discovery of the Relationship between Molecular Structure, Solubility, and Intermolecular Forces. *J. Chem. Educ.* 2021, **98** (12), 4046–4053.
- [28] M. M. Cooper, L. C. Williams, S. M. Underwood. Student Understanding of Intermolecular Forces: A Multimodal Study. *J. Chem. Educ.* 2015, **92** (8), 1288–1298.
- [29] N. Shan, M. J. Zaworotko. The Role of Cocrystals in Pharmaceutical Science. *Drug Discovery Today* 2008, **13** (9–10), 440–446.
- [30] N. Blagden, M. de Matas, P. T. Gavan, P. York. Crystal Engineering of Active Pharmaceutical Ingredients to Improve Solubility and Dissolution Rates. *Advanced Drug Delivery Reviews* 2007, **59** (7), 617–630.
- [31] R. Hilfiker. *Polymorphism in the Pharmaceutical Industry*, Wiley: Germany, 2006.
- [32] G. R. Desiraju. Crystal Engineering: From Molecule to Crystal. *J. Am. Chem. Soc.* 2013, **135** (27), 9952–9967.
- [33] G. M. J. Schmidt. Photodimerization in the Solid State. *Pure and Applied Chemistry* 1971, **27** (4), 647–678.
- [34] G. R. Desiraju. *Crystal Engineering: The Design of Organic Solids*, Elsevier Science: Amsterdam, 1989.
- [35] G. R. Desiraju. Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis. *Angew. Chem. Int. Ed. Engl.* 1995, **34** (21), 2311–2327.

- [36] S. Datta, D. J. W. Grant. Crystal Structures of Drugs: Advances in Determination, Prediction and Engineering. *Nat Rev Drug Discov* 2004, **3** (1), 42–57.
- [37] C. B. Aakeröy, K. R. Seddon. The Hydrogen Bond and Crystal Engineering. *Chem. Soc. Rev.* 1993, **22** (6), 397–407.
- [38] G. R. Desiraju. Crystal Engineering: A Holistic View. *Angew. Chem. Int. Ed.* 2007, **46** (44), 8342–8356.
- [39] J. Gong, W. Tang. Chapter 2 - Nucleation. In *Pharmaceutical Crystals Sciences and Engineering*; John Wiley & Sons, Inc., 2018.
- [40] H.-H. Tung, E. L. Paul, M. Midler, J. A. McCauley. Chapter 1 - Introduction to Crystallization Issues. In *Crystallization of Organic Compounds*; 2009.
- [41] P. G. Vekilov. Nucleation. *Crystal Growth & Design* 2010, **10** (12), 5007–5019.
- [42] J. De Yoreo. Chapter 1 - A Perspective on Multistep Pathways of Nucleation. In *Crystallization via Nonclassical Pathways*, Zhang, Ed.; Washington, 2020.
- [43] P. G. Vekilov. Chapter 2 - Nonclassical Nucleation. In *Crystallization via Nonclassical Pathways*; Zhang, Ed.; Washington, 2020.
- [44] M. Pudipeddi, A. T. M. Serajuddin. Trends in Solubility of Polymorphs. *Journal of Pharmaceutical Sciences* 2005, **94** (5), 929–939.
- [45] J. Nývlt. The Ostwald Rule of Stages. *Cryst. Res. Technol.* 1995, **30** (4), 443–449.
- [46] J. W. P. Schmelzer, A. S. Abyzov. Chapter 9 - How Do Crystals Nucleate and Grow: Ostwald's Rule of Stages and Beyond. In *Thermal Physics and Thermal Analysis*; Springer International Publishing: Cham, 2017; Vol. 11, pp 195–211.
- [47] R. A. Van Santen. The Ostwald Step Rule. *J. Phys. Chem.* 1984, **88** (24), 5768–5769.
- [48] M. R. Cairn. Chapter 5 - Crystalline Polymorphism of Organic Compounds. In *Design of Organic Solids*; Springer Berlin Heidelberg: Berlin, Heidelberg, 1998; Vol. 198, pp 163–208.
- [49] A. Bhatia, S. Chopra, K. Nagpal, P. K. Deb, M. Tekade, R. K. Tekade. Chapter 2 - Polymorphism and Its Implications in Pharmaceutical Product Development. In *Dosage Form Design Parameters*; Elsevier, 2018; pp 31–65.
- [50] H. Nie, S. R. Byrn. Chapter 5 - Polymorphism and Phase Transitions. In *Pharmaceutical Crystals Sciences and Engineering*; John Wiley & Sons, Inc., 2018.
- [51] H. G. Brittain. *Polymorphism in Pharmaceutical Solids*, CRC Press.; 2016.
- [52] T. Threlfall. Structural and Thermodynamic Explanations of Ostwald's Rule. *Org. Process Res. Dev.* 2003, **7** (6), 1017–1027.
- [53] S. R. Chemburkar, J. Bauer, K. Deming, H. Spiwek, K. Patel, J. Morris, R. Henry, S. Spanton, W. Dziki, W. Porter, J. Quick, P. Bauer, J. Donaubauer, B. A. Narayanan, M. Soldani, D. Riley, K. McFarland. Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development. *Org. Process Res. Dev.* 2000, **4** (5), 413–417.

- [54] R. Thakuria, T. S. Thakur. Chapter 5.13 - Crystal Polymorphism in Pharmaceutical Science. In *Comprehensive Supramolecular Chemistry II*; Elsevier, 2017; Vol. 5, pp 283–309.
- [55] E. Grothe, H. Meekes, E. Vlieg, J. H. ter Horst, R. de Gelder. Solvates, Salts, and Cocrystals: A Proposal for a Feasible Classification System. *Crystal Growth & Design* 2016, **16** (6), 3237–3243.
- [56] S. Aitipamula, R. Banerjee, A. K. Bansal, K. Biradha, M. L. Cheney, A. R. Choudhury, G. R. Desiraju, A. G. Dikundwar, R. Dubey, N. Duggirala, P. P. Ghogale, S. Ghosh, P. K. Goswami, N. R. Goud, R. R. K. R. Jetti, P. Karpinski, P. Kaushik, D. Kumar, V. Kumar, B. Moulton, A. Mukherjee, G. Mukherjee, A. S. Myerson, V. Puri, A. Ramanan, T. Rajamannar, C. M. Reddy, N. Rodriguez-Hornedo, R. D. Rogers, T. N. G. Row, P. Sanphui, N. Shan, G. Shete, A. Singh, C. C. Sun, J. A. Swift, R. Thaimattam, T. S. Thakur, R. Kumar Thaper, S. P. Thomas, S. Tothadi, V. R. Vangala, N. Variankaval, P. Vishweshwar, D. R. Weyna, M. J. Zaworotko. Polymorphs, Salts, and Cocrystals: What's in a Name? *Crystal Growth & Design* 2012, **12** (5), 2147–2152.
- [57] S. L. Childs, G. P. Stahly, A. Park. The Salt–Cocrystal Continuum: The Influence of Crystal Structure on Ionization State. *Mol. Pharmaceutics* 2007, **4** (3), 323–338.
- [58] J. R. Stoczek, O. Socha, I. Cisarova, T. Slanina, M. Dracinsky. Importance of Nuclear Quantum Effects for Molecular Cocrystals with Short Hydrogen Bonds. *J. Am. Chem. Soc.* 2022, **144**, 7111–7116.
- [59] A. D. Bond. Chapter 2 - Fundamental Aspects of Salts and Co-Crystals. In *Pharmaceutical salts and co-crystals*; RSC Drug Discovery Series; Royal Society of Chemistry: Cambridge, 2011.
- [60] S. M. Reutzel-Edens. Chapter 10 - Analytical Techniques and Strategies for Salt/Co-Crystal Characterization. In *Pharmaceutical salts and co-crystals*; Wouters, J., Quéré, L., Eds.; RSC Drug Discovery Series; Royal Society of Chemistry: Cambridge, 2011.
- [61] B. C. Hancock, G. Zografi. Characteristics and Significance of the Amorphous State in Pharmaceutical Systems. *Journal of Pharmaceutical Sciences* 1997, **86** (1), 1–12.
- [62] L. Yu. Amorphous Pharmaceutical Solids: Preparation, Characterization and Stabilization. *Advanced Drug Delivery Reviews* 2001, **48** (1), 27–42.
- [63] J. M. Hutchinson. Physical Aging of Polymers. *Prog. Polym. Sci.* 1995, **20**, 703–760.
- [64] F. H. Stillinger. Supercooled Liquids, Glass Transitions, and the Kauzmann Paradox. *The Journal of Chemical Physics* 1988, **88** (12), 7818–7825.
- [65] S. N. Ronkart, C. S. Blecker, C. Deroanne, M. Paquot. Phénomène de la transition vitreuse appliquée aux glucides alimentaires amorphes à l'état de poudre. *Biotechnol. Agron. Soc. Environ.* 2009.
- [66] Walter. Kauzmann. The Nature of the Glassy State and the Behavior of Liquids at Low Temperatures. *Chem. Rev.* 1948, **43** (2), 219–256.

- [67] J. Perez, J. Y. Cavaillé. Temperature Dependence of the Molecular Dynamics in Amorphous Polymers through the Rubber-Glass Transition. *Journal of Non-Crystalline Solids* 1994, **172–174**, 1028–1036.
- [68] L. R. Hilden, K. R. Morris. Physics of Amorphous Solids. *Journal of Pharmaceutical Sciences* 2004, **93** (1), 3–12.
- [69] *CultureSciences-Physique - Ressources scientifiques pour l'enseignement des sciences physiques*. <https://culturesciencesphysique.ens-lyon.fr/> (accessed 2024-03-14).
- [70] F. SERNA, J. LAGNEAU, J.-M. CARPENTIER. La Diffraction Des Rayons X: Une Technique Puissante Pour Résoudre Certains Problèmes Industriels et Technologiques. 2014, No. 116.
- [71] S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Frišić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell. Mechanochemistry: Opportunities for New and Cleaner Synthesis. *Chem. Soc. Rev.* 2012, **41** (1), 413–447.
- [72] K. Horie, M. Barón, R. B. Fox, J. He, M. Hess, J. Kahovec, T. Kitayama, P. Kubisa, E. Maréchal, W. Mormann, R. F. T. Stepto, D. Tabak, J. Vohlídal, E. S. Wilks, W. J. Work. Definitions of Terms Relating to Reactions of Polymers and to Functional Polymeric Materials (IUPAC Recommendations 2003). *Pure and Applied Chemistry* 2004, **76** (4), 889–906.
- [73] G. Kaupp. Mechanochemistry: The Varied Applications of Mechanical Bond-Breaking. *CrystEngComm* 2009, **11** (3), 388–403.
- [74] M. K. Beyer, H. Clausen-Schaumann. Mechanochemistry: The Mechanical Activation of Covalent Bonds. *Chem. Rev.* 2005, **105** (8), 2921–2948.
- [75] P. Baláž, M. Achimovičová, M. Baláž, P. Billik, Z. Cherkezova-Zheleva, J. M. Criado, F. Delogu, E. Dutková, E. Gaffet, F. J. Gotor, R. Kumar, I. Mitov, T. Rojac, M. Senna, A. Streletskii, K. Wieczorek-Ciurowa. Hallmarks of Mechanochemistry: From Nanoparticles to Technology. *Chem. Soc. Rev.* 2013, **42** (18), 7571.
- [76] A. P. Amrute, J. De Bellis, M. Felderhoff, F. Schüth. Mechanochemical Synthesis of Catalytic Materials. *Chem. Eur. J.* 2021, **27** (23), 6819–6847.
- [77] O. Eguagie, J. S. Vyle, P. F. Conlon, M. A. Gilea, Y. Liang. Mechanochemistry of Nucleosides, Nucleotides and Related Materials. *Beilstein J. Org. Chem.* 2018, **14**, 955–970.
- [78] Mechanochemistry and Organic Synthesis: From Mystical to Practical.
- [79] P. Baláž. *Mechanochemistry in Nanoscience and Minerals Engineering*; Springer Berlin Heidelberg: Berlin, Heidelberg, 2008.
- [80] A. A. L. Michalchuk, E. V. Boldyreva, A. M. Belenguer, F. Emmerling, V. V. Boldyrev. Tribochemistry, Mechanical Alloying, Mechanochemistry: What Is in a Name? *Front. Chem.* 2021, **9**, 685789.
- [81] L. Takacs. Quicksilver from Cinnabar: The First Documented Mechanochemical Reaction? *JOM* 2000, **52** (1), 12–13.

- [82] L. Takacs. Walthère Spring and His Rivalry with M. Carey Lea. *Bull. Hist. Chem.* 2018, **43** (1).
- [83] H. K. Chan, E. Doelker. Polymorphic Transformation of Some Drugs Under Compression. *Drug Development and Industrial Pharmacy* 1985, **11** (2–3), 315–332.
- [84] R. Hüttenrauch, S. Fricke, P. Zielke. Mechanical Activation of Pharmaceutical Systems. *Pharmaceutical Research* 1985.
- [85] A. J. Lynch, C. A. Rowland. *The History of Grinding*, Society of Mining; Metallurgy and Exploration; 2005.
- [86] D. Hasa, W. Jones. Screening for New Pharmaceutical Solid Forms Using Mechanochemistry: A Practical Guide. *Advanced Drug Delivery Reviews* 2017, **117**, 147–161.
- [87] L. Takacs. The Historical Development of Mechanochemistry. *Chem. Soc. Rev.* 2013, **42** (18), 7649.
- [88] P. A. Julien, T. Friščić. Methods for Monitoring Milling Reactions and Mechanistic Studies of Mechanochemistry: A Primer. *Crystal Growth & Design* 2022, **22** (9), 5726–5754.
- [89] D. Cinčić, I. Brekalo, B. Kaitner. Effect of Atmosphere on Solid-State Amine–Aldehyde Condensations: Gas-Phase Catalysts for Solid-State Transformations. *Chem. Commun.* 2012, **48** (95), 11683.
- [90] M. Nagarathinam, A. Chanthapally, S. H. Lapidus, P. W. Stephens, J. J. Vittal. Mechanochemical Reactions of Coordination Polymers by Grinding with KBr. *Chem. Commun.* 2012, **48** (20), 2585.
- [91] F. Schneider, T. Szuppa, A. Stolle, B. Ondruschka, H. Hopf. Energetic Assessment of the Suzuki–Miyaura Reaction: A Curtate Life Cycle Assessment as an Easily Understandable and Applicable Tool for Reaction Optimization. *Green Chem.* 2009, **11** (11), 1894.
- [92] N. H. Ononiwu, E. T. Akinlabi. Effects of Ball Milling on Particle Size Distribution and Microstructure of Eggshells for Applications in Metal Matrix Composites. *Materials Today: Proceedings* 2020, **26**, 1049–1053.
- [93] M. Kumar, X. Xiong, Z. Wan, Y. Sun, D. C. W. Tsang, J. Gupta, B. Gao, X. Cao, J. Tang, Y. S. Ok. Ball Milling as a Mechanochemical Technology for Fabrication of Novel Biochar Nanomaterials. *Bioresource Technology* 2020, **312**, 123613.
- [94] X. Liu, W. Kang, X. Li, L. Zeng, Y. Li, Q. Wang, C. Zhang. Solid-State Mechanochemistry Advancing Two Dimensional Materials for Lithium-Ion Storage Applications: A Mini Review. *Nano Materials Science* 2023, **5** (2), 210–227.
- [95] *Advances in Green Synthesis: Avenues and Sustainability*, Inamuddin, Boddula, R., Ahamed, M. I., Khan, A., Eds.; Advances in Science, Technology & Innovation; Springer International Publishing: Cairo, 2021.
- [96] W. Pickhardt, S. Grätz, L. Borchardt. Direct Mechanocatalysis: Using Milling Balls as Catalysts. *Chemistry A European J* 2020, **26** (57), 12903–12911.

- [97] D. A. Fulmer, W. C. Shearouse, S. T. Medonza, J. Mack. Solvent-Free Sonogashira Coupling Reaction via High Speed Ball Milling. *Green Chem.* 2009, **11** (11), 1821.
- [98] M. Wohlgemuth, M. Mayer, M. Rappen, F. Schmidt, R. Saure, S. Grätz, L. Borchardt. From Inert to Catalytically Active Milling Media: Galvanostatic Coating for Direct Mechanocatalysis. *Angew Chem Int Ed* 2022, **61** (47), e202212694.
- [99] Retsch. Catalogue Général - Broyage, Tamisage, Assistance.
- [100] Retsch. Brochure: Broyeurs - Tamiseurs.
- [101] RETSCH – Laboratory Mills, Crushers and Sieve Shakers. <https://www.retsch.com/> (accessed 2024-03-29).
- [102] FRITSCH préparation d'échantillon et mesure granulométrique - broyage and granulométrie - Accueil – fritsch.de. <https://www.fritsch-france.fr/> (accessed 2024-03-29).
- [103] S.-Y. Lu, Q.-J. Mao, Z. Peng, X.-D. Li, J.-H. Yan. Simulation of Ball Motion and Energy Transfer in a Planetary Ball Mill. *Chinese Phys. B* 2012, **21** (7), 078201.
- [104] C. F. Burmeister, A. Stolle, R. Schmidt, K. Jacob, S. Breitung-Faes, A. Kwade. Experimental and Computational Investigation of Knoevenagel Condensation in Planetary Ball Mills. *Chem Eng & Technol* 2014, **37** (5), 857–864.
- [105] C. F. Burmeister, R. Schmidt, K. Jacob, S. Breitung-Faes, A. Stolle, A. Kwade. Effect of Stressing Conditions on Mechanochemical Knoevenagel Synthesis. *Chemical Engineering Journal* 2020, **396**, 124578.
- [106] M. Abdellaoui, E. Gaffet. The Physics of Mechanical Alloying in a Modified Horizontal Rod Mill: Mathematical Treatment. *Acta Materialia* 1996, **44** (2), 725–734.
- [107] S. Rosenkranz, S. Breitung-Faes, A. Kwade. Experimental Investigations and Modelling of the Ball Motion in Planetary Ball Mills. *Powder Technology* 2011, **212** (1), 224–230.
- [108] V. V. Boldyrev. Mechanochemistry and Mechanical Activation of Solids. *Russ. Chem. Rev.* 2006, **75** (3), 177–189.
- [109] E. Boldyreva. Mechanochemistry of Inorganic and Organic Systems: What Is Similar, What Is Different? *Chem. Soc. Rev.* 2013, **42** (18), 7719.
- [110] I. A. Tumanov, A. F. Achkasov, S. A. Myz, E. V. Boldyreva, V. V. Boldyrev. Different Effect of Impact and Shear Mechanical Treatment on Mechanochemical Cocrystallization of Piroxicam and Succinic Acid. *Dokl Chem* 2014, **457** (2), 154–159.
- [111] O. V. Lapshin, E. V. Boldyreva, V. V. Boldyrev. Role of Mixing and Milling in Mechanochemical Synthesis (Review). *Russ. J. Inorg. Chem.* 2021, **66** (3), 433–453.
- [112] A. A. L. Michalchuk, I. A. Tumanov, V. A. drebuschschak, E. V. Boldyreva. Advances in Elucidating Mechanochemical Complexities via

- Implementation of a Simple Organic System. *Faraday Discuss.* 2014, **170**, 311–335.
- [113] J. Eckert, L. Schultz, E. Hellstern, K. Urban. Glass-Forming Range in Mechanically Alloyed Ni-Zr and the Influence of the Milling Intensity. *Journal of Applied Physics* 1988, **64** (6), 3224–3228.
- [114] F. Padella, E. Paradiso, N. Burgio, M. Magini, S. Martelli, W. Guo, A. Iasonna. Mechanical Alloying of the Pd-Si System in Controlled Conditions of Energy Transfer. *Journal of the Less Common Metals* 1991, **175** (1), 79–90.
- [115] J. M. Andersen, J. Mack. Decoupling the Arrhenius Equation via Mechanochemistry. *Chem. Sci.* 2017, **8**, 5447–5453.
- [116] L. Takacs, J. S. McHenry. Temperature of the Milling Balls in Shaker and Planetary Mills. *J Mater Sci* 2006, **41** (16), 5246–5249.
- [117] *Investigations and Applications of Severe Plastic Deformation*; Lowe, T. C., Valiev, R. Z., Eds.; Springer Netherlands: Dordrecht, 2000.
- [118] R. Schmidt, H. Martin Scholze, A. Stolle. Temperature Progression in a Mixer Ball Mill. *Int J Ind Chem* 2016, **7** (2), 181–186.
- [119] F. P. Bowden, A. Yoffe. *Initiation and Growth of Explosion in Liquids and Solids*; Cambridge University Press: Cambridge, 1952.
- [120] P. A. Thiessen, K. Meyer, G. Heinicke. *Grundlagen Der Tribochemie*; Akademie Verlag: Berlin, 1967.
- [121] M. J. M. Batista, D. Rodríguez-Padrón, A. R. P. Santiago, R. Luque. Mechanochemistry: Towards Sustainable Design of Advanced Nanomaterials for Electrochemical Energy Storage and Catalytic Applications.
- [122] P. G. Fox. Mechanically Initiated Chemical Reactions in Solids. *Journal of Materials Science* 1975, **10**, 340–360.
- [123] L. Batzdorf, F. Fischer, M. Wilke, K.-J. Wenzel, F. Emmerling. Direct In Situ Investigation of Milling Reactions Using Combined X-Ray Diffraction and Raman Spectroscopy. *Angewandte Chemie International Edition* 2015, **54** (6), 1799–1802.
- [124] I. Halasz, S. A. J. Kimber, P. J. Beldon, A. M. Belenguer, F. Adams, V. Honkimäki, R. C. Nightingale, R. E. Dinnebier, T. Frišćić. In Situ and Real-Time Monitoring of Mechanochemical Milling Reactions Using Synchrotron X-Ray Diffraction. *Nat Protoc* 2013, **8** (9), 1718–1729.
- [125] D. Tan, L. Loots, T. Frišćić. Towards Medicinal Mechanochemistry: Evolution of Milling from Pharmaceutical Solid Form Screening to the Synthesis of Active Pharmaceutical Ingredients (APIs). *Chem. Commun.* 2016, **52** (50), 7760–7781.
- [126] D. Gracin, V. Štrukil, T. Frišćić, I. Halasz, K. Užarević. Laboratory Real-Time and In Situ Monitoring of Mechanochemical Milling Reactions by Raman Spectroscopy. *Angew Chem Int Ed* 2014, **53** (24), 6193–6197.
- [127] D. Tan, F. García. Main Group Mechanochemistry: From Curiosity to Established Protocols. *Chem. Soc. Rev.* 2019, **48** (8), 2274–2292.
- [128] J.-L. Do, T. Frišćić. Mechanochemistry: A Force of Synthesis. *ACS Cent. Sci.* 2017, **3** (1), 13–19.

- [129] N. Tumanov, V. Ban, A. Poulain, Y. Filinchuk. 3D-Printed Jars for Ball-Milling Experiments Monitored *in Situ* by X-Ray Powder Diffraction. *J Appl Crystallogr* 2017, **50** (4), 994–999.
- [130] G. Rothenberg, A. P. Downie, C. L. Raston, J. L. Scott. Understanding Solid/Solid Organic Reactions. *J. Am. Chem. Soc.* 2001, **123** (36), 8701–8708.
- [131] T. Friščić, W. Jones. Recent Advances in Understanding the Mechanism of Cocrystal Formation via Grinding. *Crystal Growth & Design* 2009, **9** (3), 1621–1637.
- [132] T. F. C. Ic, W. Jones. Chapter 8 - Application of Mechanochemistry in the Synthesis and Discovery of New Pharmaceutical Forms: Co-Crystals, Salts and Coordination Compounds. In *Pharmaceutical Salts and Co-crystals*; RSC Drug Discovery Series; Royal Society of Chemistry: Cambridge.
- [133] T. Friščić, S. L. Childs, S. A. A. Rizvi, W. Jones. The Role of Solvent in Mechanochemical and Sonochemical Cocrystal Formation: A Solubility-Based Approach for Predicting Cocrystallisation Outcome. *CrystEngComm* 2009, **11**, 418–426.
- [134] P. Ying, J. Yu, W. Su. Liquid-Assisted Grinding Mechanochemistry in the Synthesis of Pharmaceuticals. *Adv. Synth. Catal.* 2021, **363** (5), 1246–1271.
- [135] F. Fischer, A. Heidrich, S. Greiser, S. Benemann, K. Rademann, F. Emmerling. Polymorphism of Mechanochemically Synthesized Cocrystals: A Case Study. *Crystal Growth & Design* 2016, **16** (3), 1701–1707.
- [136] D. Hasa, G. Schneider Rauber, D. Voinovich, W. Jones. Cocrystal Formation through Mechanochemistry: From Neat and Liquid-Assisted Grinding to Polymer-Assisted Grinding. *Angew. Chem. Int. Ed.* 2015, **54** (25), 7371–7375.
- [137] T. Friščić. New Opportunities for Materials Synthesis Using Mechanochemistry. *J. Mater. Chem.* 2010, **20** (36), 7599.
- [138] Y. Xiao, C. Wu, X. Hu, K. Chen, L. Qi, P. Cui, L. Zhou, Q. Yin. Mechanochemical Synthesis of Cocrystal: From Mechanism to Application. *Crystal Growth & Design* 2023, **23** (6), 4680–4700.
- [139] R. Solaimalai, G. Shinde, A. Dharamsi, C. Kokare. Exploring the Novel Green Eutectic Solvent for the Synthesis of 4-Hydroxy-2-Methyl-N-2-Pyridinyl-2H-1,2-Benzothiazine-3-Carboxamide 1,1-Dioxide with Benzoic Acid Cocrystal Using a Co-Grinding Technique. *New Journal of Chemistry* 2020, **44**, 17088–17098.
- [140] C. A. Wurtz. Sur Un Aldéhyde-Alcool. *Bull. Soc. Chim. Fr.* 1872, **17**, 436–442.
- [141] S. Itoh, S. Sonoike, M. Kitamura, S. Aoki. Design and Synthesis of Chiral Zn²⁺ Complexes Mimicking Natural Aldolases for Catalytic C–C Bond Forming Reactions in Aqueous Solution. *IJMS* 2014, **15** (2), 2087–2118.
- [142] W. J. Rutter. Evolution of Aldolase. *Federation Proceedings* 1964, **23**, 1248–1257.

- [143] W.-D. Fessner, A. Schneider, H. Held, G. Sinerius, C. Walter, M. Hixon, J. V. Schloss. The Mechanism of Class II, Metal-Dependent Aldolases. *Angew. Chem. Int. Ed. Engl.* 1996, **35** (19), 2219–2221.
- [144] A. S. Mildvan, R. D. Kobes, W. J. Rutter. Magnetic Resonance Studies of the Role of the Divalent Cation in the Mechanism of Yeast Aldolase. *Biochemistry* 1971, **10** (7), 1191–1204.
- [145] K. H. Hopmann. Quantum Chemical Studies of Asymmetric Reactions: Historical Aspects and Recent Examples. *Int. J. Quantum Chem.* 2015, **115** (18), 1232–1249.
- [146] C. F. Barbas. Organocatalysis Lost: Modern Chemistry, Ancient Chemistry, and an Unseen Biosynthetic Apparatus. *Angew. Chem. Int. Ed.* 2008, **47** (1), 42–47.
- [147] Z. G. Hajos, D. R. Parrish. Asymmetric Synthesis of Bicyclic Intermediates of Natural Product Chemistry. *J. Org. Chem.* 1974, **39** (12), 1615–1621.
- [148] P. H.-Y. Cheong, C. Y. Legault, J. M. Um, N. Çelebi-Ölçüm, K. N. Houk. Quantum Mechanical Investigations of Organocatalysis: Mechanisms, Reactivities, and Selectivities. *Chem. Rev.* 2011, **111** (8), 5042–5137.
- [149] C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. B. Kagan. Nonlinear Effects in Asymmetric Synthesis. Examples in Asymmetric Oxidations and Aldolization Reactions. *J. Am. Chem. Soc.* 1986, **108** (9), 2353–2357.
- [150] C. Agami, C. Puchot, H. Sevestre. Is The Mechanisme of the Proline-Catalyzed Enantioselective Aldol Reaction Related to Biochemical Processes? *Perqamon Press Ltd* 1986, 4.
- [151] C. Agami, F. Meynier, C. Puchot. New Insights into the Mechanism of the Proline-Catalyzed Asymmetric Robinson Cyclisation; Structure of Two Intermediates. Asymmetric Dehydration. *Tetrahedron* 1984, 8.
- [152] S. Bahmanyar, K. N. Houk. The Origin of Stereoselectivity in Proline-Catalyzed Intramolecular Aldol Reactions. *J. Am. Chem. Soc.* 2001, **123** (51), 12911–12912.
- [153] H. Gröger, E. M. Vogl, M. Shibasaki. New Catalytic Concepts for the Asymmetric Aldol Reaction. *chem. Eur. J.* 1998, 5.
- [154] T. Bach. Catalytic Enantioselective C-C Coupling-Allyl Transfer and Mukaiyama Aldol Reaction. *Angew. Chem. Int. Ed. Engl.* 1994, **33** (4), 417–419.
- [155] S. E. Denmark, R. A. Stavenger, K.-T. Wong. Lewis Base-Catalyzed, Asymmetric Aldol Additions of Methyl Ketone Enolates. *J. Org. Chem.* 1998, **63** (4), 918–919.
- [156] B. List, R. A. Lerner, C. F. Barbas. Proline-Catalyzed Direct Asymmetric Aldol Reactions. *J. Am. Chem. Soc.* 2000, **122** (10), 2395–2396.
- [157] H. E. Zimmerman, M. D. Traxler. The Stereochemistry of the Ivanov and Reformatsky Reactions. I. *J. Am. Chem. Soc.* 1957, **79** (8), 1920–1923.
- [158] L. Hoang, S. Bahmanyar, K. N. Houk, B. List. Kinetic and Stereochemical Evidence for the Involvement of Only One Proline

Molecule in the Transition States of Proline-Catalyzed Intra- and Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* 2003, **125** (1), 16–17.

- [159] K. Sakthivel, W. Notz, T. Bui, C. F. Barbas. Amino Acid Catalyzed Direct Asymmetric Aldol Reactions: A Bioorganic Approach to Catalytic Asymmetric Carbon–Carbon Bond-Forming Reactions. *J. Am. Chem. Soc.* 2001, **123** (22), 5260–5267.
- [160] S. Bahmanyar, K. N. Houk, H. J. Martin, B. List. Quantum Mechanical Predictions of the Stereoselectivities of Proline-Catalyzed Asymmetric Intermolecular Aldol Reactions. *J. Am. Chem. Soc.* 2003, **125** (9), 2475–2479.
- [161] B. List, L. Hoang, H. J. Martin. New Mechanistic Studies on the Proline-Catalyzed Aldol Reaction. *PNAS* 2004, **101** (16), 5839–5842.
- [162] F. R. Clemente, K. N. Houk. Computational Evidence for the Enamine Mechanism of Intramolecular Aldol Reactions Catalyzed by Proline. *Angew. Chem.* 2004, **116** (43), 5890–5892.
- [163] B. List. Asymmetric Aminocatalysis. *Synlett* 2001, **2001** (11), 1675–1686.
- [164] C. Liu, B. Bradshaw, F. Maseras, J. Bonjoch, M. Besora. Mechanistic Study on the Asymmetric Synthesis of the Wieland-Miescher Ketone and Analogs. *ChemCatChem* 2019, **11** (16), 4064–4071.
- [165] K. Chakrabarty, A. Ghosh, A. Basak, G. K. Das. Stabilization of the Transition Structures of Organocatalytic Asymmetric Direct Aldol Reaction in Wet Solvent Free Condition by the Formation of Water Assisted Supramolecular Network: A DFT Study. *Computational and Theoretical Chemistry* 2015, **1062**, 11–23.
- [166] M. J. Ajitha, C. H. Suresh. A Higher Energy Conformer of (S)-Proline Is the Active Catalyst in Intermolecular Aldol Reaction: Evidence from DFT Calculations. *Journal of Molecular Catalysis A: Chemical* 2011, **345** (1–2), 37–43.
- [167] A. Armstrong, R. A. Boto, P. Dingwall, J. Contreras-García, M. J. Harvey, N. J. Mason, H. S. Rzepa. The Houk–List Transition States for Organocatalytic Mechanisms Revisited. *Chem. Sci.* 2014, **5** (5), 2057–2071.
- [168] M. Orlandi, M. Ceotto, M. Benaglia. Kinetics versus Thermodynamics in the Proline Catalyzed Aldol Reaction. *Chem. Sci.* 2016, **7** (8), 5421–5427.
- [169] E. J. Mattioli, M. Calvaresi, A. Bottoni, T. D. Marforio. Hajos–Parrish–Eder–Sauer–Wiechert Reaction: The Definitive Reaction Mechanism Deciphered by DFT Calculations. *Molecular Catalysis* 2022, **522**, 112245.
- [170] C. Rougeot, H. Situ, B. H. Cao, V. Vlachos, J. E. Hein. Automated Reaction Progress Monitoring of Heterogeneous Reactions: Crystallization-Induced Stereoselectivity in Amine-Catalyzed Aldol Reactions. *React. Chem. Eng.* 2017, **2** (2), 226–231.
- [171] N. Oguni, Y. Matsuda, T. Kaneko. Asymmetric Amplifying Phenomena in Enantioselective Addition of Diethylzinc to Benzaldehyde. *J. Am. Chem. Soc.* 1988, **110** (23), 7877–7878.

- [172] C. Girard, H. B. Kagan. Nonlinear Effects in Asymmetric Synthesis and Stereoselective Reactions: Ten Years of Investigation. *Angew. Chem. Int. Ed.* 1998, **37**, 2922–2959.
- [173] D. G. Blackmond. Kinetic Aspects of Nonlinear Effects in Asymmetric Catalysis. *Acc. Chem. Res.* 2000, **33** (6), 402–411.
- [174] J.-C. M. Monbaliu. L'asymétrie en chimie organique: des effets non-linéaires jusqu'à l'apparition de la vie. *Bulletin de la Société Royale des Sciences de Liège* 2014, **83**, 61–77.
- [175] M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, U. Pandya, A. Armstrong, D. G. Blackmond. Thermodynamic Control of Asymmetric Amplification in Amino Acid Catalysis. *Nature* 2006, **441** (7093), 621–623.
- [176] R. M. Kellogg. The Crystallization Behavior of Proline and Its Role in Asymmetric Organocatalysis. *Angew. Chem. Int. Ed.* 2007, **46** (4), 494–497.
- [177] J. Jacques, A. Collet, S. H. Wilen. *Enantiomers, Racemates, and Resolutions*, Krieger Publishing, 1994.
- [178] M. Klussmann, A. J. P. White, A. Armstrong, D. G. Blackmond. Rationalization and Prediction of Solution Enantiomeric Excess in Ternary Phase Systems. *Angew. Chem. Int. Ed.* 2006, **45** (47), 7985–7989.
- [179] A. Alvarez Rodrigo, H. Lorenz, A. Seidel-Morgenstern. Online Monitoring of Preferential Crystallization of Enantiomers. *Chirality* 2004, **16** (8), 499–508.
- [180] M. Klussmann, T. Izumi, A. J. P. White, A. Armstrong, D. G. Blackmond. Emergence of Solution-Phase Homochirality via Crystal Engineering of Amino Acids. *J. Am. Chem. Soc.* 2007, **129** (24), 7657–7660.
- [181] B. Rodríguez, A. Bruckmann, T. Rantanen, C. Bolm. Solvent-Free Carbon-Carbon Bond Formations in Ball Mills. *Adv. Synth. Catal.* 2007, **349** (14–15), 2213–2233.
- [182] Y. Hayashi, S. Aratake, T. Itoh, T. Okano, T. Sumiya, M. Shoji. Dry and Wet Prolines for Asymmetric Organic Solvent-Free Aldehyde–Aldehyde and Aldehyde–Ketone Aldol Reactions. *Chem. Commun.* 2007, 957–959.
- [183] B. Rodríguez, T. Rantanen, C. Bolm. Solvent-Free Asymmetric Organocatalysis in a Ball Mill. *Angew. Chem. Int. Ed.* 2006, **45** (41), 6924–6926.
- [184] P. M. Pihko, K. M. Laurikainen, A. Usano, A. I. Nyberg, J. A. Kaavi. Effect of Additives on the Proline-Catalyzed Ketone–Aldehyde Aldol Reactions. *Tetrahedron* 2006, **62** (2–3), 317–328.
- [185] B. List. Enamine Catalysis Is a Powerful Strategy for the Catalytic Generation and Use of Carbanion Equivalents. *Acc. Chem. Res.* 2004, **37** (8), 548–557.
- [186] Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji. Highly Diastereo- and Enantioselective Direct Aldol Reactions in Water. *Angew. Chem. Int. Ed.* 2006, **45** (6), 958–961.

- [187] N. Mase, Y. Nakai, N. Ohara, H. Yoda, K. Takabe, F. Tanaka, C. F. Barbas. Organocatalytic Direct Asymmetric Aldol Reactions in Water. *J. Am. Chem. Soc.* 2006, **128** (3), 734–735.
- [188] M. C. Pirrung. Acceleration of Organic Reactions through Aqueous Solvent Effects. *Chem. Eur. J.* 2006, **12** (5), 1312–1317.
- [189] B. Rodríguez, A. Bruckmann, C. Bolm. A Highly Efficient Asymmetric Organocatalytic Aldol Reaction in a Ball Mill. *Chem. Eur. J.* 2007, **13** (17), 4710–4722.
- [190] A. Bruckmann, B. Rodríguez, C. Bolm. Nonlinear Effects in Proline-Catalysed Aldol Reactions under Solvent-Free Conditions Based on the Ternary Phase Behaviour of Scalemic Proline. *CrystEngComm* 2009, **11** (3), 404.
- [191] R. L. Kayushina, B. K. Vainshtein. Rentgenografiye Opredepenie Strukturi L-Prolina. *Kristallografiya* 1965, **10**, 833–844.
- [192] N. Tumanova, N. Tumanov, K. Robeyns, F. Fischer, L. Fusaro, F. Morelle, V. Ban, G. Hautier, Y. Filinchuk, J. Wouters, T. Leyssens, F. Emmerling. Opening Pandora's Box: Chirality, Polymorphism, and Stoichiometric Diversity in Flurbiprofen/Proline Cocrystals. *Crystal Growth & Design* 2018, **18** (2), 954–961.
- [193] J. Janczak, P. Luger. L-Proline Monohydrate at 100K. *Acta Crystallogr C Cryst Struct Commun* 1997, **53** (12), 1954–1956.
- [194] S. Myung, M. Pink, M.-H. Baik, D. E. Clemmer. DL-Proline. *Acta Crystallogr C Cryst Struct Commun* 2005, **61** (8), o506–o508.
- [195] S. Padmanabhan, S. Suresh, M. Vijayan. DL-Proline Monohydrate. *Acta Crystallogr C Cryst Struct Commun* 1995, **51** (10), 2098–2100.
- [196] F. Zhou, C. Body, K. Robeyns, T. Leyssens, O. Shemchuk. On the Pairwise Cocrystallization of Racemic Compounds. *CrystEngComm* 2023, **25** (20), 3060–3065.
- [197] C. B. Aakeroy, G. S. Bahra, C. R. Brown, P. B. Hitchcock, Y. Patell, K. R. Seddon. L-Proline 2,5-Dihydroxybenzoic Acid (1/1): A Zwitterion Co-Crystal. *Acta Chemica Scandinavica* 1995, **49**, 762–767.
- [198] A. Tilborg, T. Leyssens, B. Norberg, J. Wouters. Structural Study of Prolinium/Fumaric Acid Zwitterionic Cocrystals: Focus on Hydrogen-Bonding Pattern Involving Zwitterionic (Ionic) Heterosynthons. *Crystal Growth & Design* 2013, **13** (6), 2373–2389.
- [199] G. S. Prasad, M. Vijayan. X-Ray Studies on Crystalline Complexes Involving Amino Acids and Peptides. XXV. Structures of DL-Proline Hemisuccinic Acid and Glycyl-L-Histidinium Semisuccinate Monohydrate and a Comparative Study of Amino-Acid and Peptide Complexes of Succinic Acid. *Acta Crystallogr B Struct Sci* 1993, **49** (2), 348–356.
- [200] M. Gausmann, A. Jupke. Dynamic Modeling of Electrochemical pH-Swing Extraction. *Chemie Ingenieur Technik* 2020, **92** (12), 1953–1961.
- [201] I. Fleming. *Les réactions péricycliques*, EDP Sciences, 2020.

- [202] A. Mustafa. Dimerization Reactions in Sunlight. *Chemical Reviews* 1951, **51** (1), 1–23.
- [203] R. Stoermer, G. Foerster. Truxillic Acids and Truxones. *Ber. dtsh. Chem. Ges.* 1919, **52**, 1255–1272.
- [204] R. Stoermer, E. Laage. Über Die Siebente Säure Der Truxillsäuregruppe, Die Neo-Truxinsäure. *Ber. dtsh. Chem. Ges.* 1921, **54** (1), 96–101.
- [205] H. Stobbe. Lichtreaktionen Der Allo-und Isozimtsäuren. *Ber. dtsh. Chem. Ges.* 1919, **52**, 666–672.
- [206] H. Stobbe, K. F. Steinberger. Lichtreaktionen Der Trans-und cis-Zimtsäuren. *Ber. dtsh. Chem. Ges.* 1922, **55**, 2225–2245.
- [207] A. W. K. de Jong. β -Trans-Cinnamic Acid. *Ber. dtsh. Chem. Ges.* 1922, No. 55, 463–474.
- [208] H. I. Bernstein, W. C. Quimby. The Photochemical Dimerization of Trans-Cinnamic Acid. *J. Am. Chem. Soc.* 1943, **65** (10), 1845–1846.
- [209] A. W. K. de Jong. *Chem. Weekblad* 1929, **26**, 270.
- [210] G. Ciamician, P. Silber. Chemische Lichtwirkungen. *Ber. dtsh. Chem. Ges.* 1902, **35** (2), 1992–2000.
- [211] D. S. Noyce, H. S. Avarbock. The Effect of Substituents upon the Rate of Isomerization of Substituted Cis-Cinnamic Acid. *J. Am. Chem. Soc.* 1961, **84** (9), 1644–1646.
- [212] M. B. Hocking. Photochemical and Thermal Isomerizations of *Cis* - and *Trans* -Cinnamic Acids, and Their Photostationary State. *Can. J. Chem.* 1969, **47** (24), 4567–4576.
- [213] H. Stobbe, A. Lehfelddt. Polymerisationen Und Depolymerisationen Durch Licht Verschiedener Wellenlänge, II.: α - Und β -Trans-Zimtsäure, Allo-Zimtsäure Und Ihre Dimeren. *Ber. dtsh. Chem. Ges.* 1925, **58** (10), 2415–2427.
- [214] F. Israel Sonntag. Reactions of Organic Compounds in the Solid State: A Study of the Photochemistry of Crystalline Cinnamic Acids, Hebrew University, Jerusalem, 1963.
- [215] M. D. Cohen, G. M. J. Schmidt. Topochemistry. Part I. A Survey. *J. Chem. Soc.* 1964, 1996–2000.
- [216] M. D. Cohen, G. M. J. Schmidt, F. I. Sonntag. Topochemistry. Part II. The Photochemistry of Trans-Cinnamic Acids. *J. Chem. Soc.* 1964, 2000–2013.
- [217] M. D. Cohen. Solid-State Photochemical Reaction. *Tetrahedron* 1987, **43** (7), 1211–1224.
- [218] J. Bregman, G. M. J. Schmidt, K. Osaki, F. I. Sonntag. Topochemistry. Part IV. I The Crystal Chemistry of Some Cis-Cinnarnic Acids. *Journal of the Chemical Society* 1964, 2021–2030.
- [219] V. Ramamurthy, K. Venkatesan. Photochemical Reactions of Organic Crystals. *Chem. Rev.* 1987, **87** (2), 433–481.
- [220] S. D. M. Atkinson, M. J. Almond, P. Hollins, S. L. Jenkins. The Photodimerisation of the A- and b-Forms of Trans-Cinnamic Acid: A

Study of Single Crystals by Vibrational Microspectroscopy. *Spectrochimica Acta Part A* 2003, **59**, 629–635.

- [221] G. Kaupp. Solid-State Photochemistry: New Approaches Based on New Mechanistic Insights. *International Journal of Photoenergy* 2001, **3** (2), 55–62.
- [222] Atkins, Jones, Laverman. *Principes de Chimie*, 2nd ed.; De Boeck, 2014.
- [223] G. M. J. Schmidt. Topochemistry. Part III. The Crystal Chemistry of Some Trans-Cinnamic Acids. *J. Chem. Soc.* 1964, 2014–2021.
- [224] Y. Ito, B. Borecka, J. Trotter, J. R. Scheffer. Control of Solid-State Photodimerization of Trans-Cinnamic Acid by Double Salt Formation with Diamines. *Tetrahedron Letters* 1995, **36** (34), 6083–6086.
- [225] B. B. Yagci, Y. Zorlu, Y. E. Türkmen. Template-Directed Photochemical Homodimerization and Heterodimerization Reactions of Cinnamic Acids. *J. Org. Chem.* 2021, **86** (18), 13118–13128.
- [226] H. Zitt, I. Dix, H. Hopf, P. G. Jones. 4,15-Diamino[2.2]Paracyclophane, a Reusable Template for Topochemical Reaction Control in Solution. *Eur. J. Org. Chem.* 2002, No. 14, 2298–2307.
- [227] B. König, S. Leue, C. Horn, A. Caudan, J.-P. Desvergne, H. Bouas-Laurent. Synthesis of Medium-Size Macrocycles by Cinnamate [2 + 2] Photoaddition. *Liebigs Ann./Recl.* 2006, **1996** (8), 1231–1233.
- [228] M. W. Ghosn, C. Wolf. Stereocontrolled Photodimerization with Congested 1,8-Bis(4'-Anilino)Naphthalene Templates. *J. Org. Chem.* 2010, **75** (19), 6653–6659.
- [229] T. Caronna, R. Liantonio, T. A. Logothetis, P. Metrangolo, T. Pilati, G. Resnati. Halogen Bonding and $\pi\cdots\pi$ Stacking Control Reactivity in the Solid State. *J. Am. Chem. Soc.* 2004, **126** (14), 4500–4501.
- [230] Q. Jay, L. R. MacGillivray. Hydrogen- and Halogen-Bonded Binary Cocrystals with Ditopic Components: Systematic Structural and Photoreactivity Properties That Provide Access to a Completed Series of Symmetrical Cyclobutanes. *Crystal Growth & Design* 2020, **20** (11), 7501–7515.
- [231] I. G. Georgiev, L. R. MacGillivray. Metal-Mediated Reactivity in the Organic Solid State: From Self-Assembled Complexes to Metal–Organic Frameworks. *Chem. Soc. Rev.* 2007, **36** (8), 1239.
- [232] C. Li, G. Campillo-Alvarado, D. C. Swenson, L. R. MacGillivray. Exploiting Auophilic Interactions in a [2 + 2] Photocycloaddition: Single-Crystal Reactivity with Changes to Surface Morphology. *Inorg. Chem.* 2019, **58** (19), 12497–12500.
- [233] G. Campillo-Alvarado, C. Li, Z. Feng, K. M. Hutchins, D. C. Swenson, H. Höpfl, H. Morales-Rojas, L. R. MacGillivray. Single-Crystal-to-Single-Crystal [2 + 2] Photodimerization Involving B←N Coordination with Generation of a Thiophene Host. *Organometallics* 2020, **39** (12), 2197–2201.
- [234] L. R. MacGillivray, G. S. Papaefstathiou, T. Friščić, T. D. Hamilton, D.-K. Bučar, Q. Chu, D. B. Varshney, I. G. Georgiev. Supramolecular Control of

Reactivity in the Solid State: From Templates to Ladderanes to Metal–Organic Frameworks. *Acc. Chem. Res.* 2008, **41** (2), 280–291.

- [235] L. R. MacGillivray, J. L. Reid, J. A. Ripmeester. Supramolecular Control of Reactivity in the Solid State Using Linear Molecular Templates. *J. Am. Chem. Soc.* 2000, **122** (32), 7817–7818.
- [236] X. Gao, T. Friščić, L. R. MacGillivray. Supramolecular Construction of Molecular Ladders in the Solid State. *Angew. Chem. Int. Ed.* 2004, **43** (2), 232–236.
- [237] G. S. Papaefstathiou, A. J. Kipp, L. R. MacGillivray. Exploiting Modularity in Template-Controlled Synthesis: A New Linear Template to Direct Reactivity within Discrete Hydrogen-Bonded Molecular Assemblies in the Solid State. *Chem. Commun.* 2001, **23**, 2462–2463.
- [238] L. R. MacGillivray. From Engineering Crystals to Engineering Molecules: Emergent Consequences of Controlling Reactivity in the Solid State Using Linear Templates. *CrystEngComm* 2002, **4** (7), 37–41.
- [239] T. Friščić, L. R. MacGillivray. 'Template-Switching': A Supramolecular Strategy for the Quantitative, Gram-Scale Construction of a Molecular Target in the Solid State. *Chem. Commun.* 2003, **11**, 1306–1307.
- [240] L. R. MacGillivray. Organic Synthesis in the Solid State via Hydrogen-Bond-Driven Self-Assembly. *J. Org. Chem.* 2008, **73** (9), 3311–3317.
- [241] M. B. J. Atkinson, S. V. S. Mariappan, D.-K. Bučar, J. Baltrusaitis, T. Friščić, N. G. Sinada, L. R. MacGillivray. Crystal Engineering Rescues a Solution Organic Synthesis in a Cocrystallization That Confirms the Configuration of a Molecular Ladder. *Proc. Natl. Acad. Sci. U.S.A.* 2011, **108** (27), 10974–10979.
- [242] E. Elacqua, K. A. Kummer, R. H. Groeneman, E. W. Reinheimer, L. R. MacGillivray. Post-Application of Dry Vortex Grinding Improves the Yield of a [2 + 2] Photodimerization: Addressing Static Disorder in a Cocrystal. *Journal of Photochemistry and Photobiology A: Chemistry* 2016, **331**, 42–47.
- [243] T. Friščić, E. Elacqua, S. Dutta, S. M. Oburn, L. R. MacGillivray. Total Syntheses Supramolecular Style: Solid-State Construction of [2.2]Cyclophanes with Modular Control of Stereochemistry. *Crystal Growth & Design* 2020, **20** (4), 2584–2589.
- [244] A. N. Sokolov, D.-K. Bučar, J. Baltrusaitis, S. X. Gu, L. R. MacGillivray. Supramolecular Catalysis in the Organic Solid State through Dry Grinding. *Angewandte Chemie International Edition* 2010, **49** (25), 4273–4277.
- [245] S. P. Yelgaonkar, D. C. Swenson, L. R. MacGillivray. Supramolecular Chemistry under Mechanochemical Conditions: A Small Molecule Template Generated and Integrated into a Molecular-to-Supramolecular and Back-to-Molecular Cascade Reaction. *Chem. Sci.* 2020, **11** (13), 3569–3573.
- [246] J. Stojaković, B. S. Farris, L. R. MacGillivray. Vortex Grinding for Mechanochemistry: Application for Automated Supramolecular

- Catalysis and Preparation of a Metal–Organic Framework. *Chem. Commun.* 2012, **48**, 7958–7960.
- [247] J. Stojakovic, L. R. MacGillivray. Chapter 5 - Cocrystals and Templates to Control Solid-State [2+2] Photodimerizations. In *Comprehensive Supramolecular Chemistry II*; Elsevier: Iowa, 2017; Vol. 7, p 15.
- [248] D. A. Wierda, T. L. Feng, A. R. Barron. Structure of [Alpha]-Trans-Cinnamic Acid. *Acta Crystallographica Section C Crystal Structure Communications* 1989, **45**, 338.
- [249] I. Abdelmoty, V. Buchholz, L. Di, C. Guo, K. Kowitz, V. Enkelmann, G. Wegner, B. M. Foxman. Polymorphism of Cinnamic and α -Truxillic Acids: New Additions to an Old Story. *Crystal Growth & Design* 2005, **5** (6), 2210–2217.
- [250] M. A. Fernandes, D. C. Levendis, C. B. de Koning. Solvate and Polymorphs of Ortho-Ethoxy-Trans-Cinnamic Acid: The Crystal and Molecular Structures. *Crystal Engineering* 2001, **4** (2–3), 215–231.
- [251] R. S. Gopalan, G. U. Kulkarni. An Investigation of the Photo-Reactive and Unreactive Polymorphs of Ortho-Ethoxy Cinnamic Acid and of Its Photodimer. *J Chem Sci* 2001, **113** (4), 307–324.
- [252] M. A. Fernandes, D. C. Levendis. Photodimerization of the α' -Polymorph of Ortho-Ethoxy-Trans-Cinnamic Acid in the Solid State. I. Monitoring the Reaction at 293 K. *Acta Crystallogr B Struct Sci* 2004, **60** (3), 315–324.
- [253] M. A. Fernandes, D. C. Levendis, F. R. L. Schoening. A New Polymorph of Ortho-Ethoxy-Trans-Cinnamic Acid: Single-to-Single-Crystal Phase Transformation and Mechanism. *Acta Crystallogr B Struct Sci* 2004, **60** (3), 300–314.
- [254] Y. Cao, X. Wan, W. Li, J. Liu, R. Liu, S. Wu. Revealing the Dissolution Behavior of Trans-p-Methoxycinnamic Acid in 12 Organic Solvents by Parametric Model and Molecular Simulation. *J. Chem. Thermodynamics* 2022, **166**, 106683.
- [255] S. D. M. Atkinson, M. J. Almond, G. A. Bowmaker, M. G. B. Drew. The Photodimerisation of the Chloro-, Methoxy- and Nitro-Derivatives of Trans-Cinnamic Acid: A Study of Single Crystals by Vibrational Microspectroscopy. *J. Chem. Soc., Perkin Trans.* 2002, **2**, 1533.
- [256] H. Utsumi, K. Fujii, H. Irie, A. Furusaki, I. Nitta. The Crystal Structure of P-Coumaric Acid. *Journal of the Chemical Society of Japan* 1970, **91** (5), 407–504.