Deracemization on the Edge of Stability

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Chapter 1

Introduction

1.1 Chirality

A key feature of life on earth is the absence of mirror symmetry. When two mirror images of an object are not interconvertible via a combination of rotations and translations, the object is called chiral. An example of such a chiral object is the vegetable Romanesco, which can spiral in either clockwise or counterclockwise direction (Figure 1.1)[1]. Also a pair of hands form an example of chiral objects. Chirality is a notable feature on the macroscopic level, but is also of great significance on the molecular level. A large amount of molecules display chirality, implying the presence of two mirror image isomers. The left-handed (S, from sinister) and right-handed (R, from rectus) molecules are called enantiomers. With the exception of being able to alter the rotation plane of polarized light, most of the chemical and physical properties of enantiomers are identical.

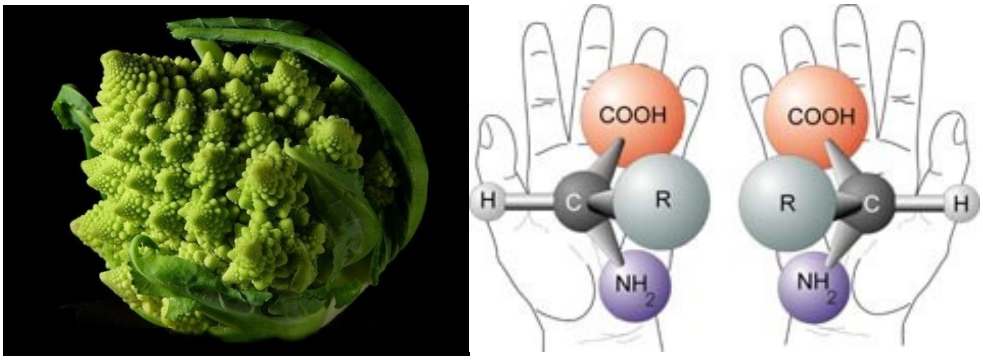

Figure 1.1: (left) Romanesco is a vegetable that exhibits a spiral that can be either clockwise or counterclockwise. (right) Chirality implies that two objects are each other's mirror images and not superimposable.

1.2 Chirality and life

In biological systems, such as the human body, it is often only one of the two enantiomers that is present. For example proteins consist of only left-handed amino acids. This single chirality has a pronounced influence on the development of new medicines by the pharmaceutical industry. The majority of drug molecules

is chiral, implying that two different enantiomers could be used.[2] However, since these drugs will be used in the human body, which is intrinsically chiral, the effect of these two enantiomers can be very different. An example is the anti-malarial drug mefloquine (marketed as Lariam), of which one enantiomer is effective in preventing and treating malaria,[3] whereas the other binds to certain receptors in the central nervous system,[4] causing severe side-effects such as depression. A problem is that in the preparation of such drugs, often both the desired and unwanted enantiomer are produced in equal amounts. It is therefore of paramount importance to find ways to produce enantiopure chiral compounds. Several conceptually different approaches have been devised to achieve the separation of enantiomers.[5]

1.3 Resolution methods

A common route in chemical synthesis to produce a single enantiomer of a compound, is to start off from already enantiopure compounds. The so-called chiral pool is made up of readily available enantiopure starting compounds. Alternatively, one could choose to develop an enantioselective synthesis pathway, in which an enantioselective step causes that a certain stage only one of the enantiomers is produced. In many cases however, no suitable enantiopure starting materials nor enantioselective methods are available so that racemic mixtures will be produced and other approaches are required to separate the enantiomers. In such cases, so-called resolution techniques can be used to obtain the desired chirality. In the ideal case, using these resolution techniques results in excellent separation and a product that contains only a single enantiomer. In many cases however, the resolution is not perfect, implying that both enantiomers are still present, but no longer in equal amounts. The ratio of the amount of these enantiomers is then described by the enantiomeric excess (*ee*):

$$ee = \frac{S - R}{S + R} * 100\%$$

An *ee* of 0% means both enantiomers are present in equal amounts (i.e. a racemic mixture), whereas a value of 100% implies the presence of only a single

enantiomer. The second important factor in these resolution experiments is the yield. The efficiency of a resolution is therefore described by the S-factor:[6]

$$S = Yield * ee * 2$$

The factor 2 is present in the equation to compensate for the fact that in a resolution experiment, which is an enantiomeric separation process, the maximum yield is 50%. An S-factor of 0 implies no resolution has taken place, whereas an S-factor of 1 indicates a perfect separation of two enantiomers.

1.3.1 Diastereomeric salt formation

The resolution technique that is most commonly used in the chemical industry is diastereomeric salt formation. An enantiopure molecule (the so-called resolving agent) is added to a racemic solution of the target compound.[7] This can result in the selective crystallization of a diastereomer of the salt containing the resolving agent and only one of the enantiomers of the target compound, leaving the solution enriched in the other enantiomer. It should be noted that diastereomeric salt formation can only be achieved when the target molecule possesses functional groups that can become charged (e.g. via protonation or deprotonation).

1.3.2 Chiral column chromatography

Chiral High Performance Liquid Chromatography (HPLC) and Supercritical Fluid Chromatography (SFC)[8] are techniques that are often used for the small-scale separation of enantiomers.[9] The difference in affinity of both enantiomers to a chiral solid phase results in separation of the (racemic) enantiomers.[10] Chiral HPLC can be very useful for obtaining small quantities of enantiopure product, and even examples of large scale (industrial) applications are becoming more common, although this remains a relatively expensive approach.[11]

1.3.3 Kinetic Resolution

In contrast to the previous methods, kinetic resolution does not separate a mixture of enantiomers, but selectively reacts one of the enantiomers into another chiral product so that straightforward separation becomes possible . For this process, an enantiopure chiral catalyst (such as an enzyme) is added to the

racemic mixture of the starting compound.[12] The catalyst quickly transforms one of the enantiomers into the desired product, whereas conversion of the other enantiomer is relatively slow. This difference in rate constant can lead to a very high enantiomeric excess.[13]

1.4 Deracemization methods

While resolution methods can be useful in obtaining an enantiopure material, it has an inherent limitation. Since only a single enantiomer is desired, the other enantiomer will be discarded, resulting in a theoretical maximum yield of 50%. It would therefore be more favorable to convert this unwanted enantiomer into the desired one. The conversion of such a racemic mixture into a single enantiopure product is called deracemization. In contrast to resolution, deracemization techniques lead to a theoretical yield of 100%.

1.4.1 Dynamic Kinetic Resolution

Dynamic kinetic resolution combines a standard kinetic resolution process with a so-called racemization step.[14] Again, a chiral catalyst is used to convert one of the two enantiomers into the desired product, but now a second catalyst is present that racemizes the remaining (undesired) enantiomer. The enantiomer that has not been converted by the first (chiral) catalyst can therefore be converted into the other one, which will consequently also be converted into the desired product.

1.4.2 Total Spontaneous Resolution

In addition to the previously mentioned method, it is possible to deracemize a compound using preferential crystallization. This implies the selective crystallization of a single enantiomer without any chiral resolving agent. A requirement for this process is that the compound crystallizes as a racemic conglomerate (Figure 1.2) meaning that the two enantiomers need to crystallize into different crystals, a process that occurs for around 5-10% of all chiral compounds.[15] For the other 90-95% of chiral compounds, both enantiomers will be present in each crystal. This can be in either an ordered (racemic compound) or disordered (solid solution) way. Total spontaneous resolution can therefore only be applied to a limited number of compounds. The process works by slowly

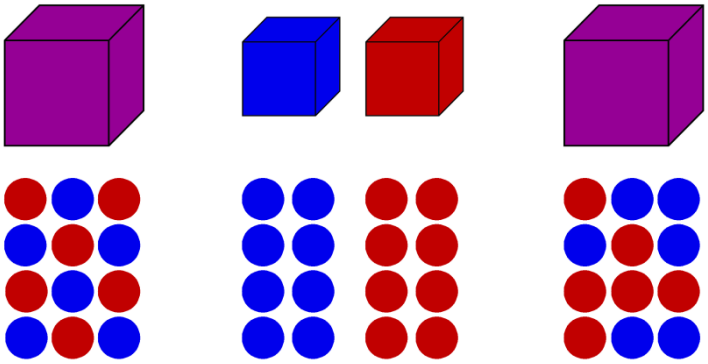

Figure 1.2: A racemic mixture of a chiral component can crystallize in three different ways; as a racemic compound, with both enantiomers regularly ordered within the same crystal (left), as a racemic conglomerate with the two enantiomers present in separate crystals (middle), or as a solid solution with both enantiomers randomly positioned within the same crystal.

increasing the supersaturation of the compound in solution (e.g. via cooling), until crystallization of the first crystal occurs. This crystal (containing only a single enantiomer) will then serve as the starting point of all further nucleation. By stirring the solution, a high enantiomeric excess can be obtained in the solid state,[16] because the stirrer will break up the first crystal into smaller ones. This secondary nucleation results in many new nuclei of the same handedness. Alternatively, enantiopure seed crystals of the desired enantiomer are added to induce further nucleation. Racemization (in solution) is required to convert the enantiomers of the wrong chirality into the desired one. It should be noted that total spontaneous resolution is a very delicate process, since crystallization of the wrong enantiomer should not occur in order to assure that complete deracemization will take place.

1.5 Viedma ripening

In 2005, Cristobal Viedma reported a new interesting case of chiral symmetry breaking. In his experiments, a suspension of sodium chlorate crystals (an achiral salt that crystallizes in a chiral fashion) was vigorously grinded, resulting in complete solid phase deracemization (Figure 1.3).[17] Noorduin et al. showed that the same approach can be applied to deracemize racemic conglomerates of intrinsically chiral molecules when racemization takes place (using a catalyst) in solution.[18]

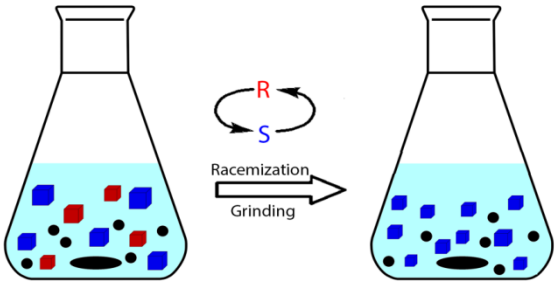

Figure 1.3: In a Viedma ripening experiment, grinding of a slurry of racemic conglomerate crystals is combined with racemization in solution, resulting in solid phase deracemization.

1.5.1 Mechanism of Viedma ripening

Similar to total spontaneous resolution, the process of Viedma ripening requires the compound of interest to crystallize as a racemic conglomerate. In addition, it is a prerequisite that the compound can be racemized in solution under the crystallization conditions. A simplified mechanism of Viedma ripening is depicted in Figure 1.4.[19, 20] During the experiment, small crystals will dissolve, whereas big crystals will grow even larger, a process that is called Ostwald ripening. However, due to the grinding of the suspension, these crystals are fragmented into smaller crystals and clusters (step 2) while retaining their chirality. These chiral clusters can be either reincorporated into crystals of the same handedness (step 3),[21] or

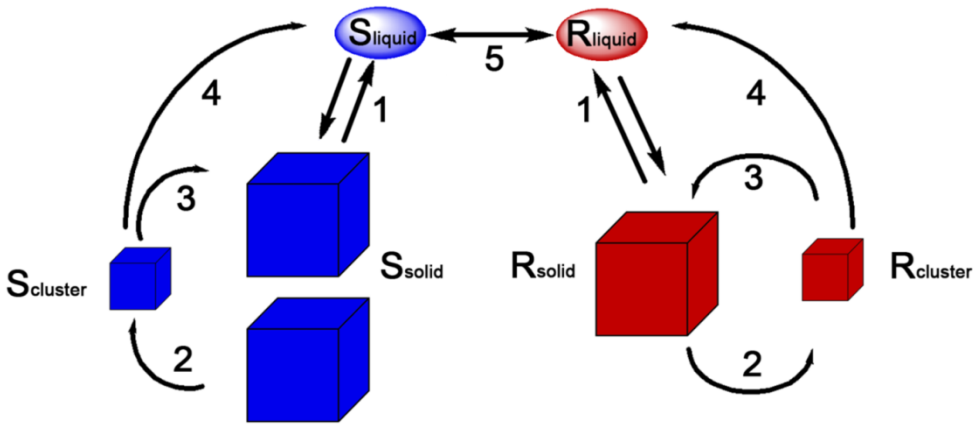

Figure 1.4: Schematic representation of the mechanism behind Viedma ripening consisting of: (1) Crystal growth and dissolution, (2) Fragmentation of crystals into smaller clusters, caused by the vigorous grinding, (3) Enantioselective incorporation of clusters into crystals, (4) Dissolution of the clusters, (5) Racemization in solution.

dissolve (step 4). Clusters of the major enantiomer are more likely to encounter a crystal in which they can be incorporated, whereas clusters of the minor handedness are more likely to dissolve, explaining the autocatalytic nature of the process. The molecules of the minor enantiomer in the solution will consequently be converted into the major enantiomer, due to the racemization (step 5). This eventually thus results in a full conversion of the minor into the major enantiomer. Compared to total spontaneous resolution, Viedma ripening provides a more robust way of deracemization, since crystals of the undesired chirality pose no problem here. Similar to Viedma ripening, the suspension can also be subjected to periodic heating-cooling cycles, again resulting in solid phase deracemization.[22] This approach is known as temperature cycling.

1.5.2 Current examples of Viedma ripening

Numerous examples of deracemization of chiral crystals composed of achiral reactants have been reported.[23] Whereas those examples are interesting from a fundamental point of view, their practical value is rather limited. More interesting are the examples that focus on intrinsically chiral molecules. Since obtaining a single enantiomers of chiral (drug) molecules is of paramount importance in chemistry and pharmaceutics, deracemization of such compounds is of high relevance in practice.[24] Most examples of the deracemization of intrinsically chiral molecules have focused on amino acids[25] and derivatives.[18] In addition the chiral drugs clopidogrel[26] and naproxen,[27] a transition metal complex,[28],and several isoindolinones have been racemized using this technique.[29] In all these examples, the experiments start from a (nearly) racemic mixture of two enantiomers. In addition, Steendam showed that enantiopure compounds can also be formed from the reaction of two achiral reactants.[30] Most of these examples of Viedma ripening involve compounds from which it was already known that they crystallize as a racemic conglomerate. The majority of chiral compounds, however, crystallize as racemic compounds, which significantly poses limitations on the scope of the process. Recently, two approaches have been devised to turn racemic compounds into conglomerates making them suitable for deracemization using Viedma ripening. The first involves chemical modification of the compound into a derivative that crystallizes as a racemic conglomerate.[18] Alternatively, Spix et al. showed that screening a series of counter ions for salt formation can also be

used to identify new racemic conglomerates.[31] An important requirement for both options is that the newly formed compound should still racemizes under the experimental conditions.

1.5.3 Directing the outcome of Viedma ripening

Since it is often only one of the enantiomers that is desired, directing the chirality of the deracemization is important. In most cases this is achieved by adding a slight enantiomeric excess of the required chirality (seeding).[18] Alternatively, small amounts of other, similar enantiopure molecules (so-called additives) can be added to the suspension.[18, 32-34] In most cases they will disturb regular crystal growth such that a product is formed that has the opposite chirality compared to the additive, an effect known as the Lahav rule of reversal.[35-37] In addition, Noorduin showed that circularly polarized light (resulting in the production of chiral impurities) can direct deracemization towards the desired enantiomer.[38]

1.6 Aim and outline of the Thesis

Obtaining chiral molecules in enantiopure form is of utmost importance for the pharmaceutical industry and other fields of chemistry. Viedma ripening is a promising technique in that respect. Although Viedma ripening has been extensively studied, many papers regarding this technique focus on the same chiral molecules. Combined with the requirement of a racemic conglomerate, the scope of the process has therefore remained rather limited. The aim of this research is therefore to widen the scope of Viedma ripening by 1) introducing new racemization methods, and (2) extending the process to compounds that crystallize as racemic compounds.

In chapter 2 we show that two amino acid derivatives, which appear to be racemic compounds, can actually be deracemized using Viedma ripening. These two compounds crystallize as a metastable racemic compound, while the conglomerate form is thermodynamically more stable. Using the conversion of the metastable form into the conglomerate, fast Viedma-mediated deracemization of these molecules can be achieved. Chapter 3 focusses on the deracemization of chiral sulfoxides. This class of compounds, several of which are

highly important chiral drugs, contains a sulfur instead of a carbon atom as the center of chirality. In the case of this molecule, racemization can be achieved via an intramolecular rearrangement. A library synthesis proved to be a fruitful approach for the identification of a suitable conglomerate-forming compound, which could be successfully deracemized.

A different type of chirality is atropisomerism, in which the hindered rotation around a covalent bond provides the chiral element. Enantiopure atropisomers are frequently encountered in living organisms and are also used as drugs. In chapter 4, we show that also such a molecule can be deracemized using Viedma ripening. In the next chapter (5), deracemization of the anti-malarial drug Mefloquine is investigated. This drug is sold as a racemic mixture, of which one enantiomer is most active against malaria parasites, whereas the other one causes severe psychotropic side effects. By deracemizing racemic Mefloquine, a more safe and effective drug can be obtained.

Although the majority of new drugs contains more than one stereocenter, deracemization of mixtures of diastereoisomers using Viedma ripening has not yet been achieved. In chapter 6 we show that Viedma ripening is feasible for two compounds both containing two chiral centers meaning that four diastereomers are converted into one in the process. Additional requirements for the deracemization of such molecules are also discussed.

A major drawback of Viedma ripening is the requirement of a racemic conglomerate, which accounts for only 5-10% of all chiral molecules. In chapter 7 we investigated whether attrition-enhanced deracemization of one of the 90-95% of molecules that crystallize as racemic compounds is also possible. This was accomplished using a chiral additive, a molecule that closely resembles one of the enantiomers of the racemic compound. A suitable additive that hampered the growth of both the racemic compound and one of the enantiopure crystal forms was identified. Using this chiral additive, the racemic compound could be rapidly converted into only a single enantiomer.

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Chapter 2

Speeding up Viedma ripening

1 Introduction

Chirality is a key issue in the development of small molecule drugs in the pharmaceutical industry. Of the majority of chiral drugs, only one of the enantiomers displays the desired physiological effect, whereas the other enantiomer is inactive or in some cases even harmful.[1] Consequently, the number of chiral drugs which are being produced in enantiopure form, has increased significantly over the last decades.[2] The synthesis of enantiomerically pure fine chemical products and pharmaceuticals often proceeds through the production of a racemic intermediate, which is then resolved into the two enantiomers through conventional techniques. One of the most widely used and robust techniques is chiral resolution through diastereomeric salt formation, requiring stoichiometric amounts of another chiral component.[3] Catalytic resolution approaches involve kinetic resolution using an enantioselective catalyst or an enzyme which preferentially reacts with one of the two enantiomers after which separation can take place.[4] Furthermore, dynamic kinetic resolution strategies can be applied (combining kinetic resolution with in situ racemization) leading to deracemization and formation of only one of the two enantiomers.[5] A recently developed deracemization method that can be applied without using chiral reagents is Viedma ripening.[6] In this process, vigorous grinding of a slurry of chiral crystals in a saturated solution is combined with racemization in solution, resulting in complete solid phase deracemization.[7] This approach has already been shown to be effective for chiral compounds such as amino acids,[8,9] their precursors[10] as well as derivatives,[11] isoindolinones[12] and also organometallic complexes.[13, 14] In addition to a conceptual qualitative understanding of this phenomenon, elaborate mechanistic investigations on Viedma ripening have been performed.[15-18]

A crucial prerequisite for Viedma ripening is that interconversion between the two enantiomers (racemization) is taking place in solution. A second prerequisite is that the two enantiomers of the chiral compound crystallize as separate crystals i.e. as a racemic conglomerate. The majority of chiral compounds (90-95%), however, crystallize as racemic compounds having both enantiomers in the same crystal. Most racemates will crystallize as either a racemic conglomerate, or a

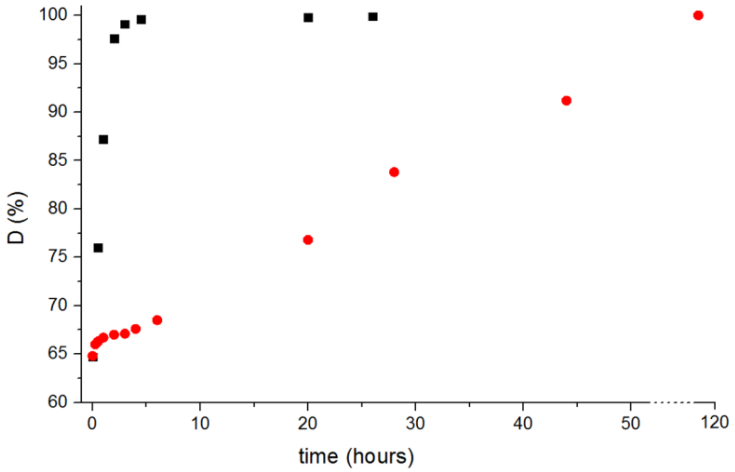

Figure 2.1: Deracemization experiments of compound 1 in a standard Viedma ripening experiment starting from the conglomerate form (D + L, red circles) or using the gradual transformation of a metastable racemic compound (D + DL, black squares) into the conglomerate. Depicted percentages refer to the solid phase.

racemic compound, but for some compounds both crystal forms can appear.

Spix et al. investigated Viedma ripening of glutamic acid, which crystallizes as a (metastable) racemic conglomerate, that converts after several days of grinding into a (stable) racemic compound.[19] They observed that it was possible to achieve full deracemization as long as the process was halted before conversion into the racemic compound had taken place.

The opposite case, in which a conglomerate forming compound first crystallizes as a racemic compound, has, to the best of our knowledge, never been studied in combination with Viedma ripening. Here, we demonstrate that the presence of such a metastable racemic compound can still lead to complete deracemization using Viedma ripening. Surprisingly, we found that using such a compound can significantly reduce the time required for complete deracemization (Figure 2.1).

2.2 Results and Discussion

Compounds **1** and **2** are both Schiff bases of phenylglycine amide (Figure 2.2). Both compounds are closely related to **3**, the first organic molecule that was deracemized using Viedma ripening.[7] Compounds **1** and **2** undergo, like compound **3**, facile racemization in solution in the presence of catalytic amounts of DBU as a base. When subjected to Viedma ripening conditions, both compounds could be readily deracemized. This suggests that both compounds crystallize as racemic conglomerates, which is a prerequisite for Viedma ripening. To our surprise, however, different X-ray powder diffraction (XRPD) patterns were obtained for crystals grown from enantiopure and racemic solutions, while for a conglomerate compound they should be identical. These patterns thus point towards a racemic compound.

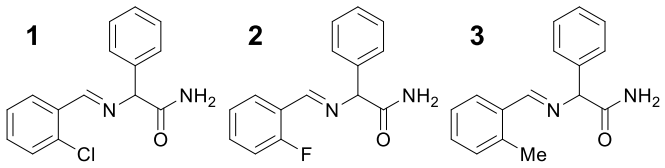

Figure 2.2: Compounds **1** and **2** crystallize as a racemic compound, but convert into conglomerate crystals upon abrasive grinding. Viedma ripening on racemic conglomerate **3** was already achieved by Noorduin et al. [7]

Further experiments showed that both compounds indeed crystallize as racemic compounds (Appendix 1, SI). However, when a slurry of the racemic compound with some enantiopure seed crystals is subjected to several hours of abrasive grinding, or a single day of gentle stirring, XRPD patterns showed complete conversion into the conglomerate. It was therefore concluded that the racemic compound is in the metastable phase, whereas the conglomerate is the thermodynamically favoured product.

This phase behaviour is in line with Ostwald's rule of stages for polymorphic forms, stating that when a molecule can be present in multiple forms, the (kinetic) metastable form will appear first, followed by the thermodynamically stable form.[20] Since compound **2** suffered from degradation (see experimental section), most further experiments were carried out using compound **1**.

The crystal structures of racemic and conglomerate compound **1** have already been determined by Leyssens et al.[21] They found that enantiopure **1** crystallizes as prisms, whereas its racemic form crystallizes as needles. A similar difference in morphology of the powders was visible in SEM images. The conglomerate crystals consisted of large blocks (Figure 2.3a). In contrast, the racemic compound always crystallized as needles (Figure 2.3b and c), which, in turn, consisted of a bundle of even thinner needles (Figure 2.3d). This crystallization behaviour turned out to have a large impact on the Viedma ripening experiments. In a typical Viedma ripening experiment, the slurry was being vigorously ground for a certain time prior to addition of the racemization catalyst. This was done to ensure homogenization of the solid phase (this period is henceforth denoted as the homogenization time).[11, 17] We observed that with decreasing homogenization times, the time required for deracemization of compounds **1** and **2** significantly decreased (Figure 2.4 and SI Figure 2.8).

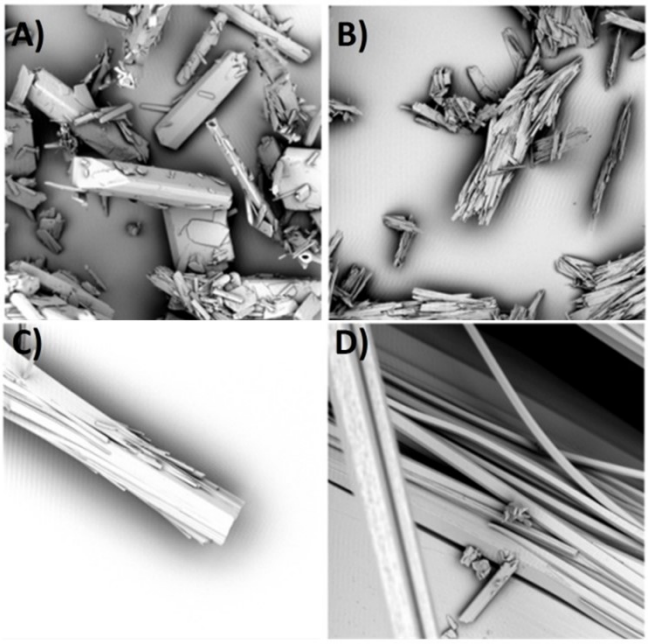

Figure 2.3: Scanning Electron Microscope (SEM) images of the powder of D-1 (A), DL-1 (B) and DL-1 crystals obtained after slow vapor diffusion of heptane into a saturated toluene solution of DL-1 (C and D). Image sizes are approximately 400 x 400 μm for A-C and 50 x 50 μm for D.

When the homogenization time was long (several hours), racemic compound crystals were completely converted into conglomerate crystals, even before the

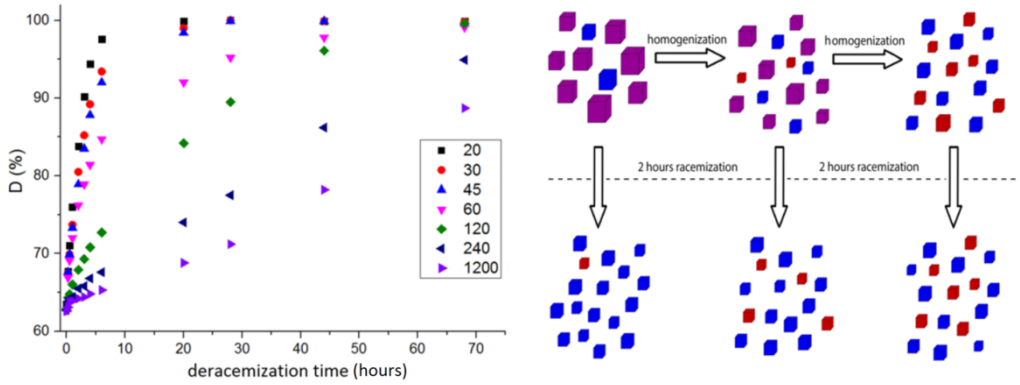

Figure 2.4: Homogenization time dependent solid phase deracemization of **1** starting from the racemic compound (purple cubes, right picture) seeded with D crystals (blue cubes). Depicted homogenization times in the legend are in minutes. All experiments were started from a mixture of D + DL-crystals as described in the experimental section. Elongated homogenization of the racemic compounds **1** and **2** results in the conversion into the conglomerate.

racemization catalyst was added. This in fact creates the starting conditions of a standard Viedma ripening experiment. Indeed, when performing a standard Viedma ripening experiment (by adding D- and L-crystals at the start), a similar long deracemization time was found. In other experiments, the homogenization time was too short to allow this (complete) conversion. The racemization catalyst (DBU) was in those cases added while the majority of the crystals were still present in the racemic compound form. During the experiment, racemic compound crystals will therefore keep on dissolving, thus providing a continuous feed of both D-and L-enantiomers for conglomerate crystallization. The presence of added D-seed crystals at the start of the experiment, then becomes important.
The feed in D-enantiomers can be used for the growth of these D-seed crystals, through secondary nucleation. Grinding then ensures a constant increase in the number of crystals.
The feed of L-enantiomers cannot be directly incorporated into crystals, since no seed crystals of the L-enantiomer are present. Primary nucleation is therefore required for L-crystal formation. Moreover, due to the fast racemization in solution, the L-enantiomer is also (partially) converted into its counterpart, allowing fast incorporation into the abundantly present D-crystals. The racemic compound crystals consequently serve as a gradual feed of building blocks for the conglomerate compound, similar to the in situ feed approach used by Noorduin et

al. for naproxen[22]. The longer the homogenization time, the more of the racemic compound is converted into the conglomerate. Consequently, more crystals of the minority enantiomer need to be converted in the Viedma ripening process and the deracemization rate decreases (Figure 2.4). Fast deracemization can thus be achieved by keeping the homogenization time short. Interestingly, at very short homogenization times, the deracemization rate of compound **1** decreased again. This is further elaborated upon in Appendix 2 (SI). The outcome of this fast deracemization could be simply directed towards the desired chirality by adding seeds of either the D- or L-enantiomer (Figure 2.5). The deracemization rate was independent of the identity of the initial enantiomer in excess, as expected.

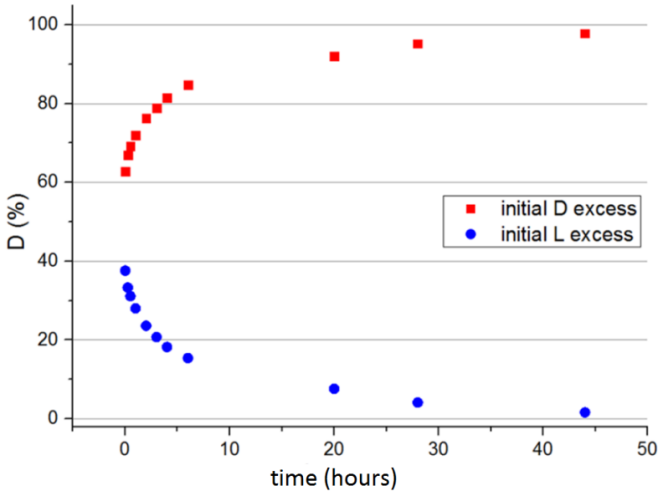

Figure 2.5: Deracemization of compound **1** after a two hour homogenization time, starting with an initial excess in D (red) or L (blue) enantiomer.

2.3 Conclusions

We demonstrated that Viedma ripening is possible starting from a metastable racemic compound. Moreover, deracemization of such a compound was much faster than in a normal Viedma ripening experiment. We found that the mechanism behind this process is a constant in situ feed of enantiomers, comparable to earlier work by Noorduin et al.[22] By optimizing the homogenization time, the time required for complete deracemization using the metastable racemic compound in combination with seed crystals could be reduced to three hours compared to two to five days for the conglomerate compound, i.e. a reduction by more than a factor ten.

2.4 Notes and References

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Chapter 3

Deracemization of a Racemic Allylic Sulfoxide Using Viedma Ripening

3.1 Introduction

Single chirality is a key feature of life and hence of utmost importance in the production of active pharmaceutical ingredients in the pharmaceutical industry. In the case of chiral drugs, it is generally one enantiomer that has the desired physiological effects, whereas its mirror image is inactive or has even harmful consequences.[1] An important class of drugs consists of chiral sulfoxides, where a sulfur instead of a carbon atom is the tetrahedral center of chirality. The best-known example of a chiral sulfoxide is probably Esomeprazole, the number two selling drug in 2013 in the US (marketed as Nexium). This drug acts as a proton pump inhibitor, reducing stomach acid production.[2] Esomeprazole is an enantiopure sulfoxide that is produced on industrial scale by asymmetric oxidation of the corresponding sulfide[3]. It contains only the (*S*)-enantiomer and was found to be more active than the racemate, known as omeprazole.[4, 5] Obtaining an enantiopure compound, however, is generally not straightforward, since (achiral) synthesis will yield both enantiomers in equal amounts while enantioselective methods in many cases cannot be easily applied. In the majority of cases, resolution using diasteriomeric salt formation is applied to obtain the desired enantiomer, which however, results in a maximum yield of 50%. As an alternative, a deracemization method might be applied, allowing yields of a single enantiomer in up to 100% yield.[6] Viedma ripening is such a method that allows the conversion of a racemic mixture of solids into a single enantiomer in theoretically 100% yield.[7, 8] It involves grinding of a suspension of racemic conglomerate crystals in combination with racemization in solution, resulting in complete deracemization of the solid phase. The scope of Viedma ripening, however, has so far remained limited due to the lack of suitable racemization strategies.[9] The majority of examples consist of base-induced racemization through deprotonation, or involve a redox reaction. Consequently, examples of molecules that have been deracemized with Viedma ripening include amino

acids[10] and derivatives[11], and metalorganic complexes.[12] In addition, the group of Håkansson demonstrated Viedma ripening and successive oxidation on a ruthenium-sulfide complex.[13] However, due to the limitations in racemization methods, and despite the relevance of chiral sulfoxides in drugs, no such molecules have yet been deracemized using Viedma ripening. The purpose of our study is therefore to expand the scope of Viedma ripening to this important class of chiral molecules. In this chapter, we describe the route that we used to screen for a suitable sulfoxide and disclose the first example of deracemization of a sulfoxide using Viedma ripening.

3.2 Results and Discussion

A few challenges need to be faced before this particular case of Viedma ripening can be applied. First, the molecule of interest must be able to undergo racemization in solution. While the majority of sulfoxides racemize at temperatures over 200 °C[14], allylic sulfoxides racemize at much lower temperatures (even below 50 °C[15]) since they are prone to undergo a 2,3-sigmatropic rearrangement, known as the Mislow-Evans rearrangement (Figure 3.1).[16-18] Such an intramolecular rearrangement is unprecedented as the racemization mechanism in Viedma ripening.

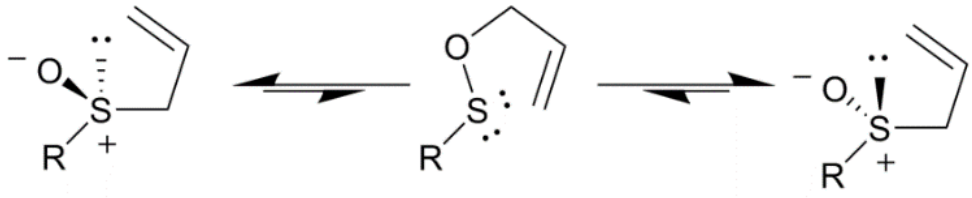

Figure 3.1: An allylic sulfoxide can reversibly rearrange into an achiral sulfenate via a 2,3-sigmatropic rearrangement, resulting in solution phase racemization of the chiral sulfoxide.

A second requirement for Viedma ripening is that the enantiomers crystallize as separate crystals i.e. form a racemic conglomerate. For the majority (90-95%) of compounds however, the enantiomers crystallize in the same crystal i.e. form a racemic compound. Thus the first step in this project is to identify a conglomerate allylic sulfoxide. Since no such conglomerate has been posted in the Cambridge Structural Database (CSD) up to now, we first performed a screening. Salt formation has been described as a route for finding conglomerate crystals.[19]

However, since many sulfoxides are not compatible with salt formation, we decided to engage in a library synthesis.

A series of 24 sulfoxides was synthesized to ensure a reasonable chance of finding a conglomerate (Figure 3.2, see SI for a complete overview). To identify sulfoxides displaying conglomerate behavior, crystals suitable for X-ray analysis were grown using slow solvent evaporation. From the 24 synthesized compounds, crystals could be grown of 14 of them, from which we found that compound **1** crystallized as a racemic conglomerate. All other compounds crystallized as racemic compounds (Figure 3.2).

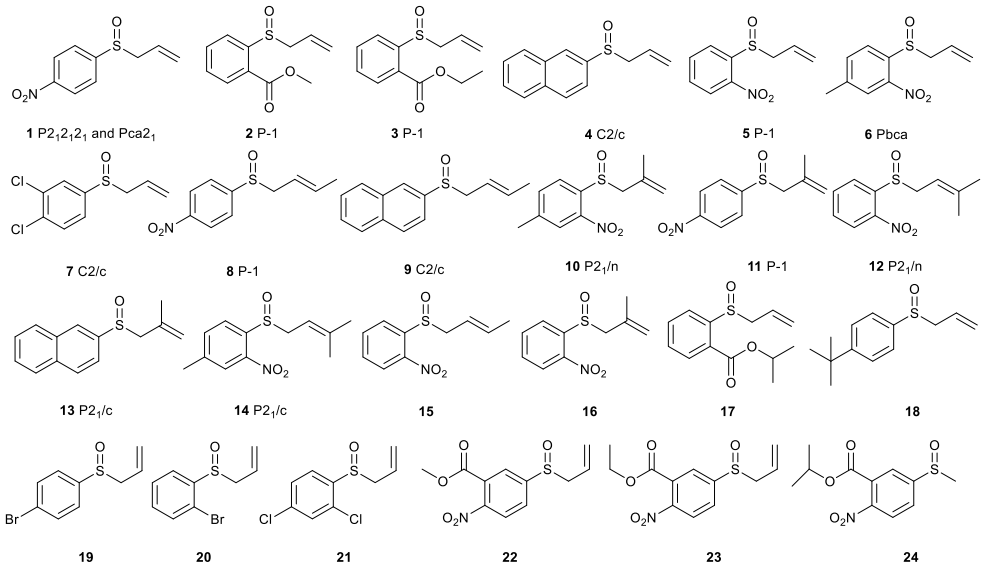

Figure 3.2: A series of 24 allylic chiral sulfoxides were synthesized, of which crystal structures could be determined for 14 of them (spacegroups are given after the compound number). Of these 14, only compound **1** crystallized as a racemic conglomerate.

Compound **1** was subsequently used for the Viedma ripening experiments. The speed of racemization of allylic chiral sulfoxides is highly solvent dependent.[20] We found that racemization of compound **1** takes place at room temperature in apolar solvents such as toluene and diethyl ether, while the optical purity of the sulfoxide can be retained in polar solvents such as methanol ($t_{1/2}$ > 4 days at RT).

By using toluene at room temperature as a solvent and starting from completely racemic conditions, an enantiomeric excess (*ee)* of 12% was obtained after a period of over a month. These promising results prompted us to investigate the racemization kinetics, in order to reduce the deracemization time. We found a relatively high barrier for the racemization of **1** in toluene at room temperature according to both DFT calculations (ΔH = 18.1 kcal/mol)[21] and temperature dependent selective exchange spectroscopy experiments (ΔH = 21.2 kcal/mol). This barrier leads to a relatively long racemization half-life ($t_{1/2}$ = 6.9 h) and results in slow deracemization. We therefore decided to increase the temperature in order to reduce the deracemization time. By changing the solvent system to refluxing diethyl ether ($t_{1/2}$ = 6.3 h at RT and 1.1 h at reflux, b.p. 35 °C) and creating a small initial bias (around 1% *ee*), complete deracemization of **1** could be achieved in just 8 days (Figure 3.3).

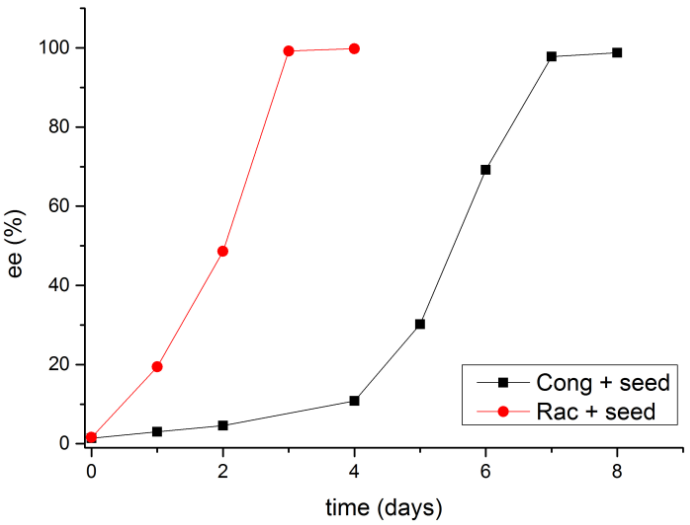

Figure 3.3: Viedma ripening of compound **1** in refluxing diethyl ether starting from the racemic conglomerate compound or metastable racemic compound. In both cases the suspension was seeded with enantiopure crystals.

In order to further decrease the deracemization time, the temperature was further increased to 50 °C. Since this temperature exceeds the boiling point of diethyl ether, the solvent was changed to toluene. Under these conditions however, deracemization experiments of compound **1** were unsuccessful due to melting of the compound. When the solution was then cooled again, **1**

recrystallized as a different polymorph with a lower melting point. We found that this low melting polymorph was in fact a metastable racemic compound (see SI). We have shown in a previous study that the speed of Viedma ripening can be increased using such a metastable racemic compound in combination with enantiopure seed crystals.[22] Hence, we investigated whether this same approach could be applied to reduce the deracemization time of chiral sulfoxide **1**. Indeed, by starting from the racemic compound in combination with enantiopure seed crystals in refluxing diethyl ether, the deracemization time could be further decreased to three days (Figures 3.3 and 3.4).

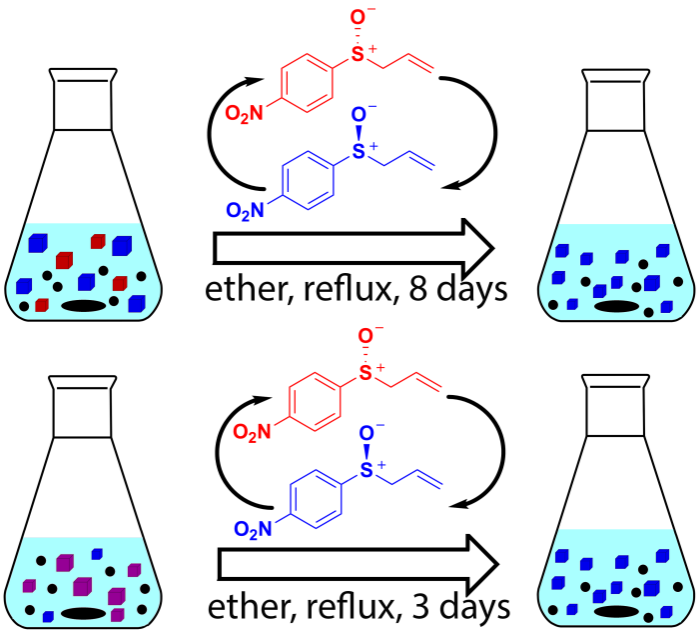

Figure 3.4: Grinding of a suspension of compound **1** in diethyl ether results in complete solid phase deracemization. By performing similar experiments at 50 °C in toluene, occasional melting and recrystallization resulted in the racemic compound and no deracemization. When grinding a suspension of this racemic compound, seeded with enantiopure crystals in refluxing diethyl ether, fast deracemization could be achieved.

3.3 Conclusions

We have demonstrated that Viedma ripening can be used to deracemize chiral sulfoxides. By synthesizing 24 chiral allylic sulfoxides which spontaneously racemize through a 2,3-signatropic rearrangement at elevated temperatures in

solution, one racemic conglomerate compound, suitable for Viedma ripening, was identified. Chiral amplification was achieved for this compound by simply heating a suspension of the molecule under grinding conditions.

This experimentally facile route allows for the straightforward preparation of an enantiopure allylic sulfoxide. That this was done for one compound out of a library of 24 candidates might be considered as a limitation. However, similar enantiopure allylic sulfoxides have been used as chiral pool starting materials, and as chiral auxiliaries for the synthesis of enantiopure acids and esters.[23] Therefore one deracemized compound can be the starting point for several enantiopure compounds. In addition, the present Viedma ripening screening not only demonstrates the preparation of a specific enantiopure sulfoxides, but also shows a general route that can be followed for the deracemization of other compounds.

3.4 Notes and References

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Chapter 4

Solid Phase Deracemization of an Atropisomer

4.1 Introduction

Single chirality is a key signature of living organisms and hence of utmost importance to the development of new drugs in the pharmaceutical industry. Obtaining molecules in an enantiopure way can however be troublesome, since straightforward synthesis typically yields a racemic mixture of both enantiomers. Viedma ripening is a process that converts a saturated slurry of crystals of a racemic conglomerate into an enantiopure end state by applying vigorous grinding. The first example of this process involved achiral sodium chlorate, which crystallizes in a chiral fashion.[1] Later studies have shown that this deracemization process can also be applied to intrinsically chiral molecules, such as amino acid derivatives,[2] but also to the enantioselective synthesis of small molecules.[3, 4] Most of these examples have focused on chiral molecules that exhibit an sp^3 hybridized carbon atom as a chiral center.[5] Notable exceptions include the work of the Hakansson group which involves a chiral transition state metal complex,[6] and one from our own group where the chiral center is a sulfur atom.[7] Other important classes of chiral compounds also exist, but have remained unexplored with regard to Viedma ripening.

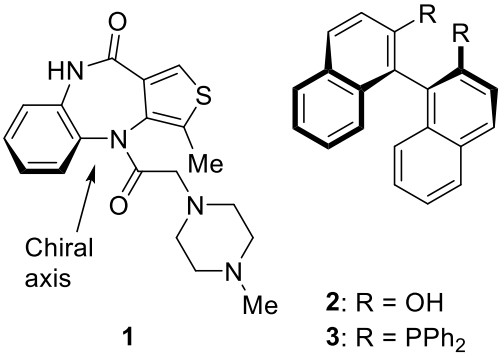

Figure 4.1: Telenzapine (**1**) is an example of an atropisomer drug, while BINOL (**2**) and BINAP (**3**) are chiral ligands often used in transition metal complexes.

One such class concerns atropisomers, non-planar molecules that display chirality through the hindered rotation around a single bond, which in many cases can be overcome by raising the temperature. Atropisomers can be very stable, however, as is shown by the fact that quite a number of natural products exist as atropisomers, featuring only one of the two possible enantiomers.[8] In addition, atropismerism is a common feature in some drugs as well. An example is Telenzepine (**1**, Figure 4.1), an antisecretory drug of which the (+)-atropisomer is the most active form.[9] In addition, axially chiral molecules such as BINOL (**2**, 1,1-binaphthalene-2,2-diol) and BINAP (**3**, 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthalene) are often used as ligands in transition metal based asymmetric synthesis.[10] Here, we report the deracemization of the atropisomer 4,6-dimethyl-1-(naphthalen-1-yl)pyrimidine-2(1*H*)-thione (**4**, Figure 4.2) using Viedma ripening or temperature cycling.

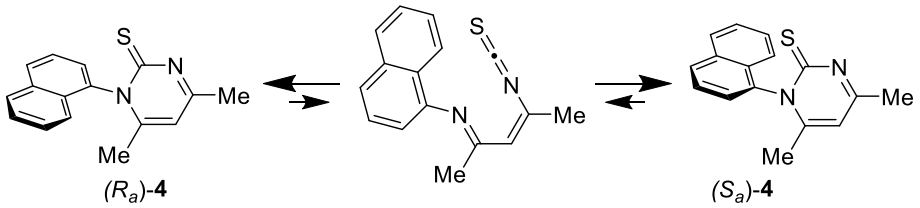

Figure 4.2: Atropisomer **4** crystallizes as a racemic conglomerate and spontaneously racemizes at elevated temperatures in apolar solvents.

4.2 Results and Discussion

Compound **4** was selected since it crystallizes as a racemic conglomerate, which is a prerequisite for Viedma ripening. In addition, this compound racemizes swiftly in apolar solvents at elevated temperatures ($t_{1/2}$ = 4 min in xylene at 50 °C), whereas racemization at room temperature in polar solvents is negligible.[11] Racemization takes place relatively easily since it proceeds via a reversible ring-opening and closing-mechanism,[12] rather than via rotation around the chiral axis. Fujita and coworkers already showed that total spontaneous resolution can be achieved for this compound.[11, 13] By slowly cooling a stirred, saturated solution of compound **4**, seeded with enantiopure crystals, they obtained an enantiomeric excess (*ee*) of up to 90%. A drawback of these experiments is that the deracemization was achieved only on small scale (50 mg). In addition, such total

spontaneous resolution experiments need to be carried out in a carefully controlled manner, or crystallization of the unwanted enantiomer will take place. We here investigate whether alternative methods can be used to deracemize a racemic mixture of compound **4**. Viedma ripening is a technique that can be applied on a much larger scale.[14] In addition, it starts from a racemic suspension of crystals, making it a more robust method since unwanted crystallization of the other enantiomer is no problem.[15] As an alternative, we also investigated the possibility of deracemization using temperature cycling.[16]

Viedma ripening experiments:

Viedma ripening experiments on compound **4** resulted in an *ee* of around 90% (see experimental part) with and without using a chiral bias. Deracemization typically took 15-20 days at 60 °C. We found that the outcome of the Viedma ripening experiments is stochastic. Out of a total of six experiments (starting from completely racemic conditions), three experiments yielded the (R_a)- and three the (S_a)-enantiomer. This is in contrast to previous examples of Viedma ripening, where often a bias was found for one chiral end state, caused by the presence of chiral impurities.[17] Apparently this system is very pure or insensitive towards a bias from impurities. When applying a small initial bias (by adding less than 1% enantiopure material), deracemization could be achieved in 15 days (Figure 4.3). During the filtration, the samples rapidly cooled down, resulting in additional crystallization of both enantiomers. This is most likely the reason why the measured *ee* was 90%, while the actual value at the end of the deracemization should be (close to) 100%.

Sonication experiments:

In order to decrease the time required for deracemization, we evaluated different experimental configurations. Sonication of such a crystal suspension can also result in deracemization[18, 19] and Noorduin et al. have shown that this can greatly enhance the deracemization speed.[18] By replacing the magnetic stirrer with a sonication bath, and starting from a small initial bias, deracemization could indeed be achieved (Figure 4.3). Since no experiments without an initial bias were performed, nothing can be said about the stochasticity of this process. The drastic decrease in deracemization time as described by Noorduin et al. was however not observed. Since racemization, solubility and sonication energy[20] are not a limiting

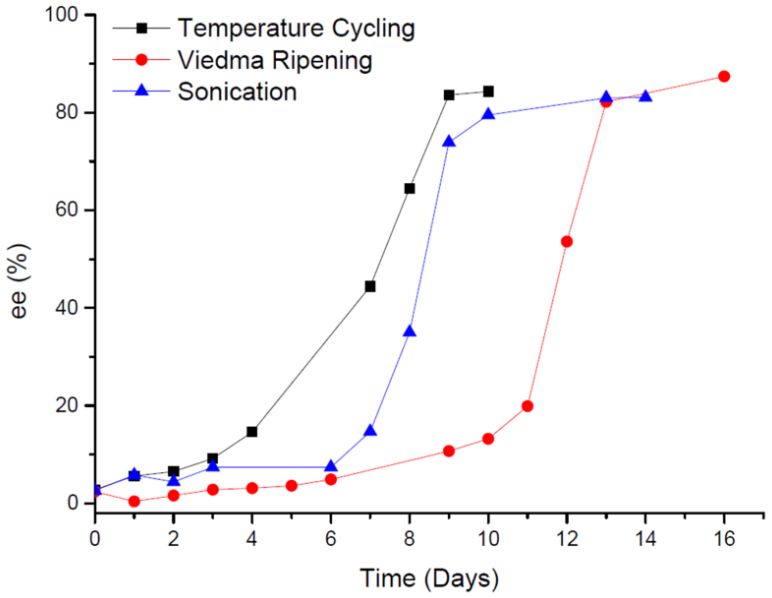

Figure 4.3: Deracemization curves of compound **4** using temperature cycling, Viedma ripening and sonication. In these experiments, a small initial *ee* was created by adding less than 1% enantiopure material.

factor here, this could possibly be due to a different hardness of the crystals, although no definite explanation can be given based on the current experiments.

Temperature cycling experiments:

Recently, the groups of Flood and Coquerel described temperature cycling of a suspension of conglomerate forming crystals as an alternative method of deracemization.[16, 21] In this process, the suspension is subjected to periodic heating-cooling cycles, resulting in solid phase deracemization.[22] By cycling the temperature between 65 and 55 °C (again with an initial bias), deracemization of **4** could also be achieved (Figure 4.3). The time required for deracemization under these conditions is not greatly different from that of the Viedma ripening experiments. Temperature cycling and Viedma ripening are however difficult to compare because of the different conditions (temperature, glass beads). In addition, the technique and temperature profile of the cycles have not been optimized for this specific system.[23]

4.3 Conclusions

In conclusion, we have successfully demonstrated the first example of the deracemization of an atropisomer using both Viedma ripening and temperature cycling at gram scale. Both methods enabled deracemization in 15-20 days at elevated temperatures.

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Chapter 5

Attrition-Enhanced Deracemization of the Antimalaria Drug Mefloquine

5.1 Introduction

Despite widespread efforts to combat malaria, the disease remains one of the main health threats for a major part of the population in tropical countries. In 2016, the number of malaria cases was estimated at 216 million leading to 445,000 malaria deaths worldwide.[1] The disease is transmitted by mosquitoes and caused by a series of different parasites, of which *Plasmodium falciparum* is the most prominent one. In the recent past, chloroquine (**2**) was the drug of choice to treat malaria, since it was effective and inexpensive. Due to resistance of *P. falciparum*, however, chloroquine as well as several other drugs have become ineffective against this parasite.[2] Currently, the WHO-recommended treatment involves the use of artemisinin (**3**): although there is no resistance to this drug yet,

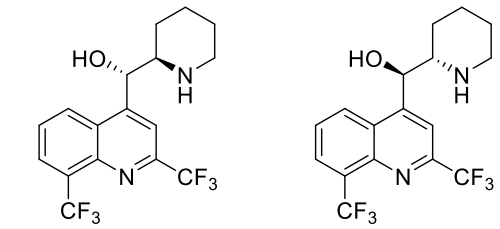


Figure 5.1: Lariam is an antimalarial drug that contains a racemic mixture of the 11*S*,12*R* and 11*R*,12*S* diastereomers of Mefloquine (**1**). Chloroquine (**2**) and artemisinin (**3**) are two other important antimalarial drugs.

it is relatively expensive and therefore not always available to malaria patients[3]. One other drug that is used to prevent and treat chloroquine-resistant *P. falciparum* malaria is Mefloquine, sold under the brand name Lariam. The drug likely functions by inhibiting the endocytosis of hemoglobin of the malaria parasites.[4] Around 10% of female travelers (aged 18-49) to malaria endemic areas use Mefloquine, and it also is the preferred drug for small children.[5, 6] In addition, combination therapies that use Mefloquine together with other anti-malaria drugs appear promising to combat drug-resistance and transmittance.[7, 8] Mefloquine (**1**) contains two stereocenters, of which only the (+)-(11*S*,12*R*) and (–)-(11*R*,12*S*) diastereoisomers are present as a racemic mixture (Figure 5.1).[9-11] The ((11*S*,12*S*) and (11*R*,12*R*)) diastereoisomers do not have the antimalarial activity.

Not surprisingly, the marketed (+)-(11*S*,12*R*) and (–)-(11*R*,12*S*) enantiomers exhibit fairly different pharmacokinetic properties.[12] The (–)-enantiomer has a high affinity for the adenosine receptors in the brain, and therefore causes side-effects on the central nervous system.[13, 14] Sleeping disorders, depression, anxiety and even psychosis have been frequently encountered among patients using Mefloquine.[2, 15-16,17] The (+)-enantiomer does not possess the adenosine receptor affinity and is the more effective enantiomer in malaria treatment.[13, 18] In addition, the (+)-enantiomer of Mefloquine can also be used to treat other diseases, such as disseminated disease for AIDS patients, while (–)-Mefloquine is ineffective.[19] By using enantiopure (+)-Mefloquine instead of the racemic mixture, obviously the efficiency of the drug would be improved, while the severe side-effects are avoided.[20] The current synthetic manufacturing routes for Mefloquine yield a racemic mixture, which is used as such for the drug product. Although kinetic resolution (e.g. via diastereomeric salt formation) has been successfully demonstrated using resolving agents,[21] this process results in a maximum theoretical yield of 50%, rendering it too expensive for commercial purposes. In order to design a commercially more feasible approach, we envisioned to develop a solid-state deracemization approach to fully convert racemic Mefloquine into the desired single (+)-enantiomer.

An emerging solid-state method capable of causing deracemization of racemic mixtures is Viedma ripening.[22, 23] This method involves vigorous glass bead enhanced grinding of a slurry of crystalline chiral compounds, resulting eventually in solid-phase deracemization and hence formation of only one of the two enantiomers (Figure 5.2). In order to successfully apply Viedma ripening, however,

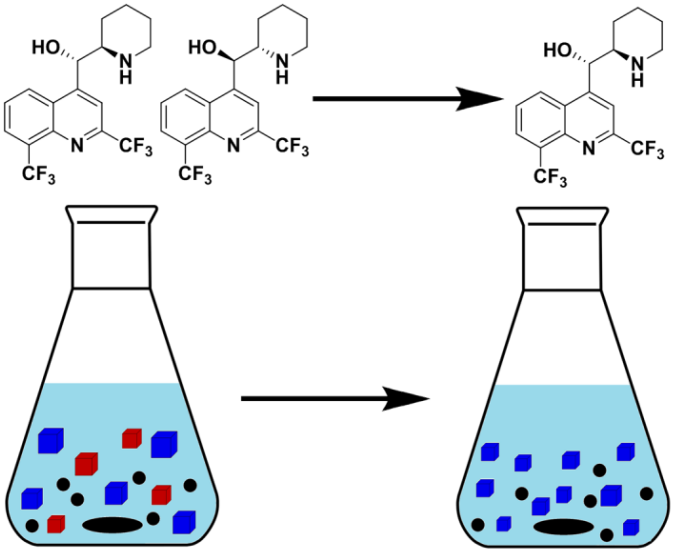


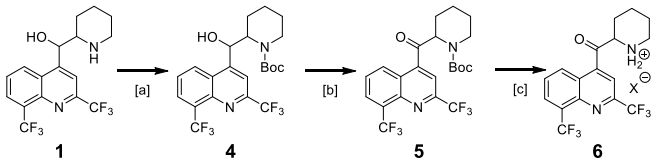
Figure 5.2: Viedma ripening involves the grinding of a slurry crystals, resulting in solid phase deracemization. This method will succeed if the compound crystallizes as a racemic conglomerate that also undergoes racemization in solution under the crystallization conditions.

two conditions need to be fulfilled.[24] Firstly, it must be possible to racemize the molecule in solution under the crystallization conditions (e.g. by using a racemization catalyst). Secondly, the molecule must crystallize as a racemic conglomerate, meaning that the two enantiomers crystallize into different crystals. Around 5-10% of all crystalline chiral molecules crystallize in such a fashion, while for the other 90-95% the two enantiomers end up in the same crystal (i.e. a racemic compound).[25] Unfortunately, all known crystal structures of Mefloquine and its HCl-salt are racemic compounds, rendering them unsuitable for Viedma ripening.[26-28] In addition, Mefloquine contains two different stereocenters which makes racemization of this molecule challenging. Therefore, direct deracemization of Mefloquine using Viedma ripening is not possible. In this chapter we highlight the identification of a precursor of Mefloquine that fulfills the two aforementioned Viedma conditions, we show that this precursor can be effectively deracemized and subsequently chemically converted into (+)-Mefloquine.

5.2 Results and discussion

Screening of the literature for suitable Mefloquine precursors, it appeared that Tiekink et al. reported that crystalline Boc-protected Mefloquine (**4**) forms a racemic conglomerate (Table 5.1).[29] However, a straightforward racemization method, requiring both stereocenters to epimerize, does not exist, rendering precursor **4** unsuitable for Viedma-induced deracemization. Further literature screening revealed ketone derivative **5**,[9, 30] possessing only one chiral center positioned next to a ketone, thereby making it susceptible to acid- or base-catalyzed racemization. Unfortunately, analysis of the crystalline material using single crystal X-ray diffraction showed that it crystallizes as a racemic compound. In order to enhance the chances of finding a racemic conglomerate, we chose to deprotect the Boc-protecting group using both HCl and a wide range of sulfonic acids.[31]

Table 5.1. Synthetic approach to synthesize a racemizable Mefloquine derivative that crystallizes as a racemic conglomerate



1 **4** **5** **6**

	1	**4**[a]	**5**[b]	**6**[c]
racemizable by base	no	no	yes	no
racemizable by acid	no	no	yes	yes
conglomerate	no	yes	no	depends on X

[a] Boc_2O, THF, 0 °C, 98% [b] DMP (1.3 equiv), DCM, 0 °C, 92% [c] Sulfonic acid (HX), various solvents, quantitative; crystal structures of 34 such compounds were elucidated.

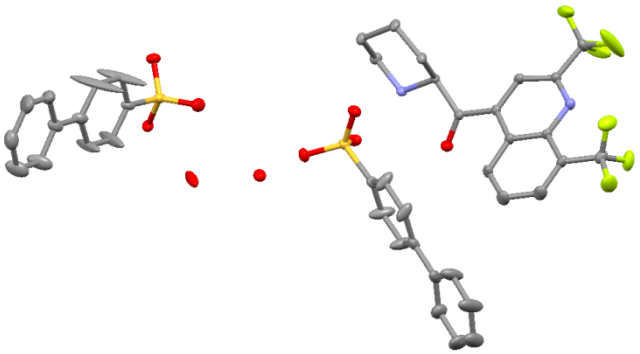


Figure 5.3: Crystal structure of the racemizable derivative of Mefloquine that crystalizes as a racemic conglomerate (50% probability level, hydrogen atoms are omitted for clarity). The unit cell contains two equivalents of both biphenylsulfonic acid and water.

Subsequently, the crystallization behavior of the resulting series of Mefloquine sulfonic acid salts **6** was determined using single-crystal X-Ray diffraction. In this way, a total of 34 new crystal structures containing the amino ketone moiety has been elucidated, with the aim to discover racemic conglomerate behavior among these salts. Underlining the rule-of-thumb that roughly 5-10% of crystalline chiral solids crystallize as racemic conglomerate, we identified three salts that crystallized in a non-centrosymmetric space group which is an indication for racemic conglomerate formation. Of these three compounds, two turned out to be kryptoracemates,[32] resulting in the identification of exactly one racemic conglomerate among these 34 crystalline salts. The crystal structure of this compound is shown in Figure 5.3, clearly showing the presence of two biphenyl sulfonic acid and two water molecules, making it a rather unique example of a conglomerate co-crystal salt solvate.[33, 34]

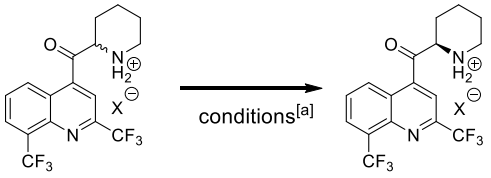
Since racemization conditions, neither for aminoketone **5** nor for the corresponding sulfonic acid salts are known, we first had to identify suitable and new racemization conditions. Gratifyingly, we have found that the conglomerate salt **6** can be efficiently racemized at temperatures of 70 °C in neat acetic acid (Table 5.2 and SI).

Due to the extremely high solubility of the salt at these temperatures (>1 g/mL), this system proved unsuited for Viedma ripening. Viedma ripening at lower temperatures, however, was unsuccessful due to a too low racemization rate. Slightly more apolar hexanoic acid seemed a more suitable solvent in terms of solubility. Unfortunately, upon carrying out the Viedma-ripening experiment starting from a small enantiomeric excess at temperatures over 70°C, the initial *ee*

was quickly lost leaving racemic material behind. This is likely due to the conversion of the initial conglomerate compound into a different (racemic) crystal form, as was observed by a change in the powder X-ray diffraction pattern.

To circumvent the problem of either slow racemization, or too high solubility, the experimental geometry of Hein et al. was used, applying an adaptation of the normal Viedma ripening procedure.[35,36,37] In these experiments, one vial containing racemic Mefloquine salt is vigorously ground (Figure 5.4). A second flask containing a small amount of enantiopure seed crystals was subjected to gentle stirring. During the experiment, a continuous exchange of the solutions between the two vials was established using a peristaltic pump.[38-40] After several hours of grinding and solvent exchange, the amount of crystals in the gently stirred vial had significantly increased. Evaluation of the solid phase using a polarimeter and/or chiral HPLC revealed that the crystals had remained nearly

Table 5.2. Screening of Viedma ripening conditions for **6**.



(*rac*)-**6** (+)-**6**

Solvent	T (°C)	k_{rac} (h^{-1})	Result
AcOH	50	0.07	Too slow racemization
AcOH	70	0.4	Too high solubility
AcOH/(*n*-Bu)$_2$O	70	0.4	Phase separation
hexanoic acid[b]	75	n.d.	Conversion of Conglomerate

[a] Grinding experiment (stirring rate 700 rpm) with glass beads at the indicated temperature and solvent [b] Both with and without approximately 1% (v/v) of water

enantiopure. The solid phase of the other vial (that was subjected to vigorous grinding) had adopted a reverse enantiomeric excess. This setup could thus be effectively used to resolve the two enantiomers (Figure 5.4).

The salt of the desired enantiomer was collected and converted into (+)-Mefloquine using the Luche reduction (Figure 5.4, step iv).[9] The salt of the unwanted enantiomer can be easily racemized, by heating it in acetic acid (see SI). It can then again be used, applying the same coupled batch grinding process. Using this two-step process, the initial racemic Mefloquine can be converted into the desired enantiomer. After reduction, the final product of the optimized experiment consists of 94% (11*S*,12*R*)-**1**, while 2.5% of the harmful (12*S*,11*R*)-**1** remains. The other 3.5% is composed of (11*R*,12*R*)-Mefloquine. Although *the* (11*R*,12*R*) and (11*S*,12*S*)-diastereomers have not been as thoroughly investigated as the marketed diastereomersof Mefloquine (11*S*,12*R* and 11*R*,12*S*), research suggests that while they are less active at treating malaria,[9] they are also less cytotoxic.[41] The overall yield of the process is 83%, making it far more efficient than standard resolution methods, such as diastereomeric salt formation.[42]

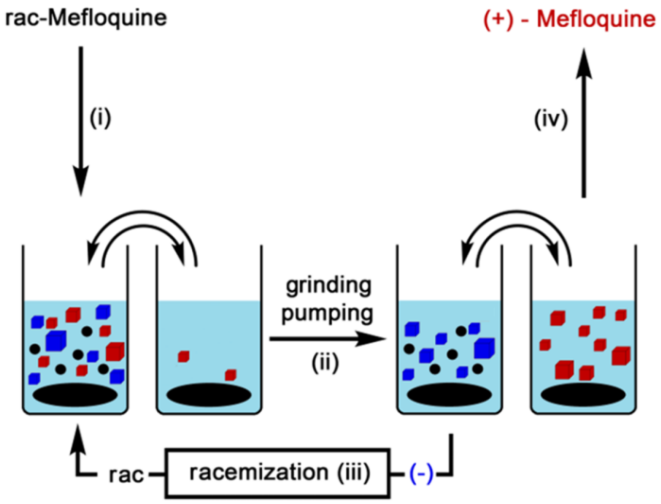


Figure 5.4: Experimental setup used for the deracemization of Mefloquine. (i) Racemic Mefloquine is converted into a racemizable precursor that crystallizes as a racemic conglomerate using the synthetic steps shown in Figure 2. (ii) Resolution of the derivative using a two vial system including continuous solvent exchange (iii) The solid of the vial containing the unwanted enantiomer is racemized using an AcOH/EtOH mixture at 75 °C. (iv) The desired enantiomer is transformed using $NaBH_4$ and $CeCl_3$ in EtOH at 0 °C, resulting in (+)-Mefloquine (*ee* = 95%, *de* = 93%).

5.3 Conclusion

The importance of single chirality to the pharmaceutical industry is becoming ever more profound. This is illustrated by the fact that all newly FDA approved chiral drugs in 2015 were marketed as a single enantiomer[43]. In addition, many drugs that were originally marketed as a racemic mixture, are now sold as a single enantiomer (the so-called racemic switch).[44, 45] Despite its widespread use and unfavorable pharmacokinetic properties of the (11*R*,12*S*) –Mefloquine enantiomer, this drug is still sold as a racemic mixture. A racemic switch would thus be highly beneficial for users of this drug. We have demonstrated an efficient strategy for the deracemization of Mefloquine, converting the initial racemic mixture into a single enantiomer. Via the crystal structure determination of a large set of salts of a Mefloquine derivative, a suitable conglomerate for this method was identified. Using a two-step approach, the racemic salt could then be deracemized towards the desired (*+*)–enantiomer. Via this route, the side-effects of Malaria can be reduced or eliminated, while increasing the effectiveness of the drug. This approach thus allows improvement of this highly important drug in the prevention and treatment of malaria. The application of attrition-enhanced deracemization to Mefloquine was challenging in terms of finding a suitable derivative that was both a conglomerate and racemizable. This example thus demonstrates that this route is also potentially available for many other drug compounds.

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Chapter 6

Solid Phase Conversion of Four Stereoisomers into a Single Enantiomer

6.1 Introduction

Among the 45 newly Food and Drug Administration (FDA) approved drugs in 2015, thirteen were achiral, three contained a single stereocenter, sixteen were small molecules containing multiple stereocenters, while thirteen were large biomolecules.[1] Due to the different bioactivity of the enantiomers, all of them (with the exception of the achiral drugs) are marketed as a single enantiomer. This clearly shows that obtaining molecules in enantiomerically pure form is of vital importance to human healthcare.[2] When synthesis yields a combination of enantiomers, diastereomeric salt formation is a frequently used method to separate the desired enantiomer from its unwanted mirror image isomer.[3, 4] This implies, however, that half of the product is discarded. Alternatively, deracemization methods can be used in which also the unwanted enantiomer is converted into the desired product. One such deracemization method is Viedma ripening.[5] This process involves the solid phase deracemization of a vigorously ground suspension of crystals, enabled by simultaneous solution phase racemization.[6] A key requirement for the process is that both enantiomers crystallize in separate crystals, i.e. as a racemic conglomerate. Over the past few years, various types of molecules have been deracemized using this approach.[7-11]
Up to now, only molecules with a single stereocenter have been deracemized using Viedma ripening. However, as mentioned, the majority of drug molecules are enantiopure and contain multiple stereocenters. Conversion of such compounds into a single enantiomer using such grinding experiments is obviously more challenging. This is due to the process involving 2^n chiral compounds (with n the number of stereocenters), instead of only two. Of these 2^n compounds, one set of enantiomers will be the thermodynamically most favorable one, whereas the other diastereomers will have a higher energy (or higher solubility). Sakamoto et al. used this difference in stability for a related experiment.[12] They studied a system with two stereocenters, of which one was enantiopure and could not

epimerize, while the second one could epimerize in solution, resulting in a solid phase that contained only a single diastereomer. Other crystallization methods that lead to the formation of a single enantiomer exist as well.[13] In the case of Viedma ripening, it is important that the thermodynamically more stable set of enantiomers crystallizes as a racemic conglomerate (Figure 6.1).

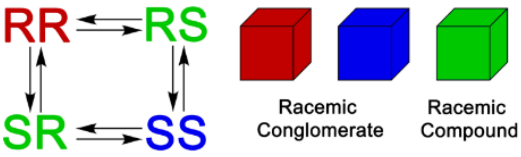

Figure 6.1. In order to successfully convert a compound with two stereocenters into a single stereoisomer using grinding experiments, epimerization of both stereocenters, as well as crystallization of the most stable pair of enantiomers as a racemic conglomerate is required.

The crystallization behavior of the less stable diastereomers is expected to be less important, since these compounds will eventually be eliminated from the solid phase. More challenging is the interconversion (racemization) of the two enantiomers, since this requires epimerization of all chiral centers. This can be achieved if the centers epimerize in a (near) identical way, or if the conditions for the different epimerization pathways are compatible. As a first step towards multiple stereocenters, we herewith show a successful demonstration on two molecules with two different stereocenters to which these conditions apply. From a total of four diastereomers a single one was obtained using grinding experiments. To the best of our knowledge, this is the first example of conversion of a stereoisomeric mixture of a compound with multiple stereocenters into only one enantiomer using such grinding experiments. So far, experiments by Hachiya et al. approximate this goal most closely, but using total spontaneous resolution

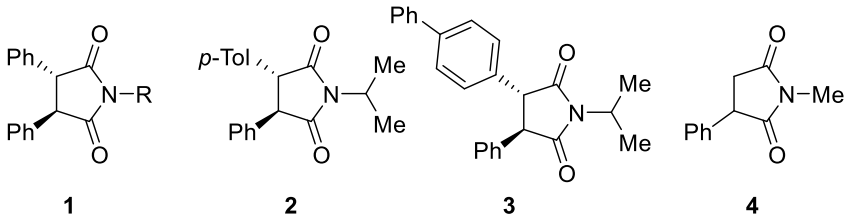

Figure 6.2: Deracemization of compounds of type **1** was previously studied by Hachiya et al.[12] This study investigates the conversion of compounds **2** and **3** into a single enantiomer, of which both are structurally closely related to the anticonvulsant drug phensuximide (**4**).

instead.[14] They succeeded in partially converting molecules having two identical stereocenters (meaning their system consisted of only three stereoisomers (one pair of enantiomers (**1**) and the corresponding achiral *meso*-compound) instead of four stereoisomers (two pairs of enantiomers), Figure 6.2).

6.2 Results and Discussion

Compounds **2** and **3** are examples of molecules with two different stereocenters, thus exhibiting four distinguishable stereoisomers. They belong to the class of succinimides, some of which exhibit anticonvulsant properties. They are structurally closely related to phensuximide (imide **4**), a drug used to treat epilepsy.[15] Related methylated succinimides are known for their antifungal activity, of which the enantiopure (*R*,*R*)-configured succinimides are the most effective ones.[16] Obtaining such succinimides in enantiopure form is therefore highly relevant.

In case of compounds **2** and **3**, the *trans*-diastereomers (3*R*,4*R* and 3*S*,4*S*) crystallize as a racemic conglomerate. For compound **2**, the *cis*-isomers (3*R*,4*S* and 3*S*,4*R*) form a rare example of a solid solution.[17] It is envisioned that the *trans*-diastereomers are more stable, since this configuration is less sterically hindered. NMR experiments confirmed this hypothesis. Epimerization of both stereocenters can be achieved by adding DBU as a base. When exposing a solution of compound

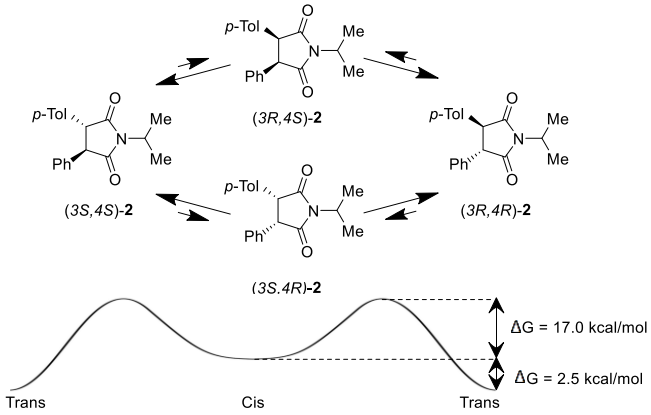

Figure 6.3: Epimerization and racemization of compound **2** takes place via reversible deprotonation of the stereocenters using 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU) as a catalyst. In this case, the two epimerization rates are nearly identical. The indicated Gibbs free energies were determined using temperature-dependent selective exchange spectroscopy.

2 to epimerization conditions, only 2% was present as the *cis*-isomer at room temperature as observed in the ^{1}H NMR spectrum. This corresponds to the conglomerate *trans*-form being more stable by 2.5 kcal/mol (in solution), making this system potentially suitable for Viedma ripening (Figure 6.3).

Since the synthesis of compound **2** solely yielded the *cis*-diastereomer (through hydrogenation of the corresponding maleimide derivative), this isomer was used as the starting point for the grinding experiments. Upon addition of the racemization catalyst (DBU), the dissolved *cis*-diastereomers were epimerized into the *trans*-form. Further dissolution and subsequent epimerization of *cis*-**2** resulted in supersaturation and consequent crystallization of *trans*-**2**. This process happened relatively fast in a time span of several minutes (Figure 6.4).

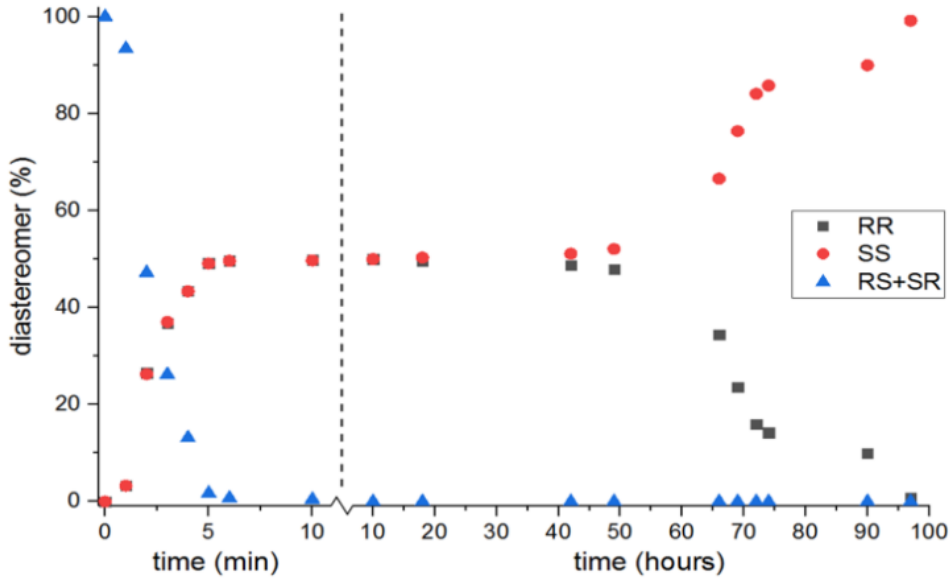

Figure 6.4: Example of a grinding experiment on a suspension of compound **2** starting from the *cis*-diastereomers (quantities given are those of the solid state). During the first 10 minutes of the experiment, racemization was deliberately slowed down (by adding only a small fraction of the final amount of DBU) to show the conversion of the *cis*- into the *trans*-diastereomers (notice the two different time scales on the *x*-axis). Note: the outcome of these experiments is stochastic, meaning that by repeating the experiment, both enantiomers are equally likely to be obtained.

Using temperature-dependent selective exchange spectroscopy measurements, it was found that the transition state barrier of the conversion of *cis* to *trans* was only ΔG = 17.0 kcal/mol. This results in a half-life of approximately one second (using the Eyring equation). The limiting factor in this process is thus the dissolution, rather than the epimerization of the *cis*-compound. Next, the Viedma

ripening conditions resulted in deracemization of the crystals to provide only one of the two *trans*-enantiomers. Racemization of one *trans*- into the enantiomeric *trans*-isomer happens at one center at a time, via sequential epimerization of both chiral centers. The *cis*-isomer is thus an intermediate in the racemization pathway (Figure 3). The racemization barrier of this process was calculated to be 19.5 kcal/mol (see SI). The deracemization process took several days, showing the exponential behavior typical for Viedma ripening. The long deracemization time is largely caused by the long "dead time" before symmetry breaking occurs. Deracemization proceeds stochastically, meaning that both enantiomers are obtained as the crystalline product in different experiments. In similar grinding experiments, the production of a single enantiomer could also be achieved for a mixture of diastereoisomers of imide **3** (see Figure S6.3 in the SI). Since it is synthetically more useful to be able to direct the outcome of a Viedma ripening experiment towards the desired enantiomer, we explored the possibility of using chiral additives, a strategy that was previously successfully applied to achieve this goal (alternatively, a small amount of enantiopure product might be added to achieve this same goal).[18, 19] A suitable chiral additive with high affinity for only one of the two crystal forms may act as a selective growth-inhibitor.[20] In practice, molecules that closely resemble one of the two enantiomers are selected for this purpose. Importantly, the chiral additive should not alter its stereochemical

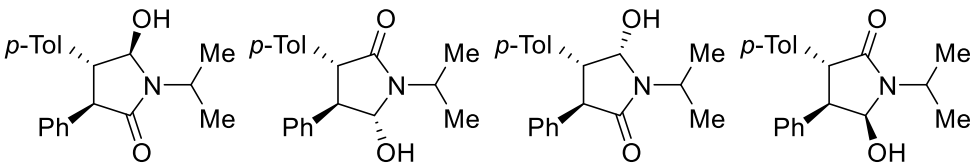

Figure 6.5: Additives for directing the outcome of the Viedma ripening experiments on compound 2. In all cases, all four (in this case (*R,R*)-based) additives were used together.

configuration during the experiment.

In this study, a combination of four enantiopure chiral additives was synthesized,[21, 22] all of which closely resemble the same enantiomer of compound **2** (Figure 6.5). All additives contain three chiral centers, of which one (carrying the hydroxyl group) cannot epimerize under the influence of DBU. The locked chirality of this stereocenter also ensures the desired chirality of the other two centers (since epimerization of these centers would result in sterically unfavored *cis*-

orientations, see SI). Using these tailor-made additives, the outcome of the grinding experiments always proceeded in the desired direction. The combination of the four additives based on (*R*,*R*)-**2** always resulted in (*S*,*S*)-**2** as the product, while (*S*,*S*)-based additives resulted in (*R*,*R*)-**2**. This phenomenon of opposing chirality has been extensively studied and is known as the Lahav rule of reversal.[19, 23-25] Since a combination of four additives was used in all experiments,[26, 27] we could not determine which of the four was most effective. The deracemization curve shows a linear behavior, typical for the use of chiral additives.[28] Not only could the desired enantiomer be obtained using this approach, the time required

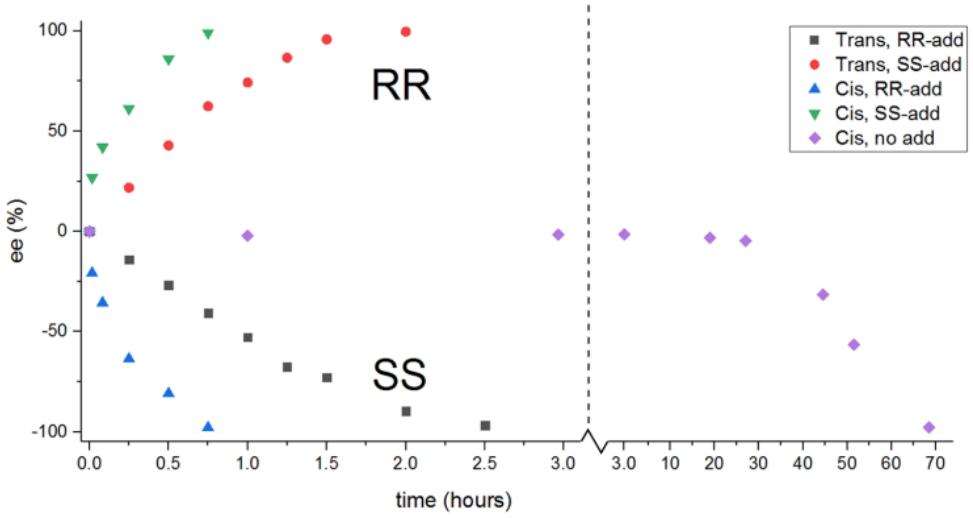

Figure 6.6: Curves showing the conversion of compound **2** into a single enantiomer, using 5 mol% of the chiral additives **5a-d** (*ee* stands for enantiomeric excess; +100% *ee* implies only *RR* while –100% *ee* means only *SS*). Experiments were either started from the racemic *trans*-(*R*,*R*/*S*,*S*) or *cis*-(*R*,*S*/*S*,*R*) diastereomers. Within a minute after adding the racemization catalyst, all experiments contained only the *trans*-diastereomer. When additives were used, **5a-d** were always used as a combination. Please note the two different time scales on the *x*-axis.

for deracemization was also significantly decreased (Figure 6.6). When starting from the racemic *trans*-diastereomers, the deracemization time was reduced from 70 to 2.5 hours. When starting from *cis*-**2**, the conversion time was even decreased to less than one hour, in other words a reduction of almost a factor 100 was achieved. This increased conversion speed is induced in the initial phase of the process. Fast epimerization of the *cis*-diastereomer results in a supersaturated solution of the *trans*-enantiomers. Since the rate of *cis*- to *trans*-epimerization is higher than that of racemization, this results in crystallization of both *trans*-

enantiomers in the absence of an additive. In the presence of the additive, however, crystallization of the enantiomer similar to the additive is hampered, resulting in preferential crystallization of the other enantiomer.[29, 30] This results in a solid phase that already has a high starting *ee* (around 25% after adding the racemization catalyst) when the Viedma ripening commences. The time required to obtain a single enantiomer is therefore even shorter than already achieved for the use of an additive only (starting from *trans*-**2**).

6.3 Conclusions

In conclusion, we have shown that the formation of one single out of four stereoisomers using isomerization and subsequent Viedma ripening is possible. The requirements are similar to those for compounds with only a single stereocenter, but can in practice be difficult. The desired pair of enantiomers should be the thermodynamically most stable pair and should also crystallize as a racemic conglomerate. However, when the most stable pair of enantiomers crystallizes as a racemic compound, derivatization[31] or salt formation[32] can additionally be used to convert it into a conglomerate. Racemization can be more challenging, since epimerization of all chiral centers should proceed under the same conditions. These principles do not only hold for a molecule with two, but also for more stereocenters. As long as these requirements are met, Viedma ripening may be used for the deracemization of any compound with multiple stereocenters.

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Chapter 7

Deracemization of a Racemic Compound Using Tailor-Made Additives

7.1 Introduction

Deracemization of chiral small molecules using Viedma ripening has attracted much attention during the past decade.[1] This method, which combines abrasive grinding of a slurry of crystals with solution phase racemization, results in complete solid phase deracemization (Figure 1a). The Viedma ripening process is operating when the compound crystallizes as a racemic conglomerate meaning that the enantiomers crystallize in separate crystals. Viedma was the first to demonstrate this method for the achiral inorganic salt sodium chlorate, which crystallizes in a chiral fashion.[2] We and others have demonstrated that Viedma ripening can also be applied to intrinsically chiral organic molecules, such as amino acid derivatives[3, 4], metal-organic complexes[5] and isoindolinones.[6] Although the outcome of a Viedma ripening experiment is in principle stochastic, it has been demonstrated that enantiopure additives (small amounts of a chiral compound that closely resembles the target compound) can be used to direct the outcome towards formation of a specific enantiomer.[7]

The requirement of formation of racemic conglomerates remains an inherent drawback for Viedma ripening. Since only 5-10% of all chiral molecules crystallize as conglomerate crystals, Viedma ripening is not suitable for the 90-95% of chiral compounds that crystallize as a racemic compound. One solution to overcome this challenge is to modify the crystallization behavior of solids in such a way that conglomerate formation occurs. Examples include salt formation and screening multiple counterions for conglomerate formation.[8] Alternatively, when deracemization of a certain class of neutral molecules is required, the problem can be solved by engaging in a library synthesis of derivatives to identify compounds that display conglomerate behavior.[9] Both approaches are however certainly not generally applicable; e.g. many compounds cannot form salts. It would therefore be beneficial to find approaches to apply attrition enhanced deracemization to racemic compounds without using any chemical modification.

In this manuscript, we show that this can be achieved by using tailor-made chiral additives.

Chiral additives:

The concept of using additives in crystallization was applied long before Viedma ripening had been developed. Extensive studies were conducted by the group of Lahav, who focused on the resolution of conglomerates using additives.[10, 11] They used enantiopure tailor-made additives that selectively bind to surfaces of crystals of the same chirality. This resulted in crystallization from solution of only the opposite enantiomer. The outcome of these additive induced resolution experiments is therefore generally described by the Lahav rule of reversal; using a chiral additive results in preferential crystallization of the opposite chirality.[10-13] This rule also holds when using additives in directing Viedma ripening processes.[7, 14, 15] Note that in all these cases additives were used to direct the outcome of the deracemization of a compound that crystallized as a racemic conglomerate.

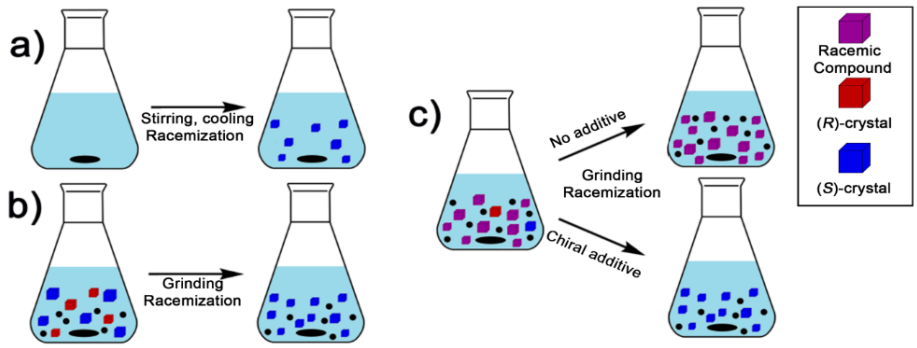

Figure 7.1: Conceptual approaches for deracemization of racemic conglomerates via a) total spontaneous resolution; b) Viedma ripening c) This paper: deracemization of a suspension of a racemic compound using chiral additives. In this scheme, the formation of enantiopure crystals is always represented by blue (*S*)-crystals.

When a compound crystallizes as a racemic compound, several methods for enantioenrichment have been reported in literature. Klussman et al. showed that, starting from nonracemic but also not enantiopure conditions the eutectic composition of a compound can be used to create a very high solution enantiomeric excess (*ee*).[16] When the eutectic composition is unfavorable, crystal engineering (via co-crystal formation) can be used to increase the *ee*.[17] In

addition, a few examples exist in which a single enantiomer of a racemic compound could be crystallized from a saturated solution using a chiral additive. The HCl-salt of histidine crystallizes as a racemic dihydrate below 45 °C and as a conglomerate monohydrate above this temperature. Using chiral polymeric additives, a single enantiomer could be crystallized under conditions, where normally the racemic compound would be stable (Figure 7.1c).[18] A similar approach has been used for the resolution of calcium tartrate hydrate.[19]

In contrast to these examples, our experiments will start from a racemic suspension of crystals, seeded with just a few conglomerate crystals. In addition, the aim is not to separate the enantiomers, but completely deracemize the solid phase. It should be noted that both examples from the literature are unsuited for this additive driven deracemization, since either racemization is very difficult (calcium tartrate), or the additive racemizes at similar conditions as the target molecule (histidine).

We now show that additives can be used to block the growth of the racemic compound of 1,1'-binaphthyl (compound **1**), favoring the growth of a single

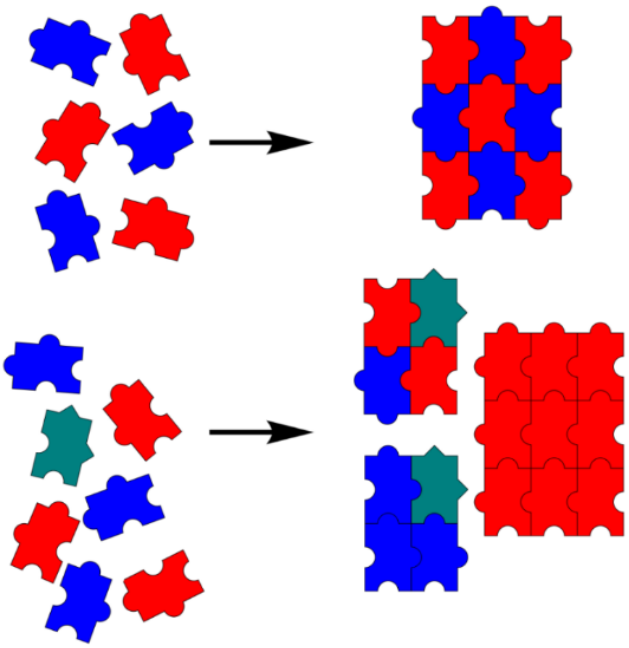

Figure 7.2: A chiral molecule that normally crystallizes as a racemic compound can, in the presence of a chiral additive (green blue, closely resembling one of the enantiomers), favor the preferential crystallization of a single enantiomer by blocking the growth of the other crystal structures.

enantiomer (Figure 7.2).

Since racemization of **1** spontaneously happens at the elevated temperatures that were used, deracemization could be achieved. In addition, the obtained handedness of the product could be directed by the chirality of the additive.

Binaphthyl (**1**, Figure 7.3) is an example of an atropisomer, a non-planar molecule that displays chirality through the hindered rotation around a single bond.[20] Binaphthyl crystallizes as a racemic compound at room temperature, but converts into a conglomerate at temperatures above 85 °C.[21,22] It racemizes readily at such temperatures ($t_{1/2}$ = 14.5 min in DMF at 50 °C), whereas racemization at room

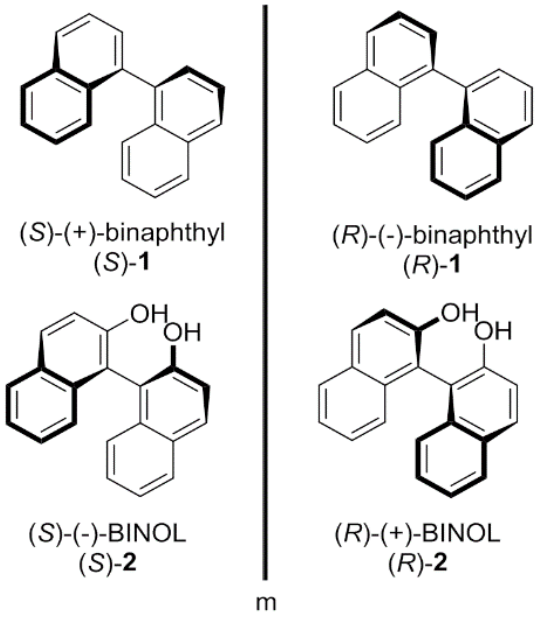

Figure 7.3: Both binaphthyl (**1**) and BINOL (**2**) are examples of atropisomers having an axis of chirality with hindered, temperature dependent rotation around the chiral axis.

temperature is slow.[23]

Since binaphthyl (**1**) crystallizes as a racemic conglomerate above 85 °C, deracemization (via total spontaneous resolution) above this temperature can be achieved, as was shown by the groups of Pincock[22] and Kondepudi.[24] Below this temperature, we tested whether additives can be used to induce deracemization. As an additive, we chose BINOL (**2**) since it closely resembles binaphthyl (**1**), but does not racemize at temperatures below 100 °C.[25, 26] The additive in these

experiments was envisioned to operate via a kinetic pathway, blocking the growth of the racemic compound and one of the two conglomerate forms.

7.2 Results and Discussion

To study whether this additive could exert such an effect, a series of Ostwald ripening experiments were performed. For these experiments, nonane was selected as a solvent since binaphtyl was very soluble in more polar solvent, resulting in a large loss of material during these experiments. In addition, it was determined that the half-life of racemization in nonane was appropriate for these experiments ($t_{1/2}$ = 2.3 min at 70°C, see SI). In these experiments, suspensions of equal amounts of racemic and conglomerate **1** (with or without additive) were

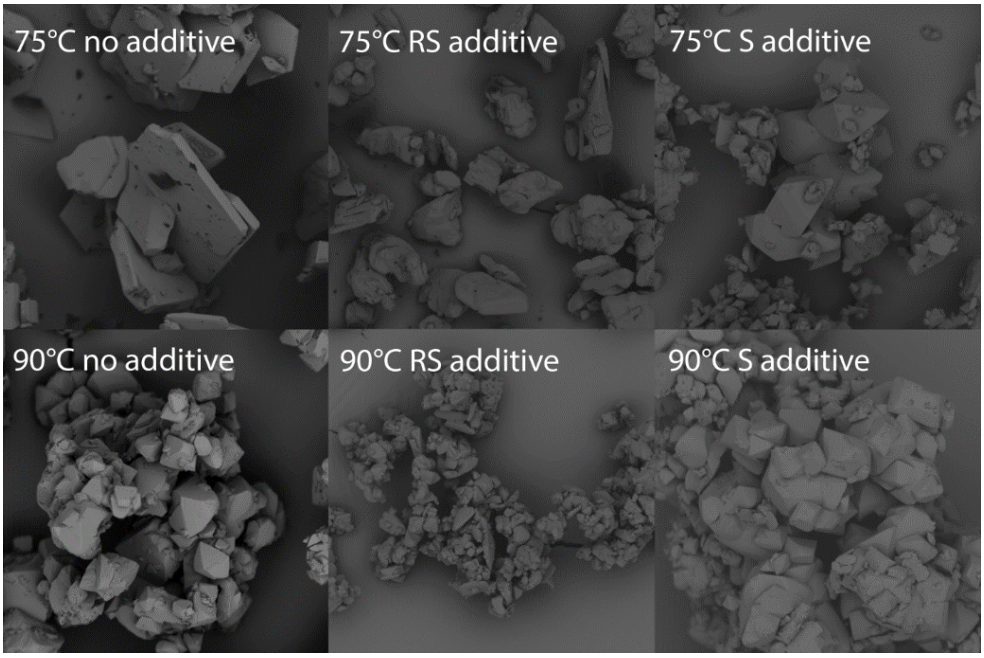

Figure 7.4: SEM images of crystals resulting from Ostwald ripening experiments of binaphthyl (**1**) in the presence and absence of 10% additive. The flat plates correspond to the racemic compound, the octahedrons to the conglomerate. In the presence of the racemic additive at 75 °C, a featureless material was obtained which by XRPD was shown to be the racemic compound.

gently stirred for two days. The solid phase was then characterized using X-Ray Powder Diffraction (XRPD), chiral HPLC and Scanning Electron Microscopy (SEM, Figure 7.4).

Ostwald ripening without an additive at 90 °C gave only octahedral crystals, corresponding to the racemic conglomerate. This indicates that the conglomerate is indeed the most stable phase at this temperature. In the presence of the enantiopure (*S*)-additive, similar size octahedrons were obtained containing only the (*S*)-enantiomer implying that deracemization had taken place during Ostwald ripening. In addition, experiments were performed in which both enantiomers of the additive were added. In these cases, the growth of all crystal forms (racemic conglomerate and racemic compound) was expected to be hampered. Indeed, when a racemic additive was used, the average size of these crystals was much smaller. Again, octahedrons of the racemic conglomerate were obtained, but now no deracemization had taken place. At temperatures of 80 and 75 °C, thin plates corresponding to the racemic compound were obtained in the absence of any additive. This proves that at these temperatures indeed the racemic compound is the most stable phase. However, in the presence of the enantiopure (*S*)-additive, again conglomerate octahedrons were obtained containing only the (*S*)-enantiomer. Growth of both the (*R*)-enantiomer and the racemic compound were hampered by the additive. When both enantiomers of the additive were added, the growth of all crystal forms was blocked. This resulted in a material with a featureless morphology, of which XRPD showed that it corresponded to the racemic compound.

Deracemization experiments:

These observations indicate that the additive does indeed exhibit the intended kinetic effect on the binaphthyl crystals. Therefore, some larger-scale deracemization experiments were performed. In these experiments, glass beads were added to a suspension of crystals to create a Viedma ripening experiment. Since binaphthyl crystallizes as a racemic compound below 85 °C, experiments at such low temperatures were unsuccessful. Therefore, the additive approach was used to change the crystallization behavior from a racemic compound to a conglomerate.

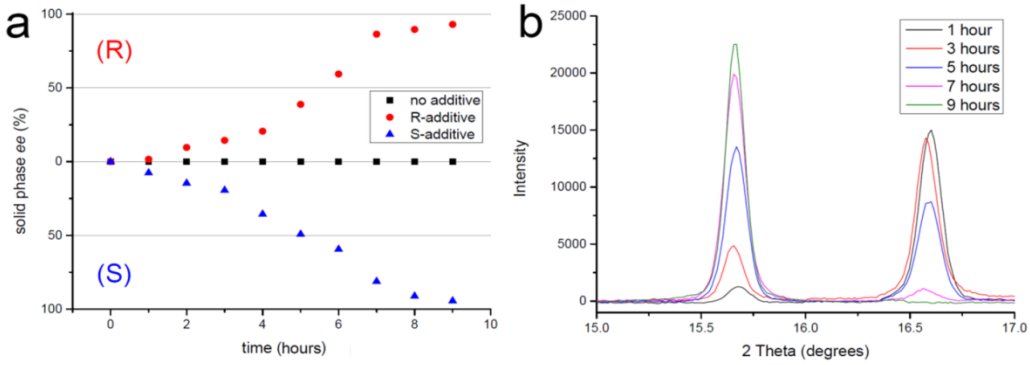

Figure 7.5: (a) Deracemization curve of a grinding experiment of compound **1** at 80 °C in the presence and absence of 10% enantiopure BINOL. (b) The XRPD of the solid phase of **1** during these deracemization experiments shows the conversion from a racemic compound to a conglomerate. The peak at 15.7 degrees corresponds to the {1 0 2} reflection of the conglomerate and the peak at 16.6 to the {1 1 -1} reflection of the racemic compound.

When using this additive, deracemization of binaphthyl became possible under conditions where it is stable as a racemic compound (in the absence of additives). When using enantiopure additive **2** and a small amount of racemic conglomerate seed crystals, complete deracemization could be achieved within 12 h (Figure 7.5a).[27] The resulting chirality could be directed by the handedness of the additive. Use of (*R*)-**2** always resulted in (*R*)-**1**, while adding (*S*)-**2** resulted in (*S*)-**1**. This implies that the outcome of these experiments does not follow Lahav's rule of reversal, which is a discrepancy that we at this point cannot explain.

To further study the deracemization process, XRPD measurements were performed on samples taken during the deracemization experiments. These measurements revealed that the deracemization of **1** took place at the same rate as the conversion of the racemic compound into the conglomerate (Figure 7.5b). This gives some indication towards a possible mechanism of deracemization. During the grinding experiments, both the racemic compound and conglomerate dissolved resulting in (*R*)- and (*S*)-enantiomers in solution. The additive then hampered crystal growth as depicted in Figure 2. When using (*S*)-**2** as an additive the growth of both the racemic and conglomerate (*R*) -crystals were blocked (reverse rule of reversal). The (*S*)-enantiomers in solution could, however, still be incorporated into the existing (*S*)-crystals. Grinding ensured a continuous increase in the number of these crystals. Since racemization took place in solution, the (*R*)-enantiomers could be converted and consequently also be incorporated into the

(*S*)-crystals. The racemic compound thus served as a gradual feed for the (*S*)-crystals in contrast to standard Viedma ripening, where only the opposite enantiomers serve as feed.[28, 29]

The scope of the additive:
Both the concentration of the additive and the temperature of the experiment are of great influence on the deracemization rate (Figures 7.6 and 7.7). As mentioned earlier, in the absence of the additive, no deracemization could be achieved at

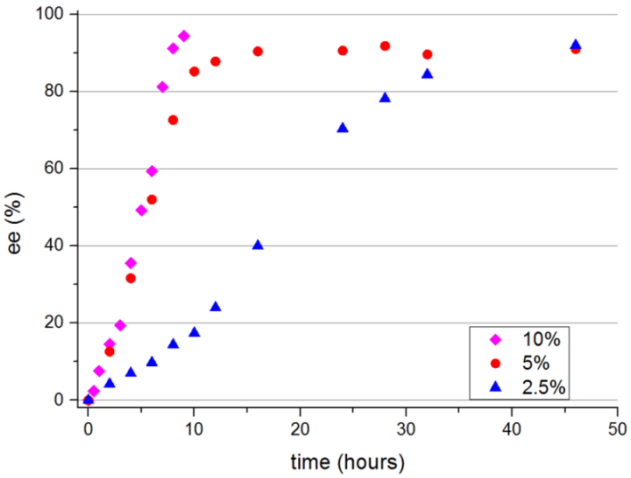

Figure 7.6: Effect of the additive concentration on the deracemization of compound **1** at 80°C.

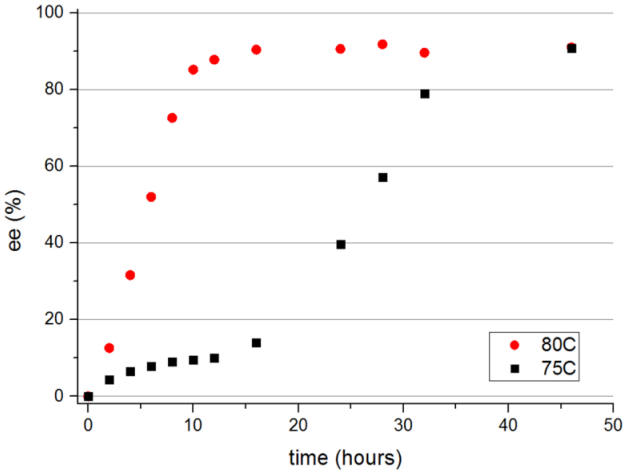

Figure 7.7: Deracemization of compound **1** in the presence of 5% additive (*S*)-2 at 80 and 75 °C.

temperatures below 85 °C. When adding 2.5 mol % of the additive, complete deracemization was achieved in around 40 h at a temperature of 80 °C. When increasing the additive concentration to 5%, the deracemization time could even be decreased to around 15 hours. Since the solution was saturated with 5% additive, further increasing this concentration had no effect at either temperature. When repeating the same experiment at 75 °C, with 2.5% additive, no deracemization was observed. However, when increasing the additive concentration to 5% deracemization was achieved after 40 h. These experiments suggest that the deracemization becomes more difficult when the system is further from the peritectic (86 °C), i.e. when the racemic conglomerate becomes increasingly unstable. Increased additive concentrations can, however, be used to increase the range at which this approach is viable.

7.3 Conclusions

The main advantage of this additive approach to effect deracemization is that Viedma ripening is no longer restricted to the 5-10% of chiral molecules that crystallize as a racemic conglomerate. When a compound is stable as a racemic compound, deracemization can still be achieved by using appropriate chiral additives. In the present case, an appropriate additive was found by selecting a structurally closely related molecule that cannot be racemized under the conditions used. These additives cannot only be applied to peritectic systems in which conglomerate and racemic compound are the stable phase at different temperatures, but potentially also for compounds for which the racemic compound is always the stable phase (as long as the energetic difference between both phases is not too large). This kinetic approach therefore expands the scope of attrition enhanced deracemization.

7.4 Notes and References

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Summary

Chiral molecules come in two enantiomers, which are each other's mirror images. Many of the biochemical molecules that make up living systems are chiral. Therefore, these molecules interact differently with the enantiomers of other chiral molecules. This, for example, is the reason that enantiopure drugs are becoming ever more important to the pharmaceutical industry. While in the past drugs used to be sold as a mixture of enantiomers, nowadays almost all chiral drugs are marketed in enantiopure form. Since synthesis often yields a racemic mixture of enantiomers, resolution or deracemization methods are required. Viedma ripening has been shown to be an effective method to achieve this goal. The Viedma process involves the grinding of a slurry of chiral crystals in a saturated solution, resulting in solid phase deracemization. The method can be used if the molecule crystallizes as a racemic conglomerate of right and left-handed crystals, and can be racemized in solution. The first requirement is a limiting factor, as an estimated 90-95% of all chiral molecules crystallize as racemic crystals, which in principle makes them unfit for Viedma ripening. The second requirement, racemization in solution, can be challenging since harsh conditions may be required or racemization is simply not possible. This thesis deals with studies to identify solutions for these two limitations.

In the first part of the thesis, two molecules were investigated which seem unsuitable for Viedma ripening, due to their crystallization as a racemic compound. It turned out that this racemic form is in fact metastable, whereas the conglomerate is most stable. Deracemization of these compounds could therefore still be achieved. By using enantiopure seed crystals in the grinding process, the racemic compound was selectively converted into this enantiopure form. Using this gradual conversion of racemic to conglomerate crystals, the speed of deracemization could be reduced from days to hours (Figure 1).

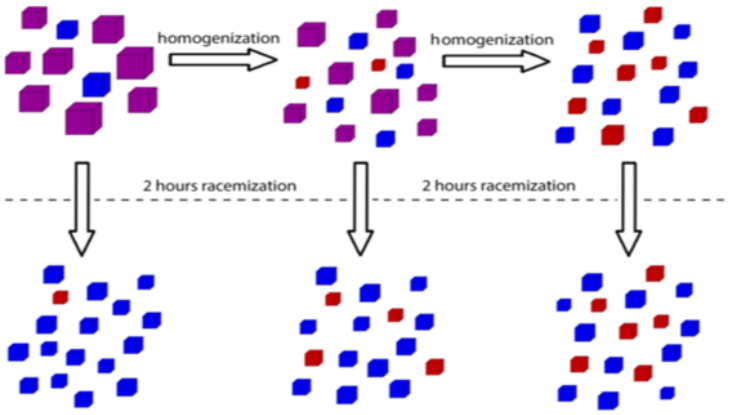


Figure 1: By adding enantiopure seed crystals to a suspension of a metastable racemic compound under racemization conditions, fast deracemization can be achieved.

The same approach could be used for the deracemization of a chiral allylic sulfoxide (chapter 3). A conglomerate was identified through a library synthesis and consecutive crystal structure elucidation of 14 of such compounds. One of these sulfoxides could be crystallized as either a racemic conglomerate or a metastable racemic compound. By heating this compound in an apolar solvent, a reversible rearrangement could be induced, resulting in racemization. Starting from a suspension of the metastable racemic compound at elevated temperatures, vigorous grinding resulted in fast deracemization.

In chapter 4, the deracemization of an atropisomer was described. Atropisomers are molecules that display chirality through the hindered rotation around a single bond, resulting in an axis of chirality. Deracemization of such a molecule could be achieved using Viedma ripening, either by grinding or sonication. In addition, temperature cycling, in which deracemization is achieved by cycling the temperature of the suspension, was used.

The fifth chapter focused on deracemization of the anti-malarial drug Mefloquine. This drug is sold as a racemic mixture of two enantiomers, of which one is most active, while its mirror image causes severe psychotropic side-effects. Using a simple oxidation reaction, a racemizable derivative of this drug was obtained. Next, a crystal structure screening of 34 salts was performed to identify a racemic conglomerate. In this case, the conditions required for racemization proved to be incompatible with those at which the conglomerate was stable. Therefore,

resolution via a two-vessel system, followed by racemization of the unwanted enantiomer was used that could be re-used as feed for the process. This approach resulted in the near complete deracemization of this important drug.

Next, deracemization of chiral compounds with two stereocenters was investigated. While Viedma ripening has only be applied to molecules with a single element of chirality, the majority of newly marketed drug molecules contain multiple stereocenters. Chapter 6 describes the deracemization of two such compounds. In both cases, the most stable of the two diastereomers crystallized as a racemic conglomerate, while epimerization of both stereocenters occurred in a similar fashion. The conditions, required for Viedma ripening, were therefore still fulfilled. The deracemization process occurred in a stochastic fashion, implying that the outcome of the experiments is random. In order to direct the process to the required chirality, a series of enantiopure additives were synthesized. In addition to obtaining the desired enantiomer, the time required for deracemization was reduced by a factor of 100, using these chiral additives.

The major drawback of Viedma ripening remains the requirement of a racemic conglomerate. A library synthesis (chapter 3) or salt screening (chapter 5) can be used to identify such a compound. This is however a laborious exercise, since 90-95% of the created compounds does not crystallizes as such a conglomerate. The direct deracemization of a racemic compound would therefore be much more favorable. In chapter 7, a chiral additive was used to achieve this goal. In these experiments, a second type of chiral molecules was added to grinding experiments of a racemic compound. This enantiopure additive closely resembled

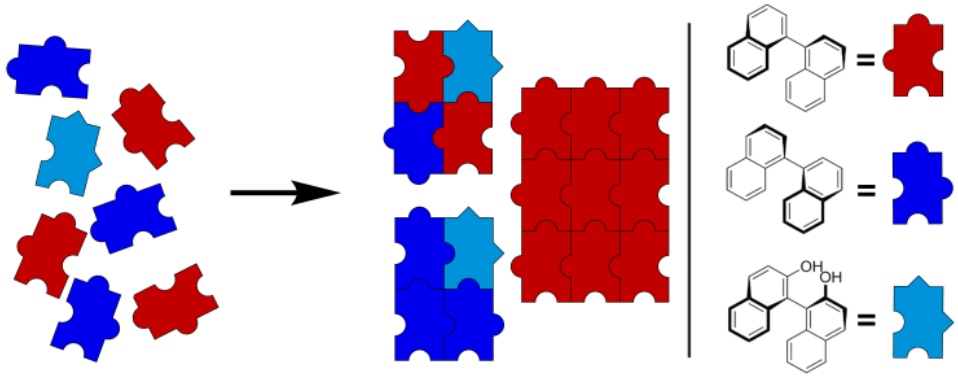


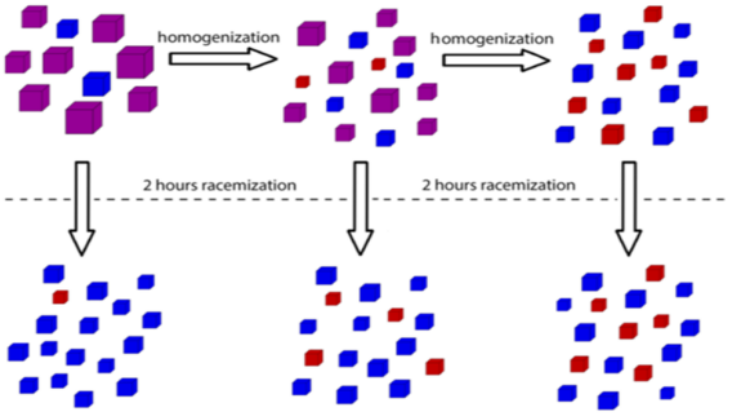
Figure 2: Enantiopure chiral additives can be used to block the growth of a racemic compound and one of the two enantiopure crystal forms, resulting in deracemization.

one of the enantiomers that had to be deracemized. It could attach to the surface of the racemic crystal, blocking crystal growth (Figure 2). In addition, growth of crystals containing only the opposite enantiomer of the metastable conglomerate was also blocked. The only crystal type of which the growth was not blocked, was that which the additive resembles. Using this growth blocking mechanism of the additive, the deracemization of a racemic compound could be achieved.

Samenvatting

Chirale moleculen komen voor in de vorm van twee enantiomeren die elkaars spiegelbeeld zijn. Een groot deel van de biochemische moleculen, waar levende systemen uit bestaan, zijn chiraal. Dit heeft als gevolg dat deze moleculen verschillende interacties aangaan met andere, ook chirale, moleculen. Dit is bijvoorbeeld de reden dat enantiozuivere medicijnen steeds belangrijker worden. Terwijl deze vroeger als een mengsel van twee enantiomeren (racemisch) verkocht werden, bestaan vrijwel alle medicijnen tegenwoordig uit een enkele enantiomeer. Omdat de synthese van deze medicijnen vaak een racemisch mengsel van enantiomeren oplevert, zijn scheiding of omzetting methodes nodig. Viedma ripening is een effectieve manier om dit doel te bereiken. Tijdens Viedma ripening wordt een slurrie van kristallen in een verzadigde oplossing gemalen, hetgeen resulteert in een enantiozuivere vaste stof. Viedma ripening werkt zolang het molecuul kristalliseert als een conglomeraat van linkse en rechtse kristallen en de enantiomeren in elkaar worden omgezet (racemisatie) in de oplossing. Deze eerste eis is een beperkende factor, omdat 90-95% van de moleculen kristalliseert als racemaat, wat ze ongeschikt maakt voor Viedma ripening. De tweede eis, racemisatie in oplossing, is vaak een grote uitdaging, omdat extreme omstandigheden nodig zijn, of dit eenvoudigweg niet mogelijk is. Dit proefschrift probeert voor beide beperkingen oplossingen te vinden.

In het eerste deel van het proefschrift wordt gekeken naar twee moleculen die ongeschikt leken voor Viedma ripening, omdat ze kristalliseren als een racemaat. Deze kristalvorm bleek echter metastabiel te zijn, terwijl juist het conglomeraat stabiel is. Deracemisatie van deze moleculen was daardoor toch mogelijk. Door enantiozuivere entkristallen toe te voegen tijdens het malen, werd het racemaat selectief omgezet in deze enantiozuivere vorm. Deze geleidelijke omzetting zorgde ervoor dat de deracemisatietijd werd teruggebracht van dagen naar uren (Figuur 1).



Figuur 1: Snelle deracemisatie kan bereikt worden door enantiozuivere entkristallen toe te voegen aan een suspensie van een metastabiel racemaat terwijl er racemisatie plaatsvindt.

Dezelfde aanpak bleek te werken om een chiraal allylisch sulfoxide te deracemiseren. Een conglomeraat werd gevonden door 14 van deze sulfoxides te synthetiseren en hun kristalstructuur te bepalen. Eén van deze sulfoxides kon zowel worden gekristalliseerd als een conglomeraat, als een metastabiel racemaat. Door dit molecuul te verhitten in een apolair oplosmiddel, kon het een reversibele omlegging aangaan, hetgeen resulteerde in racemisatie. Door een suspensie van het metastabiele racemaat te verhitten en te malen, kon snelle deracemisatie worden bewerkstelligd.

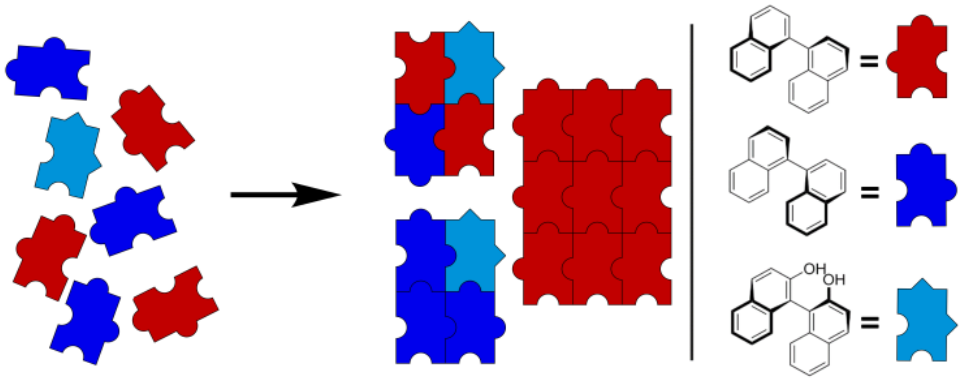
In hoofdstuk 4 wordt de deracemisatie van een atropisomeer beschreven. Een atropisomeer is een molecuul waarbij rotatie rond een bepaalde binding wordt verhinderd, resulterend in een chirale as. Deracemisatie van zo'n molecuul kon met Viedma ripening worden bereikt door middel van zowel malen als met een ultrasoon bad. Daarnaast kon ook temperature cycling worden gebruikt, waarbij deracemisatie voor elkaar wordt gekregen door de temperatuur cyclisch te variëren.

Het vijfde hoofdstuk gaat in op de deracemisatie van het anti-malaria medicijn Mefloquine. Het medicijn wordt verkocht als een racemisch mengsel van twee enantiomeren, waarvan er een het meest effectief is en het spiegelbeeld ernstige (psychotropische) bijwerkingen veroorzaakt. Door middel van een simpele oxidatie kon een racemiseerbare variant van dit medicijn worden verkregen. Om een conglomeraat te vinden werden de kristalstructuren van 34 zouten van dit

molecuul bepaald. In dit geval bleken de racemisatiecondities niet compatibel met die waarbij het conglomeraat stabiel was. Daarom werd een twee-vaten systeem gebruikt waarmee de enantiomeren van elkaar gescheiden konden worden, waarna de ongewenste enantiomeer geracemiseerd kon worden om weer te dienen als voeding voor het proces. Deze aanpak resulteerde in een bijna volledige deracemisatie van dit belangrijke medicijn.

Vervolgens werd de deracemisatie van moleculen met twee stereocentra onderzocht. Tot nu toe is Viedma ripening alleen toegepast op moleculen met één chiraal element, terwijl de meeste nieuwe medicijnen er meerdere hebben. Hoofdstuk 6 beschrijft de deracemisatie van twee dergelijke moleculen. In beide gevallen kristalliseerde de stabiele diastereomeer als een conglomeraat, terwijl de chiraliteit van beide centra op een vergelijkbare manier kon worden omgekeerd. Deze moleculen voldeden daarom nog steeds aan de eisen voor Viedma ripening. De deracemisatie gebeurde op een stochastische manier, hetgeen betekent dat de uitkomst van de experimenten (links of rechtshandig) willekeurig was. Om het experiment toch te kunnen sturen naar de gewenste uitkomst, werd een serie chirale additieven gesynthetiseerd. Deze zorgde niet alleen voor de gewenste enantiomeer, maar verminderde de deracemisatietijd ook nog eens met een factor 100.

De grote beperking van Viedma ripening blijft dat er een conglomeraat nodig is. Zowel het groeien van een serie zouten, of het synthetiseren van een serie moleculen kan gebruikt worden om een conglomeraat te vinden. Dit kost echter



Figuur 24: Enantiozuivere chirale additieven kunnen gebruikt worden om de groei van zowel het racemaat als één van de enantiozuivere kristalvormen te verhinderen. Dit resulteert in deracemisatie.

veel werk, omdat 90-95% van de moleculen niet op deze manier kristalliseert. Het direct deracemiseren van een racemaat zou daarom veel gunstiger zijn. In hoofdstuk 7 worden chirale additieven gebruikt om dit doel te bereiken. In deze experimenten werd een tweede type chiraal molecuul toegevoegd tijdens het malen. Dit enantiozuivere additief lijkt sterk op één van de twee enantiomeren van het molecuul dat gederacemiseerd moest worden. Daarom hechtte dit molecuul zich aan het kristaloppervlak van het racemaat, hetgeen verdere kristalgroei verhinderde (Figuur 2). Daarnaast blokkeerde het ook de kristalgroei van de tegenovergestelde enantiomeer van het metastabiele conglomeraat. De enige kristalvorm die nog wel kon groeien, was degene waar het additief zelf veel op leek. Door gebruikt te maken van deze blokkering van kristalgroei, kon een racemaat worden gederacemiseerd.

Perspective

The majority of enantiopure drugs are currently prepared via resolution, using diastereomeric salt formation.[1] This process suffers from the inherent drawback that stoichiometric amounts of an additional enantiomerically pure resolving agent are required.[2] In addition, the 50% of the product that is of the undesired chirality will be either discarded or racemized in a separate step and fed back into the initial process. Although Viedma ripening suffers from neither of these two disadvantages, the method is currently (to the best of our knowledge) not applied in the chemical or pharmaceutical industry yet. This is explained by the two main bottlenecks for its application: (1) the requirement that the compound crystallizes as a racemic conglomerate and (2) the need for (in situ) racemization.[3]

Although the requisite of a racemic conglomerate renders 90-95% of all compounds unsuitable for Viedma ripening,[4] we do not consider this the main limitation for the applicability of the process. Many "tricks", such as salt formation[5] or derivatization,[6] can be used to convert such a racemic compound into a conglomerate analogue. In addition, the use of chiral additives might be used to favor the desired crystallization behavior (this probably has a more limited scope).[7, 8] Therefore, in our opinion the biggest challenge in applying Viedma ripening lies in providing racemization conditions.

Most examples of Viedma ripening in the literature start from known racemization conditions and then aim at identifying a racemic conglomerate. This has resulted in several examples that involve an acidic proton at the chiral center of a molecule that can be racemized using a base.[3] Other examples are based on special racemization mechanisms, such as a reversible reaction[9] or rearrangement.[10, 11] Nevertheless, the scope of Viedma ripening with regard to different racemization pathways has remained rather limited. Racemization conditions for other classes of compounds do not always exist, for example quaternary stereocenters are notoriously difficult to racemize, but those that do exist,[12, 13] provide their own challenges with regard to Viedma ripening. For example, chiral alcohols and amines can be racemized through redox reactions using metalorganic catalysts such as iridium and ruthenium complexes.[14, 15] No examples of Viedma ripening using such catalysts have, however, been reported

in literature, which is likely due to the limited lifespan of such complexes, caused by their oxygen (or water) sensitivity. In addition, the racemization rate using such metalorganic catalysts is typically too slow at room temperature, implying that high temperatures are required to achieve adequate racemization.[16] This again can significantly reduce the lifetime of the catalyst. Another versatile direction is to make use of enzyme-based racemization catalysts.[17] Several racemases are known in literature, but these too provide their own challenges. While metalorganic catalysts can be used for entire compound classes, enzymes are mostly tailored to specific molecules. In addition, they remain only active under a narrow range of conditions, mostly requiring ambient conditions and water as a solvent. The influence of severe attrition on such enzymes remains unknown, but will be most likely detrimental for enzyme activity. Although examples of such catalysts might be feasible in a small-scale experiment, scaling up of such systems could prove to be a real bottleneck. For Viedma ripening to become an actual useful technique, research should thus focus on the exploration of new racemization pathways and catalysts.

An additional problem is that many chiral drugs that would be a valuable target for Viedma ripening possess intricate structures.[18] They contain several stereocenters of which the actual active pharmaceutical ingredient (API) might not be the most stable diastereomer. Direct deracemization of such a compound using Viedma ripening is therefore not an option. A more sensible approach for such cases is to evaluate the synthetic route leading to this drug, and identify a precursor (containing a single stereocenter) that fulfills the Viedma ripening requirements. After deracemizing this precursor using Viedma ripening, subsequent stereoselective steps may eventually produce the desired enantiopure API. Such a total synthesis of an API (with several stereocenters) using Viedma ripening, has not been demonstrated yet.

Up to now, Viedma ripening has mainly remained an academic exercise. The underlying mechanism of the process has been thoroughly investigated and is now thought to be well understood. Even though the process contains distinct advantages over resolution and deracemization techniques, its demanding requirements have imposed that it is yet to be applied in any industrial process. The total costs will always be a major consideration for choosing between a resolution or deracemization process. While in many cases diastereomeric salt

formation may remain the favored approach, Viedma ripening and its variations like thermal cycling might find applications in the future, in particular for new compounds for which more classic processes have not yet been established.

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Appendix

Supplemental Information Chapter 2

Deracemization experiments:

All experiments were performed at room temperature. In a glass vial containing an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm) were added a total of 1 g enantiopure Schiff-base (either 0.8 g DL and 0.2 g D, or 0.6 g D and 0.4 g L), 5.2 g glass beads (Ø ca. 2 mm VWR international) and 10 mL acetonitrile. The vial was closed and the resulting suspension was stirred at 700 rpm for the indicated time to ensure homogenization. After the homogenization time, 100 µL DBU was added to start the racemization process. For sampling, 0.3 mL of the suspension was taken using a syringe. The Schiff base was filtered off on a P4 glass filter and subsequently washed with 0.6 mL diisopropyl ether and air dried. The *ee* of the samples was determined using chiral HPLC (Chirobiotic T column, eluent ethanol, flow 1 mL min^{-1}, retention times: L-**1** 4.3 min, D-**1** 5.5 min, L-**2** 4.4 min, D-**2** 5.4 min).

We observed that compound **2** suffers from degradation after addition of the base (likely due to cyclization), resulting in a decrease of solid phase yield over time. No such decrease, nor side product formation was observed for compound **1**.

Crystallization of the metastable compounds:

We found that compounds **1** and **2** first crystallize from a racemic solution as a racemic compound which, upon grinding, converts into the stable conglomerate form. The metastability of the racemic compound was supported by experiments in which small amounts of enantiopure (both enantiomers) material were added to a slurry of the racemic compound. The suspension was left standing for several weeks, during which it was occasionally briefly heated to increase the rate of Ostwald ripening. After this period, all of the racemic compound had been converted into the conglomerate compound. In addition, controlled very slow cooling of a clear saturated racemic solution in acetonitrile also yielded the conglomerate compound.

To rule out the possibility that the metastable racemic compound is in fact not a metastable conglomerate, another experiment was performed. For this, the metastable (racemic) crystals were added to a solution, saturated with the D-enantiomer. If the racemate would be a metastable conglomerate compound, only the L-crystals would dissolve, leaving the D-crystals unaffected. If the racemate would be a racemic compound, complete dissolution would have been followed by crystallization of conglomerate D crystals. We observed (using XRPD) that after a few hours, the remaining crystals were indeed of the stable conglomerate form, indicating we were dealing with a metastable racemic compound. As a control experiment, the racemic crystals were added to solvent, containing no dissolved enantiomers. Even after a full day, the crystals remained of the metastable racemic form.

Relation between homogenization time and deracemization speed:

As mentioned earlier, the deracemization rate of compounds 1 and 2 greatly depends on the used homogenization time. We carried out a series of experiments for which a varying homogenization period was followed by two hours of (de)racemization. The increase in enantiomeric excess (*ee*) after these two hours is depicted in Figure S2.1 for compounds **1** and **2**. For compound **2**, an

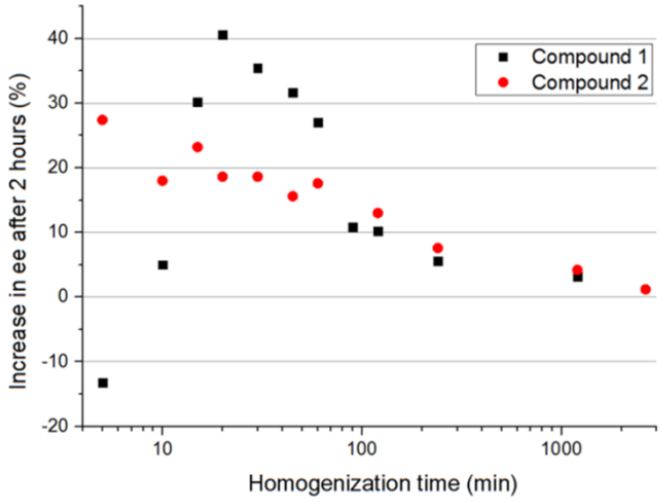

Figure S2.1: After two hours of racemization, the *ee* of the solid phase has increased, depending on the applied homogenization time. All experiments were started from a mixture of D + DL crystals as described in the experimental.

almost logarithmic relationship between homogenization time and increase in *ee* seems to exist. In contrast, for compound **1**, when very short homogenization times were used, the deracemization rate decreased and even solid phase racemization occurred.

To better understand this phenomenon, both the solid and solution phase composition were closely followed over time during the homogenization time (Figure S2.2). Early in the experiment (up to a 10 minute homogenization time), the solution was undersaturated resulting in the dissolution of both D- and DL-

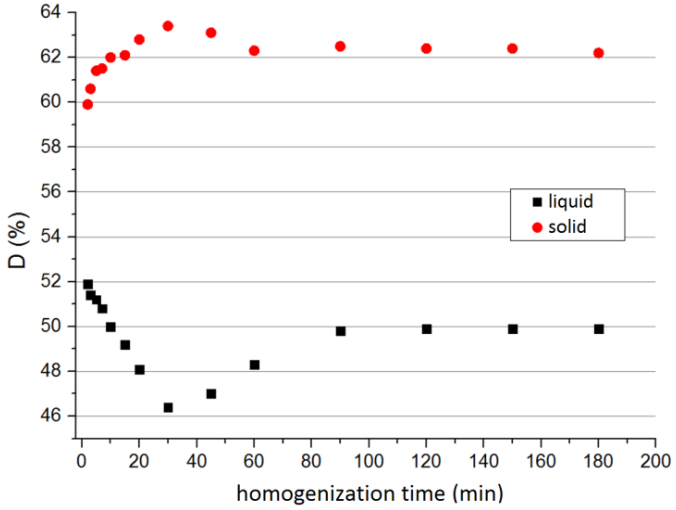

Figure S2.2: Percentage D-enantiomer in the solid (red) and liquid (black) phase during the homogenization of a D +DL mixture of compound 1.

crystals. This dissolution results in a solution enriched in the D-enantiomer. Addition of the racemization catalyst at this point, would result in the net conversion of the D- into the L-enantiomer, decreasing the amount of D-enantiomer (so net racemization, see Figure S2.2). When waiting longer, the higher solubility of the racemic compound as compared to the conglomerate will become important. The racemic compound will dissolve and will reach the point at which it is saturated in both D and L. The already present D-seed crystals will grow, whereas no L-seed crystals are present. The dissolution will lead to a solution supersaturated in L, while the solid phase will be even more enriched in D. If racemization is initiated at this point (between 10 and 30 min) the excess of L-enantiomer in solution will be converted into the D-enantiomer, resulting in an increased deracemization rate. For homogenization periods longer than 30 min,

the solution will have reached the point at which primary nucleation of the L-enantiomer starts taking place. The solution will thus slowly return to a racemic situation, whereas the *ee* of the solids towards the D enantiomer will decrease. For this regime, when DBU is added, the deracemization rate decreases with increasing homogenization time (optimum at around 30 minutes in Figure S2.2).

Synthesis of Schiff bases:

(*R*)-, (*S*)- and (*R,S*)-phenylglycine amide were prepared according to a literature procedure.[1] Prior to the condensation reaction, phenylglycine amide was recrystallized from methanol for both the enantiopure compound and racemates. In a typical experiment, the aldehyde (0.37 mmol, 1.02 equiv) was added to a stirred solution of phenylglycine amide (55 g, 0.36 mol) in 300 mL water and 150 mL methanol over a period of one hour, during which crystallization spontaneously started. The product was filtered off and washed with water (100 mL) and diisopropyl ether (100 mL). The resulting crystals were dried under reduced pressure and their purity was confirmed by NMR. In addition, XRPD diffractograms of all products were recorded.

Compound **1**:[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.14 (dt, 1H), 7.47-7.51 (m, 2H), 7.28-7.42 (m, 6H), 6.95 (br, 1H), 5.96 (br, 1H), 5.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled): δ 173.6 (s), 160.2 (s), 139.0 (s), 135.8 (s), 132.4 (s), 132.3 (s), 130.1 (s), 128.8 (s), 128.4 (s), 128.1 (s), 127.2 (s), 127.0 (s), 77.4 (s).

Compound **2**: [2]

^{1}H NMR (400 MHz, CD_3OD): δ 8.65 (s, 1H), 8.16 (dt, 1H), 7.45-7.52 (m, 3H), 7.32-7.38 (m, 2H), 7.29 (dt, 1H), 7.24 (t, 1H), 7.14 (ddd, 1H), 5.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled): δ 173.7 (s), 162.5 (d, J_{F-C} = 253.9 Hz), 156.9 (d, J_{F-C} = 4.8 Hz), 139.0 (s), 133.2 (J_{F-C} = 8.8 Hz), 128.8 (s), 128.1 (s), 127.8 (d, J_{F-C} = 2.6 Hz), 127.2 (s), 124.4 (d, J_{F-C} = 3.6 Hz), 123.1 (d, J_{F-C} = 9.2 Hz), 116.1 (d, J_{F-C} = 21.0 Hz), 77.4 (s).

XRPD diffractograms:

All diffractograms were recorded using a Bruker D8 Advance Spectrometer using a VANTEX detector. Data was recorded using reflection mode with monochromatic Cu-Kα_1 radiation.

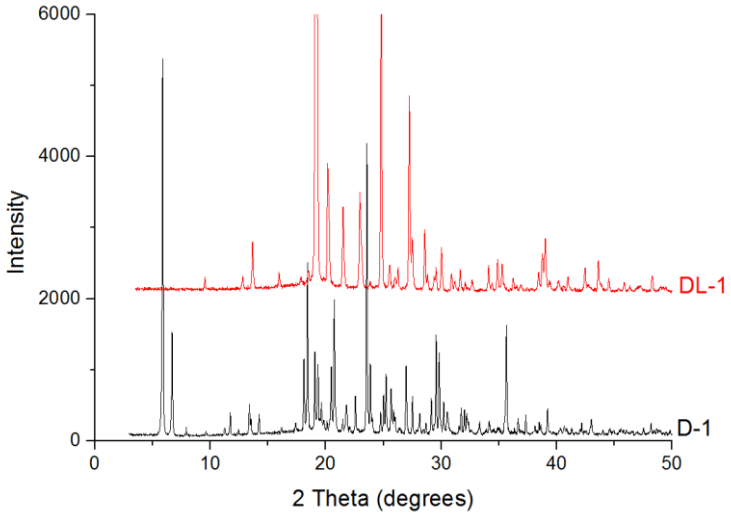

Figure S2.3: XRPD diffractogram of racemic and enantiopure (D-enantiomer) powders of compounds 1. The different diffractograms of the racemic and enantiopure compound indicate that both compounds do not crystallize as a conglomerate compound.

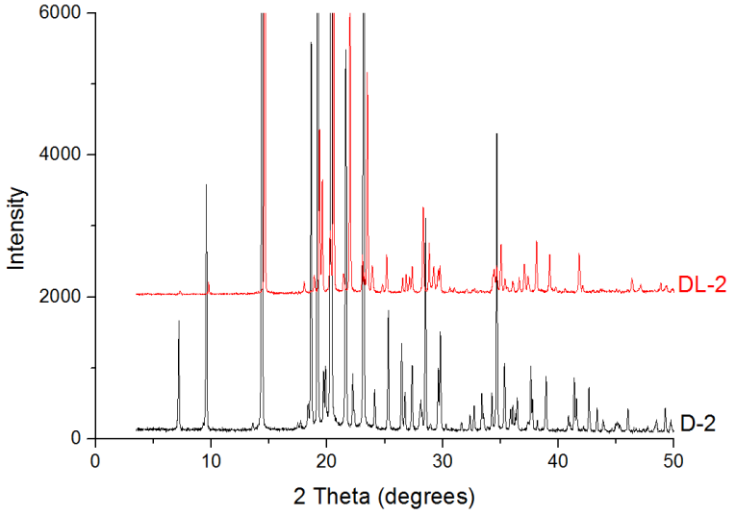

Figure S2.4: XRPD diffractogram of racemic and enantiopure (D-enantiomer) powders of compounds 1. The different diffractograms of the racemic and enantiopure compound indicate that both compounds do not crystallize as a conglomerate compound.

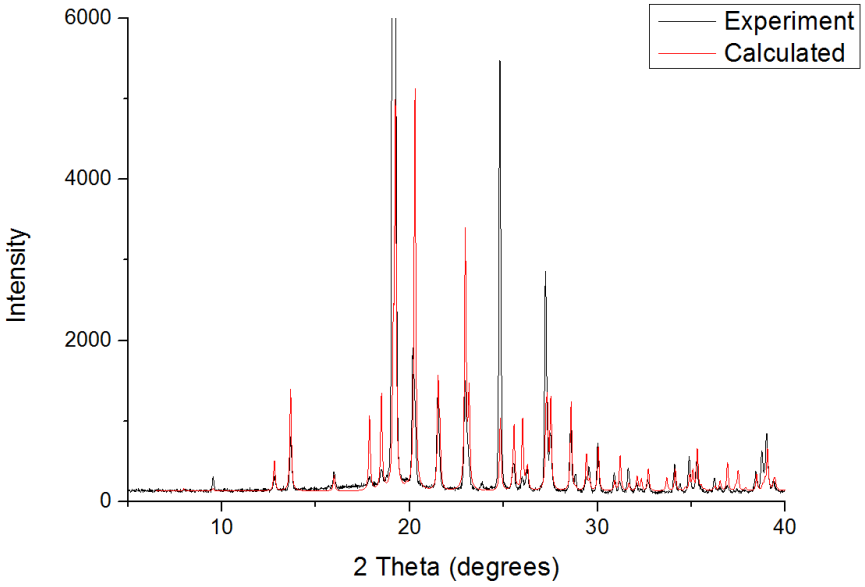

Figure S2.5: Recorded XRPD diffractogram (black) of racemic 1 as compared to the pattern calculated from the crystal structure determined by Leyssens et al.[3]

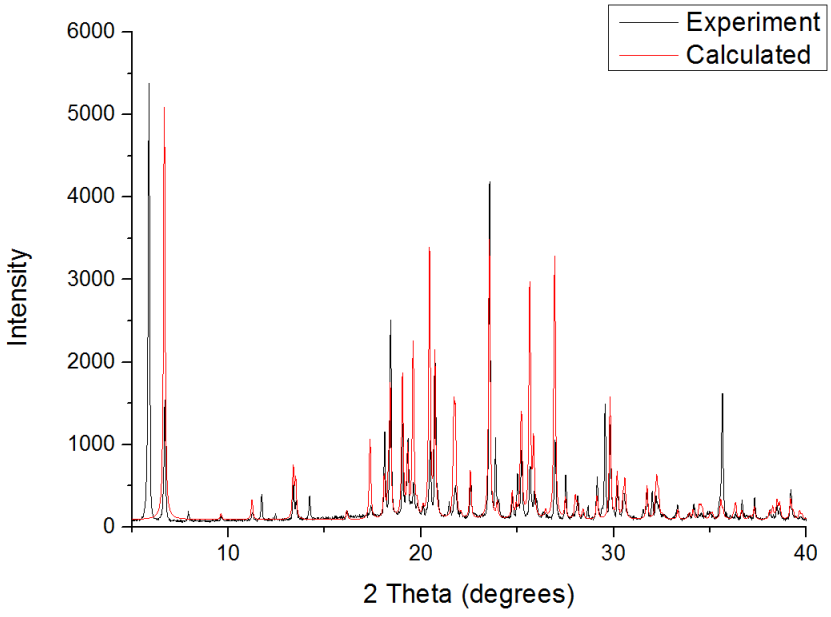

Figure S2.6: Recorded XRPD diffractogram (black) of enantiopure 1 as compared to the pattern calculated from the crystal structure determined by Leyssens et al.[3]

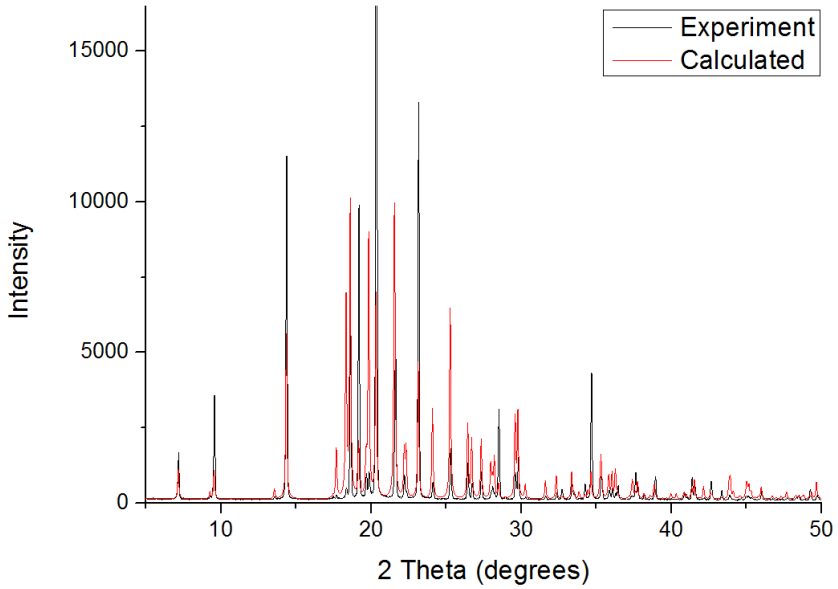

Figure S2.7: Recorded XRPD diffractogram (black) of enantiopure 2 as compared to the pattern calculated from the crystal structure determined by Leyssens et al.[3]

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Supplemental Information Chapter 3

Library synthesis:

A total of 24 chiral allylic sulfoxides were synthesized (Figure S3.1). Attempts to grow crystals of these compounds were successful for 14 of them, whereas for 9 oils were obtained and 1 was obtained as a solid that could not be successfully recrystallized.

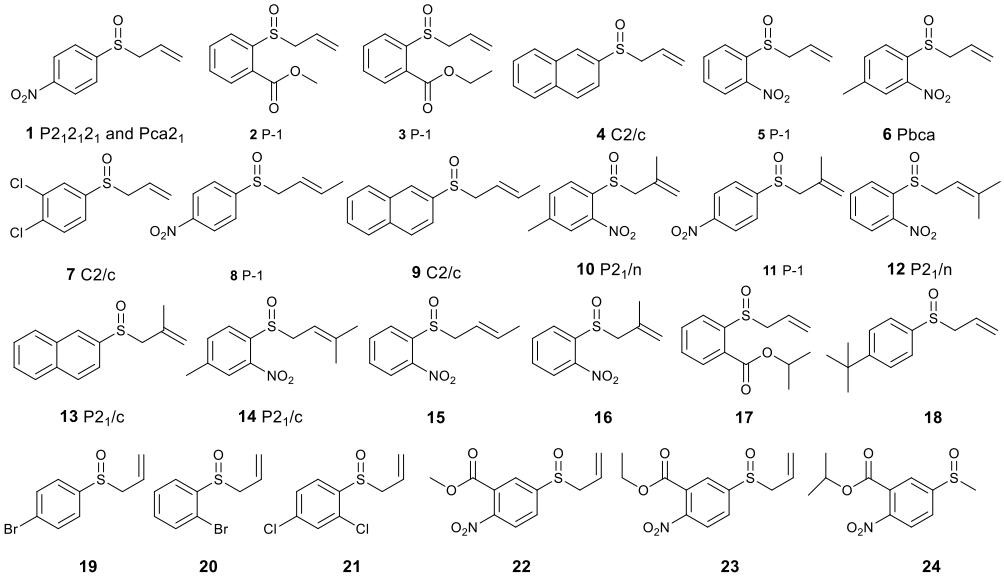


Figure S3.1: Chiral sulfoxides synthesized in this study. For compounds 1-14 crystals were successfully grown and their structure elucidated. Compound 1 crystallized as a conglomerate, whereas for all other compounds racemic crystals were obtained.

General:

All commercial chemicals were purchased from Sigma-Aldrich and were used without further purification. Reactions were followed using thin layer chromatography (TLC) on silica gel-coated plates (Merck 60 F254). Detection was performed with UV-light (254 nm), and/or by charring at ~150 °C after dipping into a solution of $KMnO_4$ (1 g/100 mL) in ethanol. Melting points were analyzed with a Büchi melting point B-545. NMR spectra were recorded on a Varian 400 (400 MHz) spectrometer in $CDCl_3$ (unless otherwise reported). Chemical shifts are given in ppm with respect to tetramethylsilane (TMS) as internal standard.

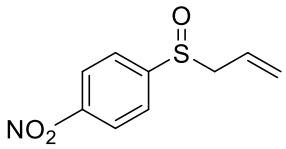
Coupling constants are reported as *J*-values in Hz. Column chromatography was carried out using Acros silica gel (43-60 µm). Optical rotations were determined with a Perkin Elmer 241 polarimeter at 589 nm. High resolution mass spectra were recorded on a JEOL AccuTOF (ESI), or a MAT900 (EI, CI, and ESI). HPLC (SFC) analysis of compound **1** was performed on a Waters Acquity UPC^2 (chiral LUX Cellulose-1 column, isocratic, 4% ^{i}PrOH/CO_2, UV detection, 286 nm).

General procedure A: one-pot sodium dithionite mediated cleavage and alkylation of disulfides:

To a solution of disulfide (1 eq.) in DMF were added: K_2CO_3 (2 eq.), allyl bromide (2.2 eq.), $Na_2S_2O_4$ (85% (w/w), 3 eq.) and H_2O (typically 8-15 drops). The mixture was stirred at ambient temperature until complete consumption of the starting material. After quenching the reaction with H_2O, the sulfide was extracted with CH_2Cl_2. The combined organic extracts were washed thoroughly with H_2O, brine, and concentrated under reduced pressure. The products were isolated in 50-70% yield and used in the next step without additional purification unless stated otherwise.

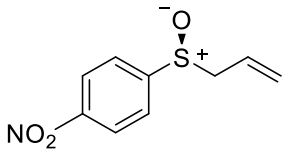
General procedure B: oxidation of sulfides by hydrogen peroxide:

Hydrogen peroxide (35% (w/w), typically 10-30 eq.) was added to a solution of the sulfide (1 eq.) in glacial AcOH. The mixture was stirred at ambient temperature until complete consumption of starting material. Next, it was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O, sat. aq. Na_2CO_3, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude products were purified by column chromatography was performed when required. The products were isolated in 60-90% yield.



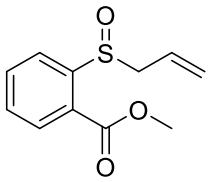
1-(allylsulfinyl)-4-nitrobenzene (**1**): [1]

The product could be obtained as either red crystals when crystallized from diethylether (racemic conglomerate, m.p. = 64°C), or as slightly yellow plates when crystallized from MeOH (racemic compound, m.p. = 51°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42-8.39 (m, 2H, Ar-*H*), 7.82-7.79 (m, 2H, Ar-*H*), 5.73-5.62 (m, 1H, -CH_2-C*H*-CH_2), 5.42-5.39 (m, 1H, -CH_2-CH-C*H*$_2$), 5.25-5.19 (m, 1H, -CH_2-CH-C*H*$_2$), 3.73-3.52 (m, 2H, -S(O)C*H*$_2$CH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.5, 125.5, 124.9, 124.1, 60.5; **GC-MS (EI):** m/z ($[M]^+$: $C_9H_9NO_3S$), calcd 211.0303; found 211.0303.



(*S*)-1-(allylsulfinyl)-4-nitrobenzene (***(S)*-1**):

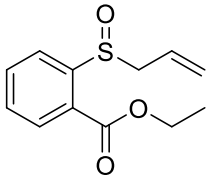
A solution of ligand (*R*)-**25** (8.00 mg, 17.8 µmol) and $VO(acac)_2$ (9.40 mg, 35.5 µmol) in CH_2Cl_2 (2 mL) was stirred for 30 min. The solution was cooled with an ice-water bath and a solution of allyl(4-nitrophenyl)sulfane (250 mg, 1.18 mmol) in CH_2Cl_2 (3 mL) was added. After 30 min, H_2O_2 (35% (w/w), 122 µL, 1.31 mmol) was added. The reaction mixture was stirred for 5 h and quenched with aq. $Na_2S_2O_3$ (10% (w/w), 5 mL). The organic layer was separated and the aqueous layer were extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over Na_2SO_4. The organic extracts were cooled as much as possible during work-up. After filtration, the solution was concentrated at 0 °C to give crude (*S*)-**1**, which was immediately purified by column chromatography (10 g silica, 10-50% EtOAc/*n*-heptane) to afford the title compound as yellow oil that solidified upon standing. For spectroscopic data, see the experimental procedure of **1**.



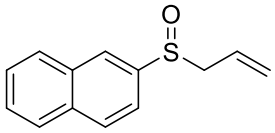
methyl 2-(allylsulfinyl)benzoate (**2**):[2]

The title compound was obtained as clear colorless oil that crystallized over time as colorless needles. (mp = 24 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.18 (m, 1H, Ar-*H*), 8.10-8.08 (m, 1H, Ar-*H*), 7.93-7.89 (m, 1H, Ar-*H*), 7.77-7.68 (m, 1H, Ar-*H*), 5.88-5.76 (m, 1H, (m, 1H, -CH_2-C*H*-CH_2), 5.37-5.34 (m, 1H, (m, 1H, -CH_2-CH-C*H*$_2$), 5.28-5.22 (m, 1H, (m, 1H, -CH_2-CH-C*H*$_2$), 3.99-3.92 (m, 4H, -C(O)OC*H*$_3$; -S(O)C*H*$_2$CH-), 3.57-3.52 (m, 1H, -S(O)C*H*$_2$CH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 147.5, 133.5,

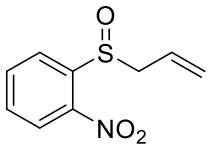
130.8, 130.2, 126.7, 126.6, 125.6, 123.2, 59.8, 52.7; **MS (ESI):** m/z ([M+Na]$^+$: $C_{11}H_{12}O_3SNa$), calcd 247.0405; found 247.0405.



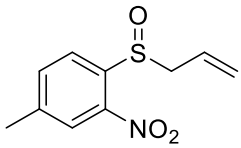
ethyl 2-(allylsulfinyl)benzoate (**3**):
Purification by column chromatography (40 g silica, 10-50% EtOAc/*n*-heptane) gave the title compound as a clear colorless oil (300 mg, 1.26 mmol) that crystallized as colorless needles over time. (mp = 29 °C) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (m, 2H, Ar-*H*), 7.81 (m, 1H, Ar-*H*), 7.58 (m, 1H, Ar-*H*), 5.81 (m, 1H, -CH_2-C*H*-CH_2), 5.39 – 5.31 (m, 1H, -CH_2-CH-C*H*$_2$), 5.24 (m, 1H, -CH_2-CH-C*H*$_2$), 4.43 (q, *J* = 7.1 Hz, 2H, -OC*H*$_2$$CH_3$), 3.88-3.52 (m, 2H, -S(O)C*H*$_2$CH-), 1.45 (t, *J* = 7.1 Hz, 3H, -OCH_2C*H*$_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 147.4, 133.4, 130.7, 130.1, 127.1, 126.6, 125.6, 123.2, 61.9, 59.8, 14.3.



2-(allylsulfinyl)naphthalene (**4**):[3]
Recrystallization from acetone/heptane afforded plate like crystals. (m.p. = 67°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H, Ar-*H*), 8.06-7.93 (m, 3H, Ar-*H*), 7.652-7.59 (m, 3H, Ar-*H*), 5.74-5.34 (m, 2H, -CH_2-CH-C*H*$_2$), 5.27-5.21 (dq, *J* = 17.0, 1.3 Hz, 1H, -CH_2-CH-C*H*$_2$), 3.73-3.58 (m, 2H, -S(O)C*H*$_2$CH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 134.5, 132.7, 129.2, 128.5, 128.0, 127.7, 127.3, 125.2, 125.1, 124.0, 120.1, 60.5.

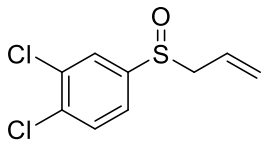


1-(allylsulfinyl)-2-nitrobenzene (**5**):[2]
After crystallization, the title compound was obtained as yellow crystals. (m.p. = 79 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45-8.42 (m, 1H, Ar-*H*), 8.16-8.13 (m, 1H, Ar-*H*), 8.08-8.04 (m, 1H, Ar-*H*), 7.88-7.81 (m, 1H, Ar-*H*),5.88-5.78 (m, 1H, (m, 1H, -CH_2-C*H*-CH_2), 5.41-5.37 (m, 1H, -CH_2-CH-C*H*$_2$), 5.29-5.22 (m, 1H, -CH_2-CH-C*H*$_2$), 4.05-3.62 (m, 2H, -S(O)C*H*$_2$CH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 135.0, 131.4, 127.6, 125.8, 125.1, 124.0, 119.2, 59.5.

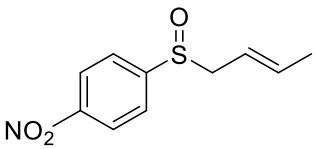


1-(allylsulfinyl)-4-methyl-2-nitrobenzene (**6**):
Recrystallization from EtOAc/*n*-heptane yielded the title compound as golden block crystals. (mp = 78 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 8.05 (m,

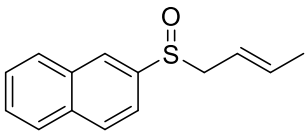
1H, Ar-*H*), 7.69 (m, 1H, Ar-*H*), 5.95-5.85 (m, 1H, -CH_2-C*H*-CH_2), 5.36-5.26 (dqt, 1H, *J* = 1.35, *J* = 17.12 Hz, -CH_2-CH-C*H*$_2$), 5.28-4.48 (m, 2H, -S(O)C*H*$_2$CH-), 2.56 (s, 3H, Ar-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 149.1, 128.1, 127.8, 126.0, 125.3, 124.6, 123.8, 60.5, 53.6.



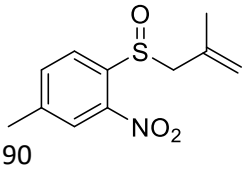
1-(allylsulfinyl)-3,4-dichlorobenzene (**7**):
Recrystallization from DCM/*n*-heptane afforded the title compound as colorless needles. (mp = 33°C); ^{1}H NMR (400 MHz, MeOD) δ 7.84-7.81 (m, 1H, Ar-*H*), 7.78-7.76 (m, 1H, Ar-*H*), 7.59-7.56 (dd, 1H, *J* = 8.4, 2.0 Hz, Ar-*H*), 5.77-5.66 (m, 1H, -CH_2-C*H*-CH_2), 5.40-5.21 (m, 2H, -CH_2-CH-C*H*$_2$), 3.84-3.79 (m, 1H, -S(O)C*H*$_2$CH-), 3.66-3.60 (m, 1H, -S(O)C*H*$_2$CH-); -); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 137.9, 135.5, 131.0, 127.7, 126.4, 125.4, 124.4, 60.6.



1-(crotylsulfinyl)-4-nitrobenzene (**8**):
The product was obtained as colourless blocks upon recrystallization from acetone/heptane. (m.p. = 81°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40-8.35 (m, 2H, Ar-*H*), 7.79-7.74 (m, 2H, Ar-*H*), 5.68-5.55 (m, 1H, -CH_2-C*H*-CH-CH_3), 5.35-5.25 (m, 1H, -CH_2-CH-C*H*-CH_3), 5.25-5.19 (m, 1H, -CH_2-CH-C*H*$_2$), 3.63-3.44 (m, 2H, -S(O)C*H*$_2$CH-), 1.73-1.70 (m, 3H, CH-CH-*CH*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ; 151.5, 134.1, 125.4, 124.1, 119.7, 66.6, 23.0.

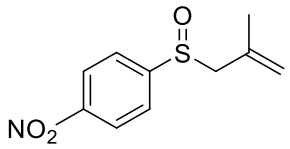


2-(crotylsulfinyl)naphthalene (**9**):
Recrystallization from acetone/heptane yielded colorless crystals (m.p. = 61°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H, Ar-*H*), 8.01-7.91 (m, 3H, Ar-*H*), 7.63-7.58 (m, 3H, Ar-*H*), 5.70-5.59 (m, 1H, -CH_2-C*H* –CH-), 5.40-5.30 (m, 1H, -CH_2-CH –C*H*CH_3), 3.64-3.51 (m, 2H, -S(O)C*H*$_2$CH-), 1.68-1.72 (m, 3H, CH-CH-C*H*$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.7, 134.5, 133.5, 132.8, 129.1, 128.5, 128.1, 127.7, 127.2, 120.3, 117.9, 60.3, 18.2.

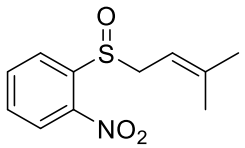


4-methyl-1-((2-methylallyl)sulfinyl)-2-nitrobenzene (**10**):
Slow evaporation from EtOAc/heptane yielded the compound as yellow needles (m.p. = 78°C); ^{1}H NMR (400

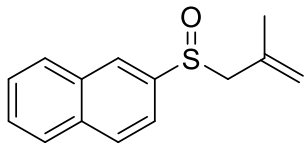
MHz, $CDCl_3$) δ 8.19 (d, 1H, *J* = 8.1 Hz, Ar-*H*), 8.15-8.12 (m, 1H, Ar-*H*), 7.78-7.74 (m, 1H, Ar-*H*), 5.14-5.12 (m, 1H, -CH_2-CCH_3-C*H*$_2$), 5.03-5.00 (m, 1H, -CH_2-CCH_3-C*H*$_2$), 3.87-3.32 (m, 2H, -S(O)C*H*$_2$CH-), 2.56 (s, 3H, Ar-C*H*$_3$), 1.96 (s, 3H, -CH_2-CC*H*$_3$-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 140.4, 136.2, 135.7, 126.8, 125.5, 119.0, 114.1, 66.4, 22.7, 21.1.



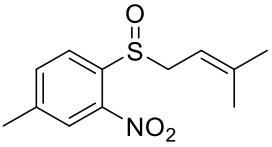
1-((2-methylallyl)sulfinyl)-4-nitrobenzene (**11**):
Despite several recrystallization attempts, no sufficient crystal data for deposition in the CSD could be obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37-8.32 (m, 2H, Ar-*H*), 7.81-7.76 (m, 2H, Ar-*H*), 5.06-5.03 (m, 1H, -CH_2-CCH_3-C*H*$_2$), 5.78-5.76 (m, 1H, -CH_2-CCH_3-C*H*$_2$), 3.56-3.44 (m, 2H, -S(O)C*H*$_2$$CCH_3$-), 1.83 (s, 3H, -$CH_2$CC*H*$_3$-$CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 138.2, 134.2, 125.4, 124.1, 119.6, 66.5, 22.9.



1-((3-methylbut-2-en-1-yl)sulfinyl)-2-nitrobenzene (**12**):
Recrystallization from acetone gave the title compound as golden needles (m.p. = 83°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33-8.28 (m, 1H, Ar-*H*), 8.25-8.21 (m, 1H, Ar-*H*), 7.96-7.90 (m, 1H, Ar-*H*), 7.73-7.67 (m, 1H, Ar-*H*), 5.33-5.25 (m, 1H, -CH_2-C*H*-C(CH_3)$_2$), 3.95-3.55 (m, 2H, -S(O)C*H*$_2$CH-), 1.75 (s, 3H CH-C(*C**H*$_3$)$_2$), 1.50 (s, 3H CH-C(*C**H*$_3$)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 143.1, 142.8, 134.9, 131.2, 127.5, 124.9, 112.1, 55.4, 126.0, 18.2.

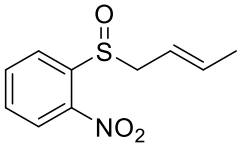


2-((2-methylallyl)sulfinyl)naphthalene (**13**):
Crystallization from CH_2Cl_2 resulted in colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H, Ar-*H*), 8.00-7.90 (m, 2H, Ar-*H*), 7.82-7.72 (m, 1H, Ar-*H*), 7.66-7.57 (m, 2H, Ar-*H*), 7.47-7.42 (m, 1H, Ar-*H*), 5.06-5.04 (m, 1H, -CH_2-CCH_3 -C*H*$_2$), 4.86-4.84 (m, 1H, -CH_2-CCH_3 -C*H*$_2$), 3.63-3.49 (m, 2H, -S(O)C*H*$_2$$CCH_3$-), 1.85-1.87 (m, 3H, CH_2C*H*$_3$$CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 134.9, 132.8, 128.9, 128.5, 128.0, 127.7, 127.2, 126.7, 126.2, 124.9, 118.8, 66.6 ,23.0.



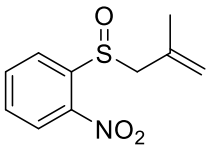
4-methyl-1-((3-methylbut-2-en-1-yl)sulfinyl)-2-nitrobenzene (**14**):

Recrystallization from acetone/heptane gave the title compound as golden needles (m.p. = 102°C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.08 (m, 2H, Ar-*H*), 7.75-7.71 (m, 1H, Ar-*H*), 5.32-5.26 (m, 1H, -CH_2-C*H*-C(CH_3)$_2$), 3.92-3.53 (m, 2H, -S(O)C*H*$_2$CH-), 2.55 (s, 3H, Ar-C*H*$_3$), 1.76 (s, 3H CH-C(*CH*$_3$)$_2$), 1.52 (s, 3H CH-C(*CH*$_3$)$_2$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 142.2, 139.8, 135.7, 127.3, 125.2, 112.2, 55.4, 25.9, 21.1, 18.2



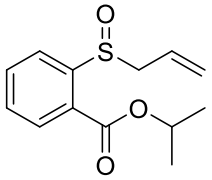
1-(crotylsulfinyl)-2-nitrobenzene (**15**):

Despite attempting various crystallization methods, no suitable crystals of **15** could be obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35-8.31 (m, 1H, Ar-*H*), 8.22-8.18 (m, 1H, Ar-*H*), 7.96-7.91 (m, 1H, Ar-*H*), 7.74-7.68 (m, 1H, Ar-*H*), 5.72-5.60 (m, 1H, -CH_2-C*H*-CH-CH_3), 5.51-5.40 (m, 1H, -CH_2-CH-C*H*-CH_3), 5.25-5.19 (m, 1H, -CH_2-CH-C*H*$_2$), 3.86-3.46 (m, 2H, -S(O)C*H*$_2$CH-), 1.72-1.69 (m, 3H, CH-CH-*CH*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 142.8, 135.9, 131.3, 127.5, 125.0, 122.8, 118.6, 59.3, 18.2



1-((2-methylallyl)sulfinyl)-2-nitrobenzene (**16**):

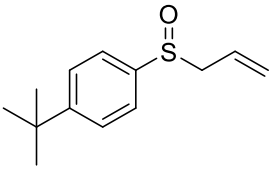
Despite various attempts to crystallize the compound, compound **16** was never obtained as a solid. ^{1}H NMR (400 MHz, $CDCl_3$ δ 8.33-8.27 (m, 1H, Ar-*H*), 7.78-7.67 (m, 1H, Ar-*H*), 7.34-7.18 (m, 1H, Ar-*H*), 6.72-6.65 (m, 1H, Ar-*H*), 5.14-5.10 (m, 1H, -CH_2-CCH_3-C*H*$_2$), 4.98-4.96 (m, 1H, -CH_2-CCH_3-C*H*$_2$), 3.94-3.76 (m, 2H, -S(O)C*H*$_2$$CCH_3$-), 1.78-1.75 (s, 3H, -$CH_2CCH_3$-$CH_2$)



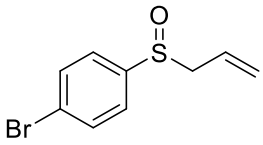
Isopropyl 2-(allylsulfinyl)benzoate (**17**):

Purification by column chromatography (30 g silica, 20-50% EtOAc/*n*-heptane) afforded the title compound as a clear colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20-8.10 (m, 2H, Ar-*H*), 7.82-7.78 (m, 1H, Ar-*H*), 7.59-7.55 (m, 1H, Ar-*H*), 5.87-5.76 (m, 1H, -CH_2-C*H*-CH_2), 5.37-5.21 (m, 3H, -CH_2-CH-C*H*$_2$; -OC*H*(CH_3)$_2$), 3.91-3.86 (m, 1H, -S(O)C*H*$_2$CH-), 3.55-3.50 (m, 1H, -S(O)C*H*$_2$CH-), 1.43 (t, *J*=6.4 Hz, 6H -OCH(C*H*$_3$)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 147.3, 133.2, 130.7, 130.1, 127.5,

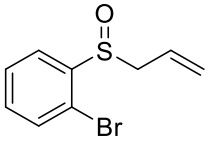
126.6, 125.6, 123.2, 69.8, 59.8, 21.9; MS (ESI): m/z ([M+Na]$^+$: $C_{13}H_{16}O_3SNa$), calcd 275.0718; found 275.0718.



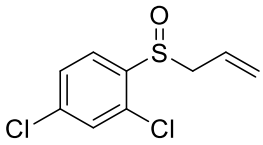
1-(allylsulfinyl)-4-(tert-butyl)benzene (**18**):
Sulfoxide **18** was obtained as a clear, colorless oil (60 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 4H, Ar-*H*), 5.72-5.61 (m, 1H, -CH_2-C*H*-CH_2), 5.35 (m, 1H, -CH_2-CH-C*H*$_2$), 5.27-5.21 (m, 1H, -CH_2-CH-C*H*$_2$), 3.59-3.49 (m, 1H, -S(O)C*H*$_2$CH-), 1.35 (s, 9H, Ar-C(C*H*$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 139.7, 126.1, 125.6, 124.2, 123.7, 61.0, 35.0; **MS (ESI):** m/z ([M+Na]$^+$: $C_{13}H_{18}OSNa$), calcd 245.0976; found 245.0976.



1-(allylsulfinyl)-4-bromobenzene (**19**):
Sulfoxide **19** was obtained as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69-7.65 (m, 2H, Ar-*H*), 7.50-746 (m, 2H, Ar-*H*), 5.70-5.59 (m, 1H, -CH_2-C*H*-CH_2), 5.39-5.35 (m, 1H, -CH_2-CH-C*H*$_2$), 5.23-5.18 (m, 1H, -CH_2-CH-C*H*$_2$), 3.61-3.47 (m, 2H, -S(O)C*H*$_2$CH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 132.3, 130.1, 126.0, 125.6, 124.8, 124.3, 60.8.

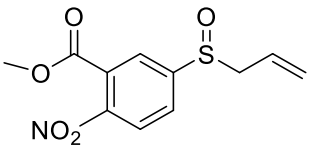


1-(allylsulfinyl)-2-bromobenzene (**20**):[4]
Sulfoxide **20** was obtained as a clear, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.81 (m, 1H, Ar-*H*), 7.60-7.52 (m, 2H, Ar-*H*), 7.41-7.37 (m, 1H, Ar-*H*), 5.80-5.70 (m, 1H, -CH_2-C*H*-CH_2), 5.39-5.36 (m, 1H, -CH_2-CH-C*H*$_2$), 5.27-5.22 (dq, *J* = 17.0, 1.3 Hz, 1H, -CH_2-CH-C*H*$_2$), 3.84-3.78 (m, 1H, -S(O)C*H*$_2$CH-) 3.63-3.76 (m, 1H, -S(O)C*H*$_2$CH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 132.8, 132.2, 128.2, 127.3, 125.1, 124.0, 118.7, 57.5.

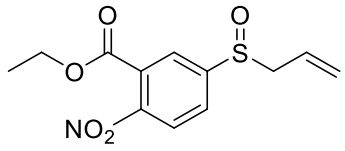


1-(allylsulfinyl)-2,4-dichlorobenzene (**21**):
Sulfoxide **21** was afforded as a clear yellow oil (1.10 g, 4.70 mmol, 83.9% over two steps).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, 1H, *J* = 0.2, *J* = 8.4 Hz, Ar-*H*), 7.49 (dd, 1H, *J* = 1.9 Hz, *J* = 8.4 Hz, Ar-*H*), 7.42 (d, 1H, *J* = 0.2 Hz, *J* = 2.0 Hz, Ar-*H*), 5.75-5.65 (m, 1H, -CH_2-C*H*-CH_2), 5.36 (dq, 1H, *J* = 0.7 Hz, *J* = 10.1 Hz, -CH_2-CH-C*H*$_2$), 5.23-5.19 (dqt, 1H, *J* = 1.2 Hz, *J* = 17.0 Hz, -CH_2-CH-C*H*$_2$), 3.80-3.75 (m, 1H, -S(O)C*H*$_2$CH-),

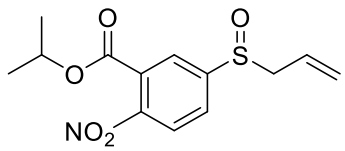
3.59-3.53 (m, 1H, -S(O)C$\underline{H_2}$CH-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 137.6, 130.6, 129.5, 128.1, 128.1, 124.7, 124.3, 57.1.



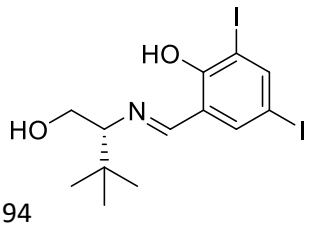
methyl 5-(allylsulfinyl)-2-nitrobenzoate (**22**):
Purification by column chromatography (50-90% EtOAc/*n*-heptane) gave sulfoxide **22** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 1H, Ar-$\underline{H}$), 7.96 (d, *J* = 1.9 Hz, 1H, Ar-$\underline{H}$), 5.72-5.61 (m, 1H, -CH_2-C$\underline{H}$-CH_2), 5.43-5.40 (m, 1H, -CH_2-CH-C$\underline{H_2}$), 5.26-5.20 (m, 1H, -CH_2-CH-C$\underline{H_2}$), 3.96 (s, 3H, Ar-C(O)OC$\underline{H_3}$), 3.73-3.68 (m, 1H, -S(O)C$\underline{H_2}$CH-), 3.58-3.52 (m, 1H, -S(O)C$\underline{H_2}$CH-).



ethyl 5-(allylsulfinyl)-2-nitrobenzoate (**23**):
Purification by column chromatography (50% EtOAc/*n*-heptane) gave sulfoxide **23** as a dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.05 (m, 1H, Ar-$\underline{H}$), 7.97-96 (m, 1H, Ar-$\underline{H}$), 7.88 (dd, *J* = 8.4, 1.9 Hz, 1H, Ar-$\underline{H}$), 5.74-5.64 (m, 1H, -CH_2-C$\underline{H}$-CH_2), 5.46-5.43 (m, 1H, -CH_2-CH-C$\underline{H_2}$), 5.29-5.23 (m, 1H, -CH_2-CH-C$\underline{H_2}$), 4.45 (q, *J* = 7.1 Hz, 2H, -C(O)C$\underline{H_2}$$CH_3$), 3.74-3.69 (m, 1H, -S(O)C$\underline{H_2}$CH-), 3.59-3.54 (m, 1H, -S(O)C$\underline{H_2}$CH-), 1.40 (t, *J* = 7.1 Hz, 3H, -C(O)CH_2C$\underline{H_3}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 149.6, 149.0, 128.4, 127.7, 125.9, 125.3, 124.5, 123.9, 63.1, 60.5, 13.8.



isopropyl 5-(allylsulfinyl)-2-nitrobenzoate (**24**):
Purification by column chromatography (25 g silica, 20-50% EtOAc/*n*-heptane) gave sulfoxide **24** an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06-8.04 (m, 1H, Ar-$\underline{H}$), 7.95-7.94 (m, 1H, Ar-$\underline{H}$), 7.87-7.85 (m, 1H, Ar-$\underline{H}$), 5.75-5.62 (m, 1H, -CH_2-C$\underline{H}$-CH_2), 5.46-5.43 (m, 1H, -CH_2-CH-C$\underline{H_2}$), 5.35-5.24 (m, 2H, -CH_2-CH-C$\underline{H_2}$; -OC$\underline{H}$(CH_3)$_2$), 3.74-3.68 (m, 1H, -S(O)C$\underline{H_2}$CH-), 3.60-3.54 (m, 1H, -S(O)C$\underline{H_2}$CH-), 1.39 (dd, *J* = 6.3, 0.5 Hz, 6H, -OCH(C$\underline{H_3}$)$_2$).



(*R*,*E*)-2-(((1-hydroxy-3,3-dimethylbutan-2-yl)imino)methyl)-4,6-diiodophenol (**(*R*)-25**):
A mixture of 2-hydroxy-3,5-diiodobenzaldehyde (1.00 g, 2.67 mmol) and (*R*)-2-amino-3,3-dimethylbutan-1-ol

(313 mg, 2.67 mmol) in MeOH (20 mL) was stirred for 2 h. The yellow solution was concentrated under reduced pressure to obtain the title compound as a bright yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.88 (bs, 1H, Ar-O*H*), 8.14 (bs, 1H, -ArC*H*NC-), (d, *J*=2.1 Hz, 1H, Ar-*H*), 7.56 (d, *J*=2.2 Hz, 1H, Ar-*H*), 4.03-4.00 (m, 1H), 3.73 (t, *J* = 10.4 Hz, 1H), 3.08 (dd, *J* = 9.5, 2.8 Hz, 1H), 1.90 (bs, 1H), 1.02 (s, 9H, -CHC(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 164.5, 149.8, 141.0, 117.5, 91.8, 78.6, 76.5, 61.9, 33.0, 26.9.

Racemization kinetics of compound 1:

Room temperature racemization:
The racemization constant (*k,* in h^{-1}) of **1** in several solvents was determined using chiral SFC (for Et_2O and MeOH) or polarimetry (for Et_2O and toluene). Each racemization constant was determined in duplo using *S*-**1** (96% *ee*) obtained from Viedma ripening experiments (figures S3.2-S3.5).

Polarimetry:
A solution of 2 mg/mL (*S*)-**1** in the appropriate solvent was transferred to the polarimeter (Perkin Elmer Polarimeter, model 241 MC). The cell was stored outside of the polarimeter in between measurements to prevent heating of the sample by the Na-lamp.

SFC:
Solutions of 2 mg/mL (*S*)-**1** were prepared in the appropriate solvent. The temperatures of the column and sample storage compartment were set to 20°C to ensure a constant temperature. SFC analysis was performed on a Waters Acquity UPC^2 (chiral LUX Cellulose-1 column, isocratic, 4% ^{i}PrOH/CO_2, UV detection, 286 nm).

Racemization in Et_2O at 35°C:
A solution of *S*-**1** (100 mg)in Et_2O (10 mL) was heated to reflux. Sampling was done by taking 100 µl solution and immediately adding this to cold methanol to halt racemization. Samples were analyzed directly using SFC as described below.

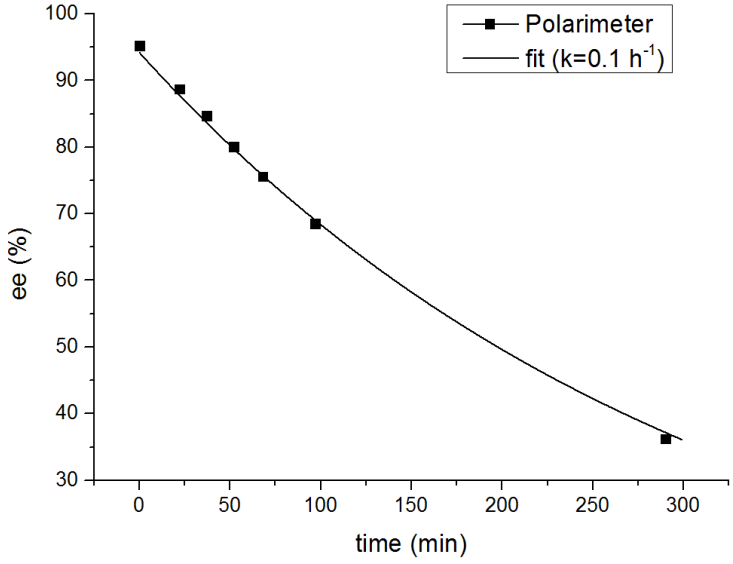


Figure S3.2: The racemization of (*S*)-1 in toluene at room temperature.

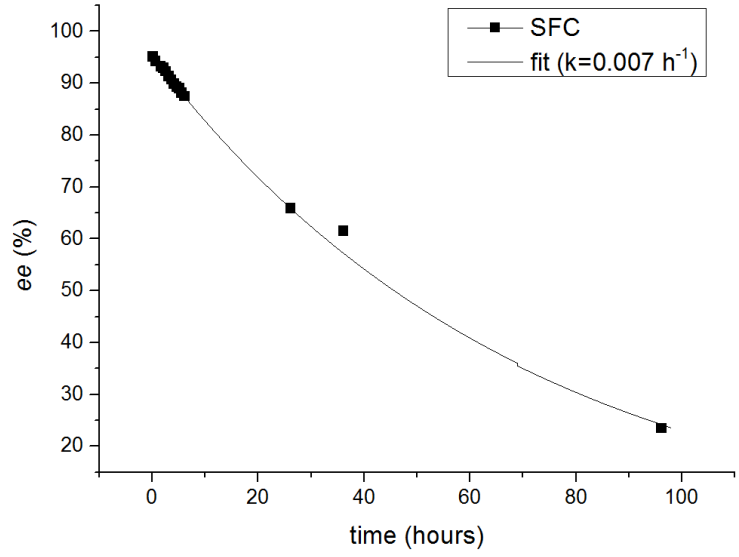


Figure S3.3: Racemization of (*S*)-1 in methanol at room temperature

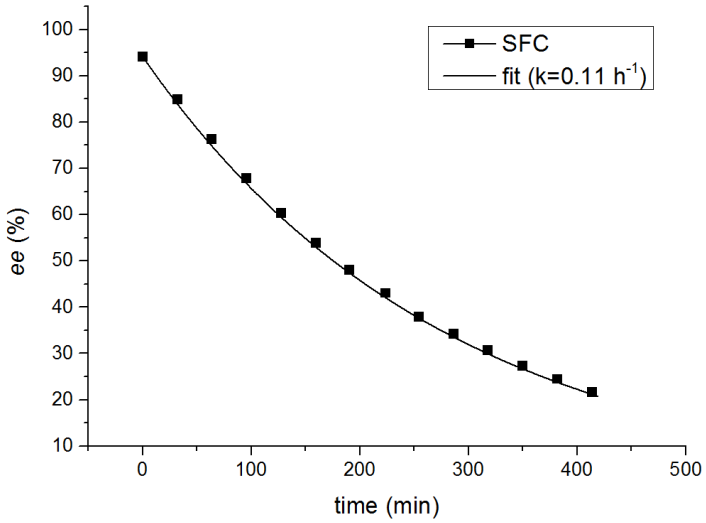


Figure S3.4: Racemization of of (*S*)-1 in refluxing diethylether.

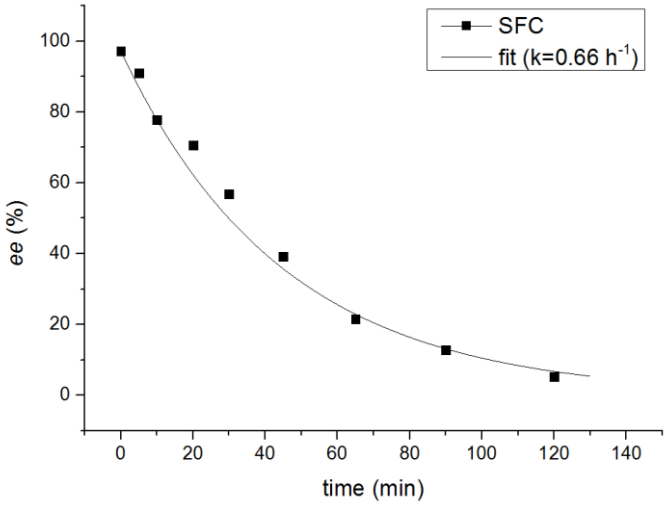


Figure S3.5: Racemization of of (*S*)-1 in refluxing diethylether.

Table S1: Racemization constants and racemization half-lives of compound **1** in various solvents:

Solvent	Racemization constant (h^{-1})	$t_{1/2}$ (h)
Methanol (RT)	0.007	99
Toluene (RT)	0.10	6.9
Diethylether (RT)	0.11	6.3
Diethylether (Reflux, 35°C)	0.66	1.1

XRPD diffractograms:

All diffractograms were recorded using a Bruker D8 Advance Spectrometer using a VANTEX detector. Data was recorded using reflection mode with monochromatic Cu-Kα_1 radiation.

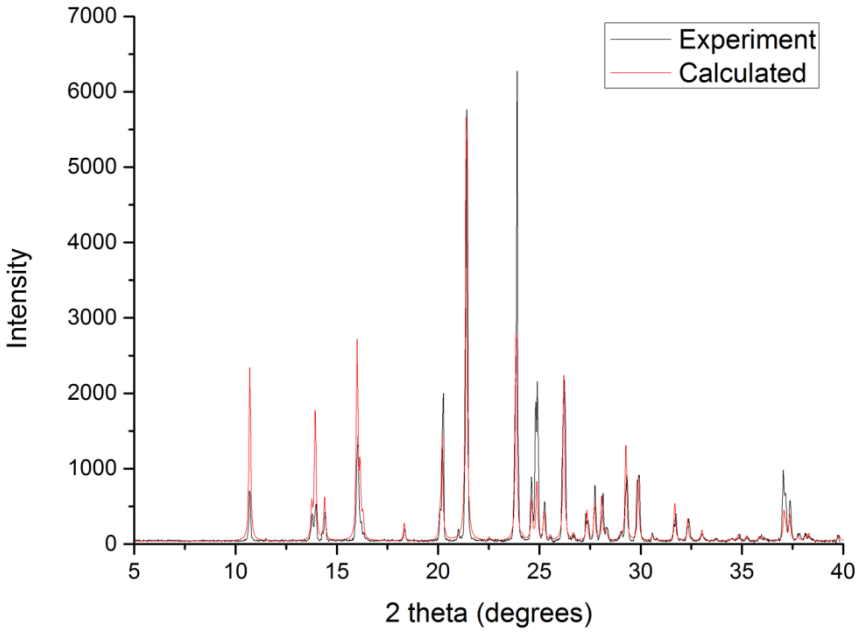


Figure S3.6: Recorded XRPD diffractogram (black) of conglomerate 1 ($P2_12_12_1$) as compared to the pattern calculated from the temperature corrected crystal structure (red).

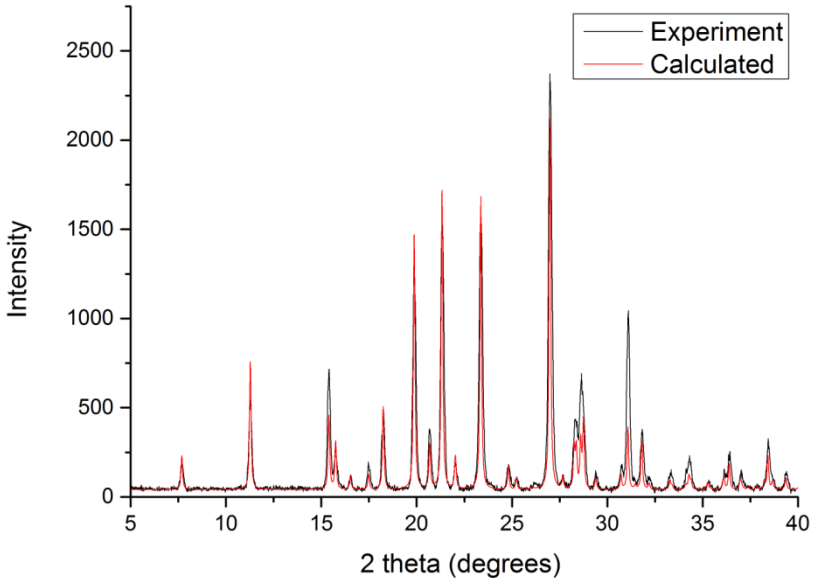
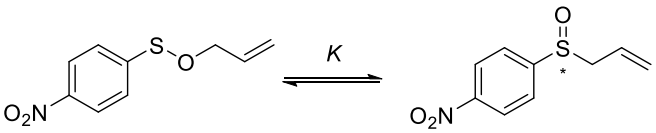


Figure S3.7: Recorded XRPD diffractogram (black) of racemic 1 ($Pca2_1$) as compared to the pattern calculated from the temperature corrected crystal structure (red).

Temperature dependent NMR studies:

The thermal equilibrium between the sulfoxide and sulfonate ester of compound **1** in toluene was studied using temperature dependent NMR measurements:

$$K_{eq} = \frac{[Sulfoxide]}{[Sulfenate]}$$



Sulfenate - **1** Sulfoxide - **1**

Whereas some protons of the sulfonate ester are hidden underneath the dominant peaks of the sulfoxide, three different protons could be clearly distinguished (Figure S7). The CH_2 protons of both the sulfoxide and sulfonate ester were used to determine the equilibrium constant (*K*). The measurements clearly indicated a shift towards the sulfonate ester at elevated temperatures (Figure S3.9). Using the Van 't Hoff plot, the thermodynamic data of the equilibrium between sulfoxide and sulfonate could be determined (Figure S10).

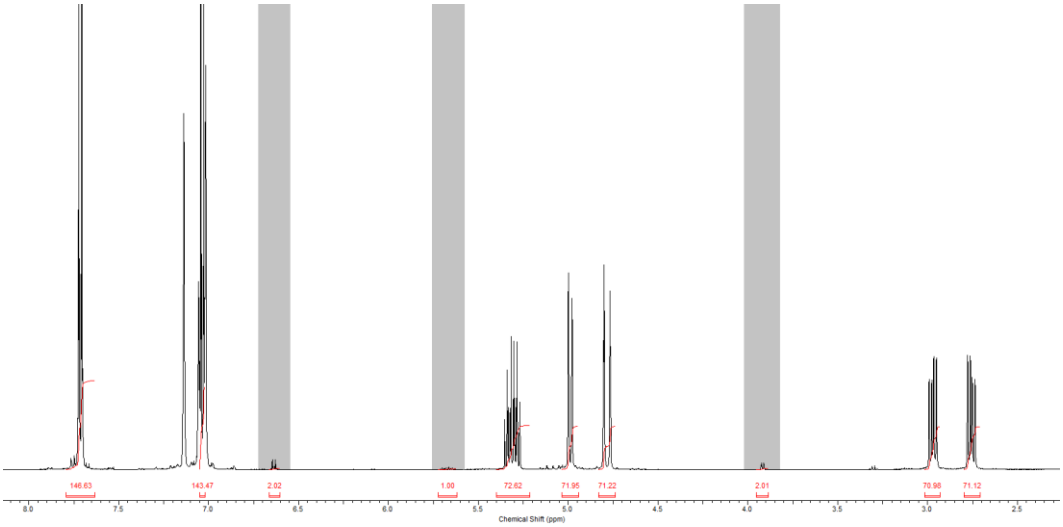


Figure S3.8: ^{1}H NMR spectrum of 1 at 25 °C. ^{1}H NMR (500 MHz,Tol-d8) δ 7.67-7.66 (m, 2H, Ar-*H*), 7.02-6.98 (m, 2H, Ar-*H*), 5.31-5.23 (m, 1H, -CH_2-C*H*-CH_2), 4.96-4.94 (m, 1H, -CH_2-CH-C*H*$_2$), 4.77-4.72 (m, 1H, -CH_2-CH-C*H*$_2$), 2.95-2.91 (m, 1H, -S(O)C*H*$_2$CH-), 2.74-2.70 (m, 1H, -S(O)C*H*$_2$CH-). Highlighted protons of sulfonate ester: δ 6.61-6.59 (o-Ar-*H*), 5.67-5.59 (-OCH_2C*H*-), 3.91(-OC*H*$_2$CH-).

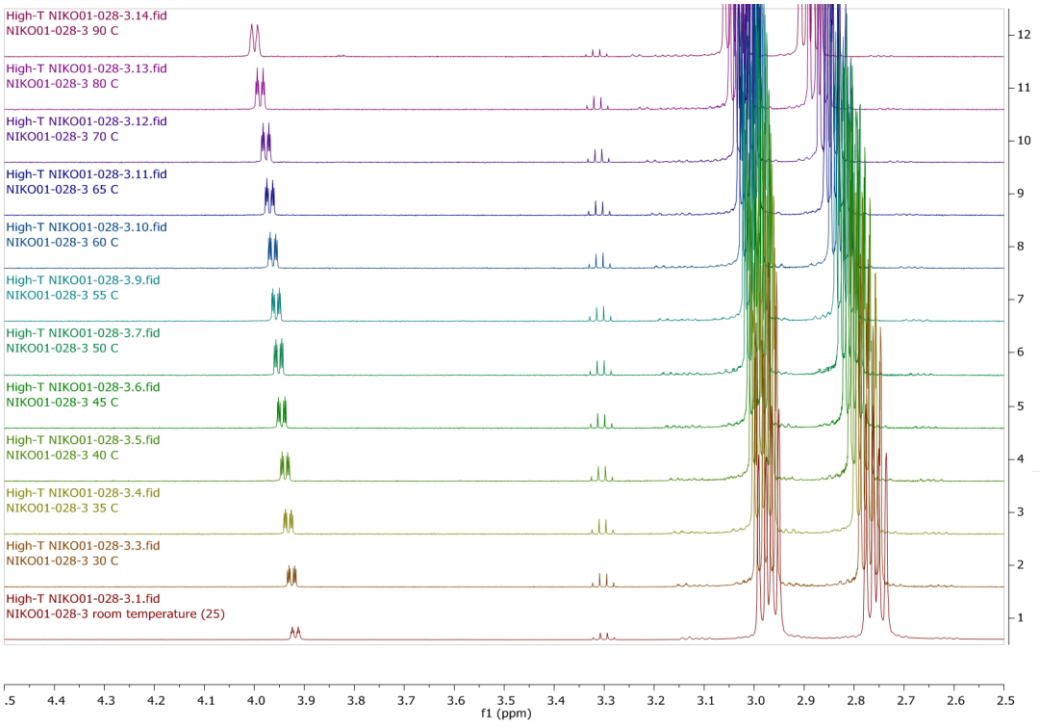


Figure S3.9: close up of the stacked ^{1}H NMR spectra of **1** at various temperatures in the 4.5-2.5 ppm region, showing the increase in intensity of the signal δ 3.91 (-OC*H*$_2$CH-) of the sulfonate ester as the temperature is raised.

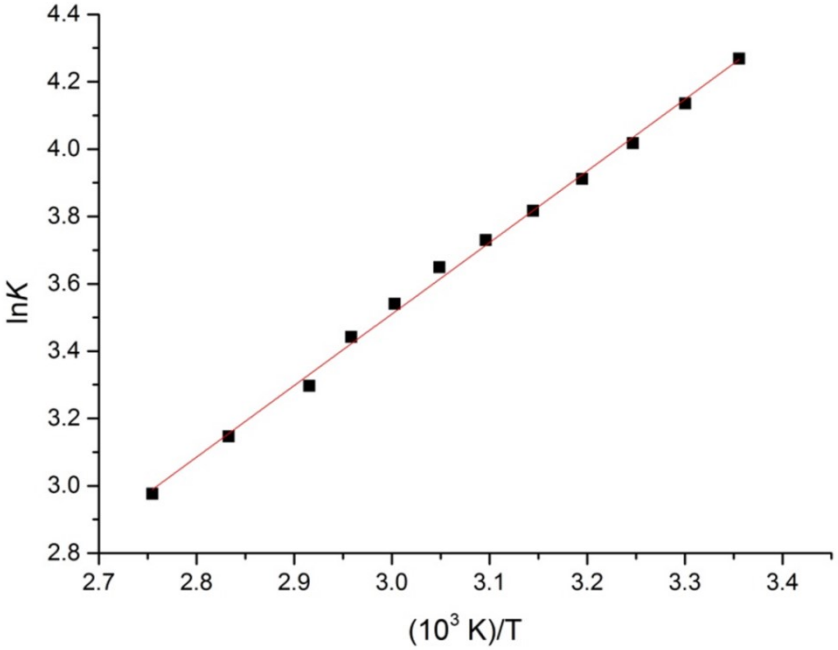
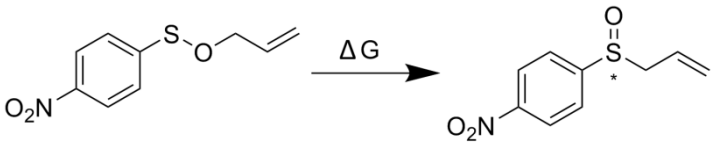


Figure S3.10: Van 't Hoff plot of the equilibrium between the sulfonate ester and corresponding sulfoxide 1

Table S3.2: Thermodynamic data of the equilibrium between the sulfonate and sulfoxide of **1**:

Δ_rG^Θ (kcal mol^{-1}, 298K)	Δ_rH^Θ (kcal mol^{-1})	$T\Delta_rS^\Theta$ (kcal mol^{-1}, 298K)	Δ_rS^Θ (cal mol^{-1}K^{-1})
-2.55	-4.22	-1.67	5.60



Sulfenate-**1** Sulfoxide-**1**

In order to determine the energy barrier of racemization, temperature dependent selective Exchange Spectroscopy (EXSY) experiments were performed. In these experiments, the NMR CH_2 peak of the sulfonate of **1** was excited and conversion into the sulfoxide was observed after several mixing (waiting) times (figure S3.11). The rate constant of this process was determined at various temperatures (figure S3.12), from which the Eyring plot could be constructed (figure S3.13). Using the Eyring plot, the entropy, enthalpy and Gibbs free energy of the transition state could be determined (Table S3.3 and S3.4).

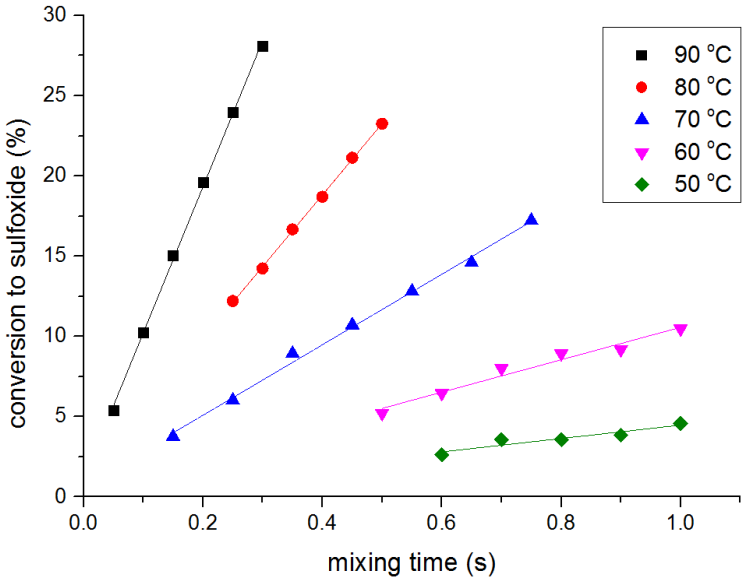


Figure S3.11: Conversion of the sulfenate of **1** into the sulfoxide determined using temperature dependent selective Exchange Spectroscopy Experiments.

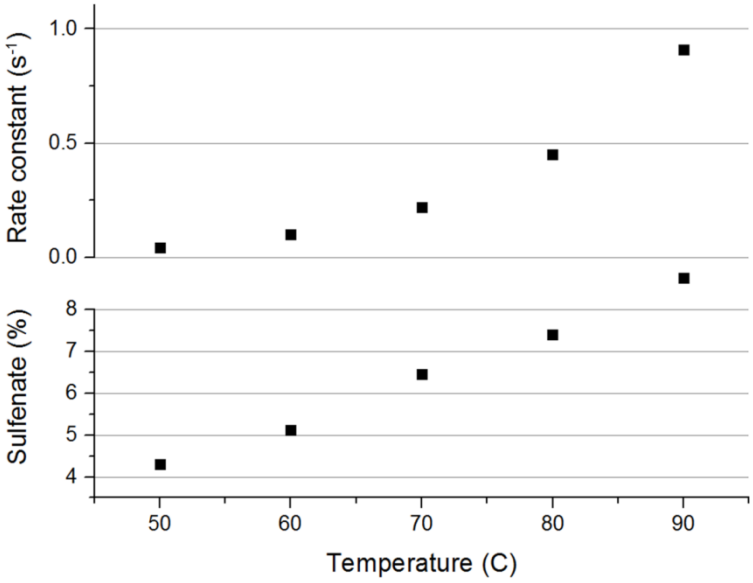


Figure S3.12: Presence of the sulfenate of compound **1** as percentage of the amount of sulfoxide and the rate constant of the conversion of the sulfonate into the sulfoxide.

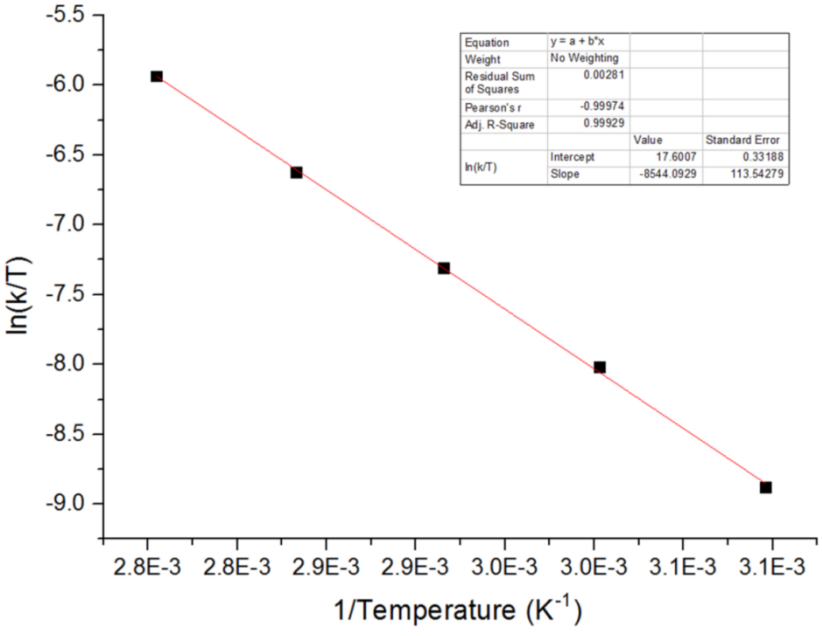
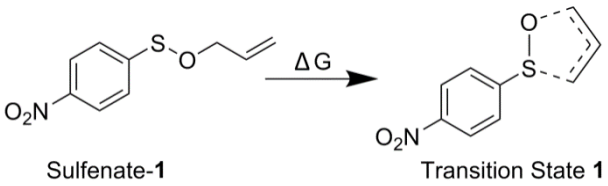


Figure S3.13: Eyring plot of the rate constant of the conversion of the sulfonate into sulfoxide **1**.

Table S3.3: Thermodynamic data of the transition state between sulfonate and sulfoxide **1**:

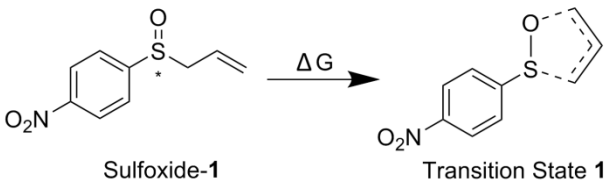
$\Delta_rG^{\ominus}$ (kcal mol^{-1}, 298K)	$\Delta_rH^{\ominus}$ (kcal mol^{-1})	$T\Delta_rS^{\ominus}$ (kcal mol^{-1}, 298K)	$\Delta_rS^{\ominus}$ (cal mol^{-1}K^{-1})
20.7	17.0	-3.65	-12.3



Sulfenate-**1** Transition State **1**

Table S3.4: Thermodynamic data of the racemization of sulfoxide and sulfonate of **1**:

$\Delta_rG^{\ominus}$ (kcal mol^{-1}, 298K)	$\Delta_rH^{\ominus}$ (kcal mol^{-1})	$T\Delta_rS^{\ominus}$ (kcal mol^{-1}, 298K)	$\Delta_rS^{\ominus}$ (cal mol^{-1}K^{-1})
23.2	21.2	-1.98	-6.6



Sulfoxide-**1** Transition State **1**

Deracemization Experiments:

Viedma ripening experiments in toluene at room temperature:
For a typical experiment, 6 mL toluene was added to 1.6 g of the racemic conglomerate **1** and 5.4 g glass beads in a glass vial. After a period of one month grinding at 600 rpm, an *ee* of 12% was observed.

Viedma ripening experiments of conglomerate **1** in refluxing diethylether:
For a typical experiment, 8 mL Et_2O was added to 1.5 g of the racemic conglomerate **1** and 5.4 g glass beads in a 10 mL round-bottom flask. The flask was attached to a reflux condenser, after which grinding was started at 600 rpm under reflux conditions. After one hour, a total of 30 mg (*S*)-**1** (>98% *ee*) was added. Additional Et_2O was occasionally added to compensate for evaporation of the solvent.

Viedma ripening experiments of the racemic compound in refluxing diethylether:
For a typical experiment, 8 mL Et_2O was added to 1.5 g of the racemic compound **1** and 5.4 g glass beads in a 10 mL round-bottom flask. The flask was attached to a reflux condenser, after which grinding was started at 600 rpm under reflux conditions. After one hour, a total of 30 mg (*S*)-**1** (>98% *ee*) was added. Additional Et_2O was occasionally added to compensate for evaporation of the solvent. During the first day of grinding, the rate of deracemization could be significantly increased (Figure S3.14) compared to standard Viedma ripening, in agreement with earlier work.[5] However, after this first day, XRPD measurements indicated all the racemic compound had been converted into the conglomerate. From this point, standard Viedma ripening was required to complete deracemization. The deracemization rate was therefore no longer accelerated.

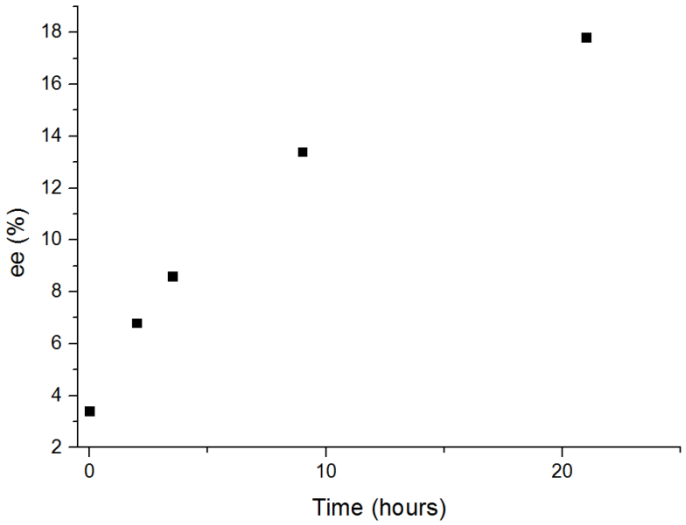


Figure S3.14: Deracemization curve of compound 1 during the first day, starting from the racemic compound seeded with some enantiopure crystals.

Viedma ripening experiments in toluene at 50°C:
For a typical experiment, 8 mL toluene was added to 3 g of the racemic conglomerate **1** and 5.4 g glass beads in a 10 mL round-bottom flask. The flask was attached to a reflux condenser, and the suspension grinded at 600 rpm at 50°C.

Due to the occasional melting **1**, these experiments were continued at room temperature. After a period of two months, no *ee* was observed by SFC measurements. Differential Scanning Calorimetry (DSC) measurements of the solid phase of compound **1** (figure S3.15) showed two different endotherms. The racemic conglomerate had a melting point of 64°C, but upon melting and recrystallization, an additional melting peak (51°C) was observed. We found that by crystallization from methanol/water instead of diethylether, a second, racemic,

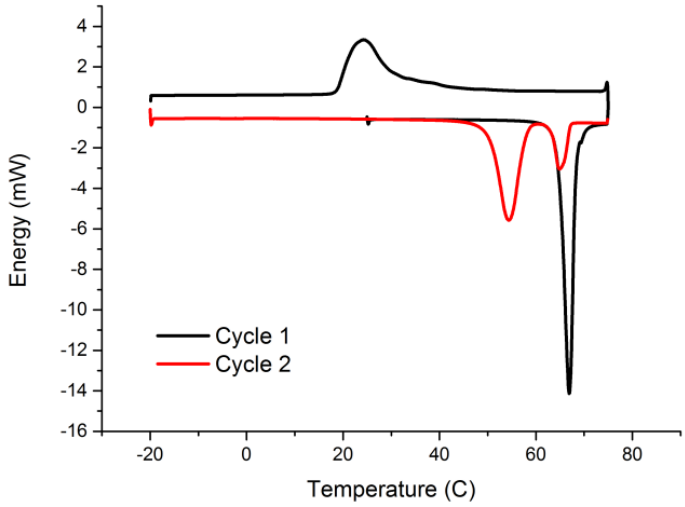


Figure S3.15: Differential Scanning Calorimetry thermogram of compound 1 showing the conversion of the conglomerate into a metastable form upon melting and recrystallization.

polymorph (spacegroup $Pca2_1$) of **1** could be obtained that corresponded to this melting peak. These initial deracemization experiments were thus unsuccessful because the conglomerate had been converted into a racemic compound upon melting.

Sampling:

0.3 mL Of the reaction mixture was taken using a 1 mL syringe without needle. The suspension was filtered on a P4 glass-sintered funnel and the filtrate was dried in air. A solution of the dried filtrate was prepared in MeOH (1 mg/mL) and analysed by SFC.

Crystal stability experiments:

Room temperature:
A suspension of **1** was prepared by adding 0.5g racemic compound and 0.5 g racemic conglomerate to 10 mL toluene. The suspension was multiple times briefly heated to increase the rate of Ostwald ripening. After a week, XRPD analysis of the solid phase showed almost exclusively racemic conglomerate **1**.

Refluxing diethylether:
A suspension of racemic **1** (800 mg) in Et_2O (8 mL) was heated to reflux, after which conglomerate **1** (200 mg) was added. The reaction mixture was stirred at 100 rpm. Conversion of the racemic into the conglomerate compound was observed by analysis of the solid phase by XRPD after 1,2,4 and 24 h (figure S3.16 and S3.17).

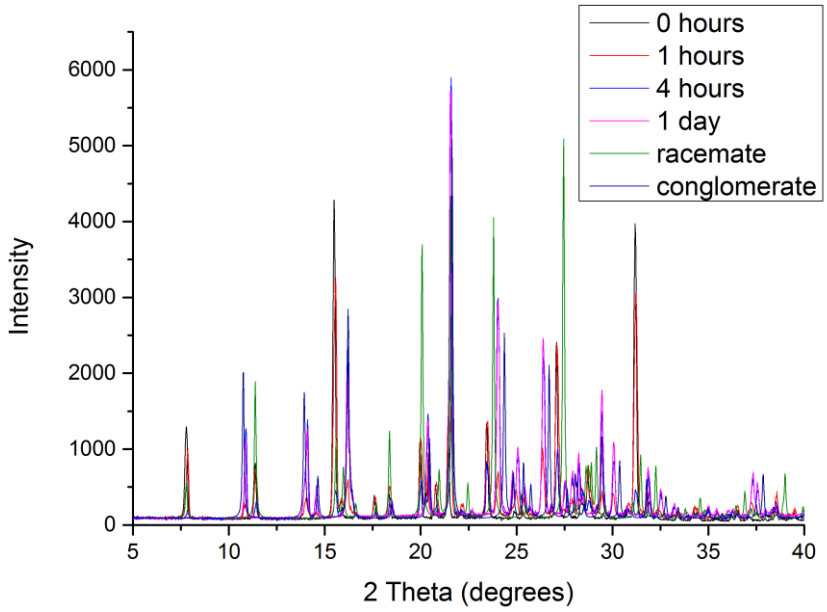


Figure S3.16: XRPD diffractogram of the conversion of rac to cong 1 under slow stirring and reflux in ether

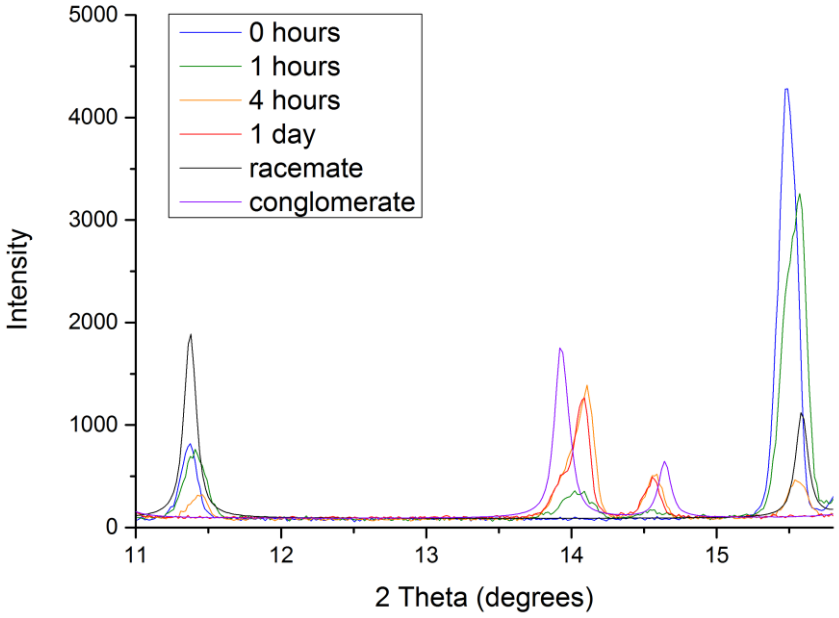
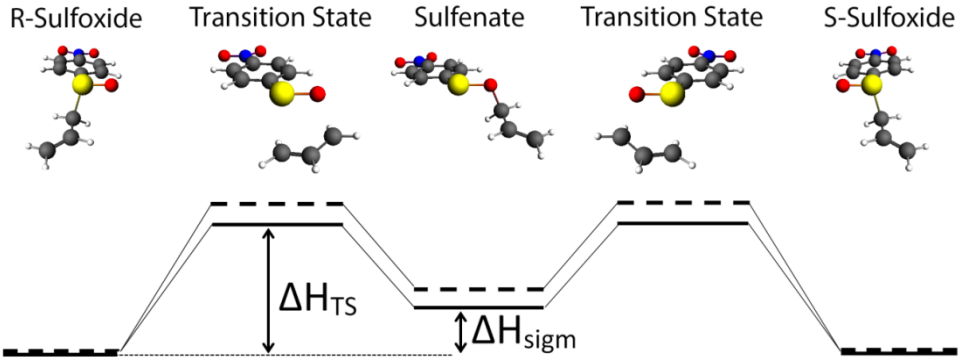


Figure S3.17: Part of the XRPD diffractogram, showing the conversion of racemic compound 1 into the conglomerate

DFT Computational details:

All calculations were performed using the Amsterdam Density Functional (ADF) 2013 software.[6] Both the optimized geometries and transition states were calculated using the OLYP level of the generalized gradient approximation (GGA).[7-9] A TZ2P basis set was used in combination with a small frozen core.[6] The COSMO solvation model[10-13] was used to incorporate the expected solvent effects on the Mislow-Evans rearrangement.[14] Verification of energy minima as well as transition states was performed using vibrational analysis. No imaginary frequencies were found for all energy minima, whereas a single imaginary frequency was found for the transition states.

Table S3.5: Racemization mechanism and kinetic data of compound 1 in toluene (solid) and methanol (dotted line)



Solvent	$\Delta H_{sigm, exp}$[a]	$\Delta H_{sigm, DFT}$	$\Delta H_{TS, exp}$[b]	$\Delta H_{TS, DFT}$	k_{rac} (h^{-1})[c]	$t_{1/2}$ (h)	k_{rel} (exp)[d]	k_{rel} (DFT)[d]
Methanol	n.d.[f]	3.3	n.d.[f]	18.7	0.007	99	1	1
Toluene	4.2	3.6	21.2	18.1	0.10	6.9	14	18

All energy units are in kcal/mol

[a] Determined using Van 't Hoff analysis of temperature dependent NMR measurements.

[b] Determined using temperature dependent selective EXSY experiments.

[c] At 20°C, determined using polarimetry measurements (for toluene) and additional SFC measurements (for methanol).

[d] Defined as k_{rac} / $k_{rac\ methanol}$, assuming an identical frequency factor for methanol and toluene in the Arrhenius equation for the DFT data.

Notes and References supporting information chapter 3:

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Supplemental Information Chapter 4

Synthesis of 4,6-dimethyl-1-(naphthalen-1-yl)pyrimidine-2(1*H*)-thione (4):
Ammonium thiocyanate (2.0 g, 26 mmol) was added to 100 mL acetone (100 mL), followed by the dropwise addition of benzoyl chloride (3.0 mL, 26 mmol). The resulting suspension was refluxed for 20 min and then allowed to cool to room temperature. Next, 1-naphthaleneamine (2.5 g, 17.5 mmol) was added and the mixture was refluxed for 1 h. The solution was poured into water (300 mL) and the resulting residue was filtered off. The precipitate was washed with water and added to 5% aqueous NaOH (100 mL). The suspension was heated to 80 °C for 30 min and then cooled to room temperature. 1M aqueous HCl was added after which the pH was adjusted to 9 by adding aqueous saturated Na_2CO_3. The residue was filtered off, washed with water and dried in air to yield 1-(naphthalen-1-yl)thiourea as a white powder in quantitative yield.
This product was added to ethanol (50 mL), followed by the addition of 2,4-pentadione (2.5 mL, 24 mmol). Next, 5M aqueous HCl (20 mL) was added and the mixture was refluxed for 3 h. The mixture was added to icewater containing NaOH (2.5 g). The product was extracted using DCM and dried with $MgSO_4$. The solvent was removed after which a thick red oil was formed. Upon addition of small quantities of acetone, product **4** precipitated as a yellow/orange powder in 52% yield.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97-7.90 (m, 2H), 7.60-7.55 (m, 1H), 7.54-7.44 (m, 2H), 7.41-7.38 (m, 1H), 7.38-7.35 (m, 1H), 6.59 (s, 1H), 2.48 (s, 3H), 1.89 (s, 3H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ 184.9, 169.9, 158.3, 137.6, 134.6, 129.6, 128.8, 128.0, 127.8, 126.9, 125.8, 125.1, 121.2, 110.8, 25.0, 21.5

Viedma ripening experiments:
Compound **4** (800 mg), glass beads (5 g, Ø ca. 2 mm VWR international), an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm) and toluene (10 mL) were added to a round-bottom flask to which a condenser was attached. The vial was heated to 60 °C and stirred at 600 rpm. Samples were taken regularly.

Sonication experiments:
Compound **4** (800 mg), glass beads (5 g, Ø ca. 2 mm VWR international) and toluene (10 mL) were added to a round-bottom flask. The flask was sealed and placed inside a sonication bath (35kHz, 320W) at 60 °C. Samples were taken regularly.

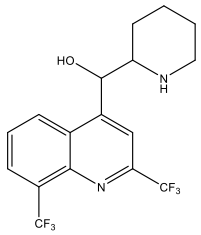
Temperature cycling experiments:
Compound **4** (800 mg), an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm) and toluene (10 mL) were added to a round-bottom flask to which a condenser was attached. The temperature was cycled between 55 and 65 °C on a regular basis (5 min at 55 °C, 2 °C/min to 65 °C, 5 min at 65 °C, 1 °C/min to 55 °C), while the suspension was gently stirred. Samples were taken after 5 min at 65 °C.

Sampling:
For sampling, 100 µL of the suspension was taken using a syringe. The crystals were filtered off on a P4 glass filter and air dried.

Sample analysis:
Analysis of the samples taken during the experiment was performed using chiral HPLC, which gave good separation, but not the absolute configuration of the two peaks in the chromatogram. To determine the absolute configuration, X-Ray diffraction was used to elucidate the structure of a single crystal. Designation of the HPLC peaks was done by sampling this single crystal, giving only a single peak.
The *ee* of the samples was determined using chiral HPLC (ADH column, 20% IPA in heptane, flow 1 mL min^{-1}, retention times: (S_a)-**4** 11.7 min, (R_a)-**4** 25.0 min).

Supplemental Information Chapter 5

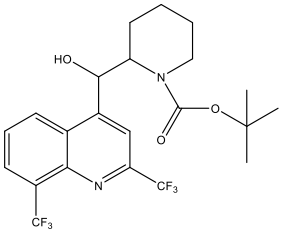
Synthesis of Mefloquine derivatives:



Extraction of Mefloquine (**1**) from Lariam tablets:
A total of 104 Lariam tablets (purchased from Roche) containing 250 mg Mefloquine per tablet) were powdered using a mortar. The powder was added to methanol (500 mL) and the resulting suspension was refluxed for 3 hours. The suspension was cooled to room temperature, filtered and the residue was thoroughly washed using methanol. To the filtrate was added dropwise a 2M NaOH solution. Seed crystals (0.2 g) were added to induce crystallization of the racemic mefloquine, which was obtained as a white powder (24.0 g, 100% yield).
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (C$\underline{H}_{arom}$, d, *J* = 8.6 Hz, 1H), 8.16 (C$\underline{H}_{arom}$, d, *J* = 7.4 Hz, 1H), 8.13 (C$\underline{H}_{arom}$, s, 1H), 7.70 (C$\underline{H}_{arom}$, t, *J* = 7.9 Hz, 1H), 5.50 (C$\underline{H}$OH, d, *J* = 3.4 Hz, 1H), 3.13 (C$\underline{H}$, d, *J* = 12.0 Hz, 1H), 3.04 (C$\underline{H}$, dt, *J* = 11.3, 3.2 Hz, 1H), 2.73 (C$\underline{H}$, td, *J* = 12.2, 2.8 Hz, 1H), 1.73 (C$\underline{H}$, d, *J* = 13.5 Hz, 1H), 1.58 (C$\underline{H}$, d, *J* = 13.1 Hz, 1H), 1.36 (C$\underline{H}$, m, 2H), 1.12 (C$\underline{H}$, m, 1H), 0.97 (C$\underline{H}$, m, 1H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 155.0, 147.1, 143.2, 130.3, 130.0, 127.9, 127.6, 127.3, 125.6, 122.9, 116.2, 72.6, 62.2, 46.9, 27.7, 26.6, 24.6.

Resolution of Mefloquine:
A total of 2 g racemic Mefloquine and 2 g (-)-O,O-di-p-toluoyl-D-tartaric acid were added to 20 mL ethyl acetate. The solution was stirred for 2 hours, after which the white precipitate was filtered off. The work-up of both the filtrate and the residue were handled separately;
-The residue was added to a 2M NaOH solution and was extracted with ethylacetate. The combined organic extracts were washed with brine, and concentrated under reduced pressure to yield (+)-(11S, 12R)-Mefloquine as a white solid which was immediately BOC-protected using the general protocol (yield = 0.86 g, 84% *ee*).
-The filtrate was added to a 2M NaOH solution which was extracted with ethylacetate. The combined organic extracts were washed with brine, and concentrated under reduced pressure to yield (-)-(11R, 12S)-Mefloquine as a white solid which was immediately BOC-protected using the general protocol (yield = 1.66 g, 44% *ee*).

Boc-protected Mefloquine (**4**):

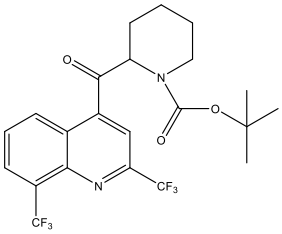


A total of 22.4 g racemic Mefloquine was dissolved in 400 mL THF at 0°C. After adding triethylamine (29 mL) and BOC_2O (15.7g, 1.2 eq) the solution was stirred for 2 hours. The solution was concentrated and after after addition of brine solution, the product was extracted with diethylether. The combined organic extracts were washed thoroughly with H_2O, brine, and concentrated under reduced pressure to yield BOC-protected mefloquine as a slightly yellow oil (27.7 g, 98% yield). In contrast to an earlier reported spectrum in the literature (same temperature and solvent), the compound did not appear as a mixture of rotamers.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.65 (C$\underline{H}_{arom}$, d, *J* = 8.7 Hz, 1H), 8.17 (C$\underline{H}_{arom}$, d, *J* = 6.9 Hz, 1H), 8.04 (C$\underline{H}_{arom}$, s, 1H), 7.76 (C$\underline{H}_{arom}$, m, 1H), 5.83 (C$\underline{H}$OH, t, *J* = 4.1 Hz, 1H), 4.29 (C$\underline{H}$, q, *J* = 5.5 Hz, 1H), 3.82 (C$\underline{H}$, d, *J* = 13.6 Hz, 1H), 3.24 (C$\underline{H}$, m, 1H), 1.78 (C$\underline{H}$, m, 1H), 1.61 (C$\underline{H}$, m, 1H), 1.55 (C$\underline{H}$, m, 2H), 1.48 (C$\underline{H}$, m, 1H), 1.37 (C$\underline{H}$, m, 1H), 1.32 (C$\underline{H}_3$, s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 151.1, 148.3, 147.9, 143.8, 128.8, 128.4, 127.1, 127.0, 124.9, 122.2, 115.6, 85.2, 80.3, 71.5, 57.0, 42.0, 28.2, 27.4, 24.3, 19.9.

Boc-protected Mefloquine-ketone (**5**):



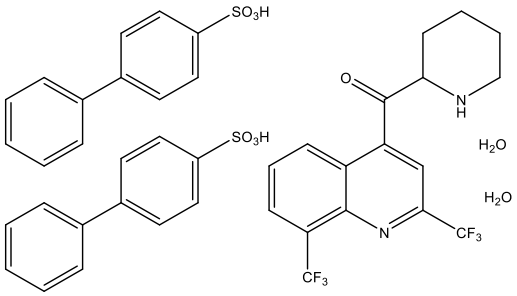
In a flame-dried round-bottom flask, 20.0 g Boc-protected Mefloquine (**4**) was dissolved in 200 mL DCM and cooled to 0°C under argon. During 20 minutes, Dess-Martin periodinane (23.0 g, 1.3 eq) added in small portions to the mixture. The mixture was allowed to reach room-temperature and stirred for 6 hours. The mixture was concentrated and partitioned between Et_2O (200 ml) and Brine (200 ml). The aqueous layer was extracted one more time with Et_2O (50 ml) and the combined organic layers where washed one more time with brine (50 ml), dried with anhydrous Na_2SO_4 and concentrated in vacuo. After addition of a few seed crystals, Boc-protected Mefloquine-ketone was obtained as a colorless solid (18.3 g, 92%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 (C$\underline{H}_{arom}$, d, *J* = 8.6 Hz, 1H), 8.23 (C$\underline{H}_{arom}$, d, *J* = 7.3 Hz, 1H), 8.08 (C$\underline{H}_{arom}$, s, 1H), 7.80 (C$\underline{H}_{arom}$, t, *J* = 8.0 Hz, 1H), 5.52 (C$\underline{H}$, m, 1H),

3.99 (C<u>H</u>, d, *J* = 13.0 Hz, 1H), 2.96 (C<u>H</u>, m, 1H), 1.75 (C<u>H</u>, m, 3H), 1.53 (C<u>H</u>, m, 3H), 1.43 (C<u>H</u>$_3$, bs, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 203.2, 156.0, 155.7, 145.3, 144.4, 129.5, 129.3, 128.8, 128.6, 125.5, 122.2, 119.5, 115.3, 80.9, 59.5, 43.3, 28.2, 24.9, 24.8, 20.7.

Conglomerate salt of Mefloquine ketone (**6**):



A total of 14.0 g Boc-protected Mefloquine-ketone was dissolved in 30 mL EtOAc and filtered over celite to obtain a clear colorless solution. A second solution containing 20.0 g Biphenylsulfonic acid (85%, hydrate form, approximately 2.1 eq) in 15 mL EtOAc was added. The combined solution was heated to 50°C. Ceasing of bubbling indicated the completion of the Boc-deprotection, after which 20 mL heptane and 0.5 mL water was added. After cooling the solution to room temperature, 50 mg of seed crystals were added to initiate crystallization (note: spontaneous crystallization of the conglomerate compound never occurred without seeding). The suspension was filtered, and the resultant crystals washed with a 2:1 EtOAc:heptane mixture to obtain the Mefloquine salt as colorless crystals (25.6 g, 99.0%).

^{1}H NMR (400 MHz, Methanol-*d*) δ 8.50 (C<u>H</u>$_{arom}$, d, *J* = 8.7 Hz, 1H), 8.41 (C<u>H</u>$_{arom}$, s, 1H), 8.35 (C<u>H</u>$_{arom}$, d, *J* = 7.3 Hz, 1H), 7.96 (C<u>H</u>$_{arom}$, t, *J* = 8.3 Hz, 1H), 7.91-7.86 (C<u>H</u>$_{arom}$, m, 4H), 7.68-7.64 (C<u>H</u>$_{arom}$, m, 4H), 7.64-7.59 (C<u>H</u>$_{arom}$, m, 4H), 7.47-7.40 (C<u>H</u>$_{arom}$, m, 4H), 7.37-7.32 (C<u>H</u>$_{arom}$, m, 2H), 5.23 (C<u>H</u>, dd, *J* = 12.4, 3.3 Hz, 1H), 3.62 (C<u>H</u>, d, J=13.1Hz, 1H), 3.22 (C<u>H</u>, dt, J=12.8Hz, 3.5 Hz, 1H), 2.07-1.58 (C<u>H</u>, m, 6H).

^{13}C NMR (101 MHz, Methanol-*d*) δ 198.9, 145.2, 144.6, 143.5, 141.5, 131.6, 131.7, 131.2, 130.6, 130.0, 129.0, 128.2, 128.0, 127.6, 118.0, 118.0, 64.0, 45.4, 27.1, 23.1, 23.0.

Reduction of Mefloquine ketone salt:

Mefloquine salt **6** (0.5 g) and $CeCl_3.7H_2O$ (0.5 g) were added to 20 mL ethanol. The suspension was cooled to 0°C, after which 23 equivalent (0.5 g) of $NaBH_4$ were added during 2 h. After 3 hours, the solution was quenched with saturated

Na_2CO_3, after which Mefloquine was extracted with DCM. The organic layer was washed with brine, dried using Na_2SO_4 and the solvent removed to yield Mefloquine as a white solid (202 mg, 93%).

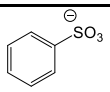
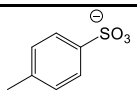
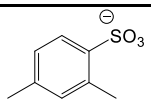
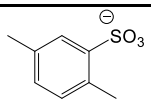
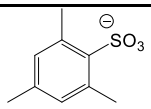
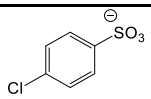
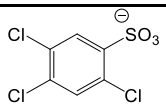
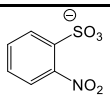
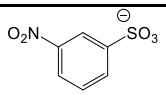
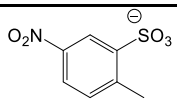
Crystal screening experiments:

In order to find a racemic conglomerate derivative of Mefloquine-ketone, the crystal structure of 34 Mefloquine derivatives were determined. Single crystals were grown by Boc-deprotection of **5** in solution and consequent evaporation of the solvent. In many cases, solvates were obtained. For this reason, the crystallization experiments were carried out in various solvent, since each different solvate could potentially be a racemic conglomerate.

In a typical crystallization experiment, 50 mg (0.1 mmol) compound **5** and an equimolar amount of sulfonic acid were each dissolved in 2 mL solvent. Cloudy solutions were filtered (using a 0.45 µm microfilter), after which the two solutions were added together and heated to 50°C. After bubbling of the solutions had ceased (indicating complete Boc-deprotection), the solutions were left standing at room temperature to allow for slow solvent evaporation. It should be noted that the majority of experimental conditions (different solvents and sulfonic acids), did not yield any crystals.

Crystal structures:

The spacegroups of the determined crystal structures are given in table S5.1. The ratio between Mefloquine-ketone, sulfonic acid and solvate are given for each structure. For the compounds which are not solvates, the solvent in which the crystallization was carried out is given. In one crystal structure, two types of solvent (water and acetic acid) were present.

Table S5.1: Composition of Mefloquine derivative salts		
Acid	**Space group**	**MQ:X:Solvent**
$CF_3SO_3^-$	P-1	1:1:0 (from EtOH)
$CH_3SO_3^-$	$P2_1/c$	1:1:0 (from toluene)
	$P2_1/c$	1:1:0 (from toluene)
	$P2_1/c$	1:1:0 (from EtOH)
	C2/c	1:1:1 (toluene)
	$P2_1/c$	1:1:2 (THF)
	P-1	1:1:0 (from Acn)
	P-1	1:2:3 (H_2O, from EtOH)
	P-1	2:2:1 (toluene)
	$P2_1/c$	1:1:0 (from EtOAc)
	$P2_1/c$	12:12:6 (toluene)
	$P2_1/c$	1:1:1:2 ($AcOH:H_2O$, from acetic acid)
	$P2_1/n$	3:3:2 (toluene)
	P-1	2:2:1 (toluene)
	$Pna2_1$	1:1:1 (AcOH)
	P-1	1:1:1 (Acn)
	C2	2:2:1 (toluene, cryptoracemate)
	P-1	1:1:0 (from toluene)
	$P2_1/c$	1:1:0 (from EtOH)
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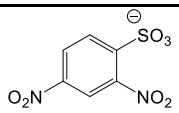
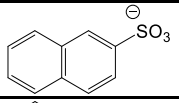
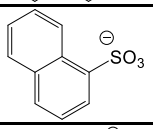
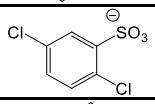
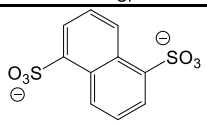
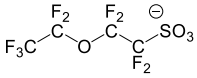
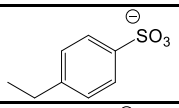
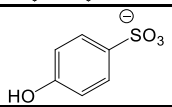
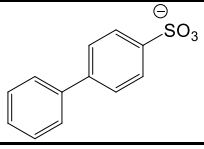
	P-1	1:1:? (toluene, bad quality)
	$P2_1/c$	2:2:1 (EtOAc)
	C2/c	1:1:1 (EtOAc)
	$Pna2_1$	1:1:1 (EtOH)
	$P2_1$	? (From EtOAc, very bad quality, not clear if solvate, cryptoracemate)
	Pbca	1:1:0 (from toluene)
	C2/c	1:1:2 (EtOH)
	C2/c	1:1:1 (THF)
	C2/c	1:1:1 (Acn)
	P-1	2:2:1 (toluene)
	$P2_1/n$	1:1:0 (from EtOH)
	$P2_1/n$	1:1:1 (toluene)
	P-1	1:1:0 (from EtOAc)
	$P2_1$	1:2:2 (from EtOH, water, conglomerate)

Racemization experiments:

The half-life of racemization of compound **6** in acetic acid was determined using deuteration experiments, and was also checked using polarimetry. For the deuteration experiments, a solution of 500 mg compound **6** was dissolved in d_4-acetic acid and heated to 80°C. Every hour, a sample of the solution was analyzed

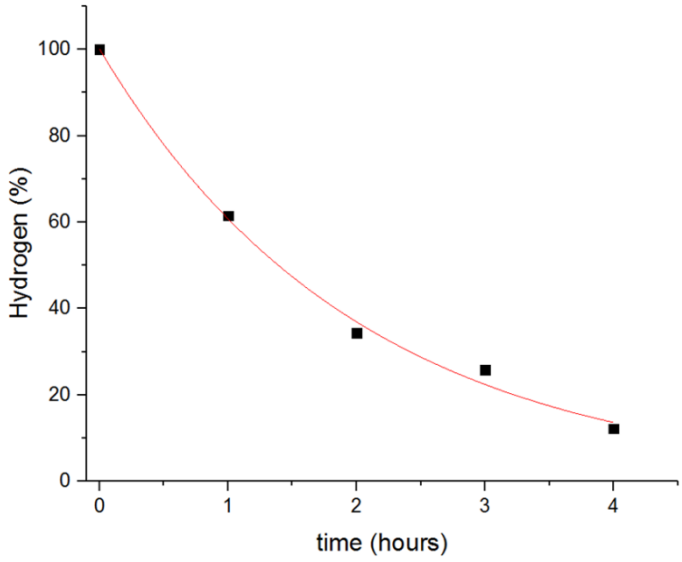


Figure S5.1: Racemization curve of compound 6 in deuterated acetic acid (containing 10% d-methanol). The degree of racemization was determined from the amount of deuteration of the chiral proton. The solid line is a fit of the data to an exponential decay.

using ^{1}H NMR. During the first hour of the experiment, the signal of all Mefloquine peaks (relative to the sulfonic acid) dropped to 80%, probably due to the keto-enol equilibrium (Figure S5.1). No further decomposition of the product was observed, as the intensity of the Mefloquine peaks remained constant at 80%, even after several days at 80°C. The deuteration rate of compound **6** was determined using the integral of the chiral proton peak, which decreased due to deuteration. It was determined that the half-life of racemization is $t_{1/2}$= 1.4 hours. Additional experiments, in which the loss of optical rotation upon heating compound **6** in (protonated) acetic acid was measured, gave similar values.

Product recovery after racemization:
After complete racemization was achieved, the solvent was removed under reduced pressure. Next, the resultant oil was dissolved in 2 mL EtOAc and 20 µL water, after which 10 mL heptane was added. Upon addition of 5 mg seed crystals, compound **6** crystallized as a white solid in 89% yield (443 mg).

Deracemization experiments:
For the resolution experiments, the experimental setup described by Hein[1] and more elaborately by Levilaine[2] was used (Figure S5.2). Since diastereomeric salt formation of Mefloquine yielded an *ee* up to only 84%, preparative chiral column chromatography of Boc-protected Mefloquine was used to obtain enantiopure material.

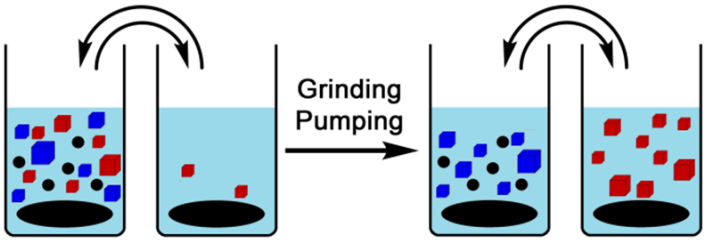


Figure S5.2: Schematic representation of the performed resolution experiments on compound 4.

In a typical resolution experiment, a total of 1.5 g of racemic compound **6**, 5 g glass beads (4 g, Ø ca. 2 mm VWR international) and an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm) were added to 15 mL EtOAc in a 20 mL vial. The suspension was ground at 600 rpm throughout the experiment. A second vial containing 50 mg enantiopure compound **6** and a small magnetic stirring bar (L 15 mm, Ø 5 mm) was stirred at 200 rpm. A peristaltic pump was used to exchange liquid between the two vials (flow rate =8.7 mL/min in both directions continuously). To prevent the exchange of solid material between both vials, both the inlet and outlet of both tubes were equipped with a proplast cannula filter (1 micron). To prevent clogging of the filters, the flow direction was reverted for 2 seconds during every minute. After a period of 3 hours, the solids of both vials were collected, the yield determined and the *ee* determined using chiral HPLC (after both Luche reduction and Boc-protection).

Outcome of a typical experiment:
The mass of the initially enantiopure solid phase had increased from 50 mg to 160 mg (after drying), while the solid phase contained 90% of the required enantiomer. The *ee* of the second (initially racemic) vial had changed to -9%. (Note: by reducing the experimental time, the yield of the experiment decreased, but the enantiomeric composition of the final product consisted of 94% of the desired 11*S*,12*R*-MQ).

Powder X-ray diffractograms:
All diffractograms were recorded using a Bruker D8 Advance Spectrometer using a VANTEX detector. Data was recorded using reflection mode with monochromatic Cu-Kα_1 radiation.
As mentioned in the main manuscript, upon heating of conglomerate **6** above 70°C, a change in the XRPD diffractogram was observed, likely due to the presence of a second polymorph. When starting from enantio-enriched material, all optical rotation was lost upon this conversion, indicating the presence of a racemic compound (Figure S5.3).

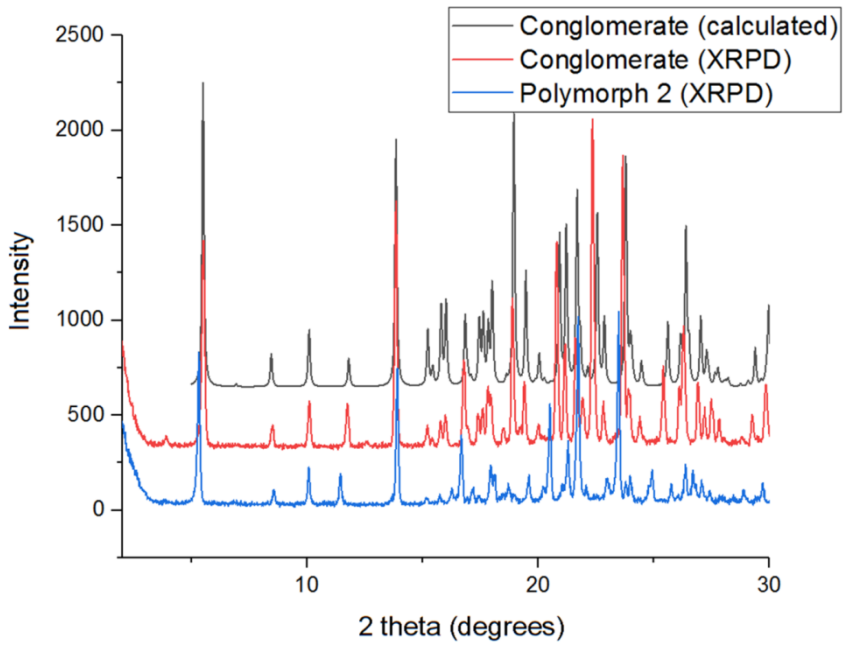


Figure S5.3: Powder diffratogram of compound **6**, compared to that calculated from the crystal structure and the second polymorph (obtained upon heating).

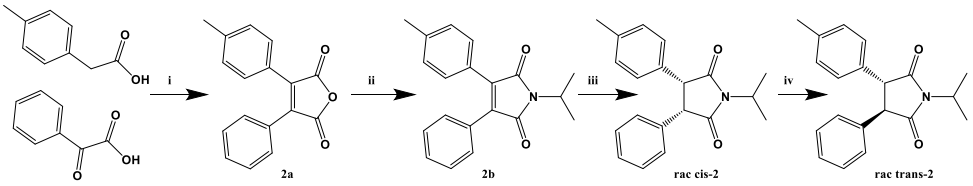
Notes and References supporting information chapter 5:

1. J. E. Hein, B. H. Cao, C. Viedma, R. M. Kellogg and D. G. Blackmond, *J. Am. Chem. Soc.*, **2012**, 134, 12629-12636.
2. G. Levilain, M. J. Eicke and A. Seidel-Morgenstern, *Cryst. Growth Des.*, **2012**, 12, 5396-5401.
3. J. Y. Ding and D. G. Hall, *Angew. Chem. Int. Ed.*, **2013**, 52, 8069-8073.

Supplemental Information Chapter 6

Synthesis of diastereomers:

Compound **2** was synthesized, starting from 4-methylphenylacetic acid and phenylglyoxylic acid in three steps, based on the procedure of Hachiya et al.. In contrast to their procedure, Pd/C was used as a hydrogenation catalyst instead of PtO_2.



Synthesis of 3-phenyl-4-(4-methylphenyl)maleic anhydride (**2a**):

4-Methylphenylacetic acid (10.4 g, 69.2 mmol) and phenylglyoxylic acid (10.4 g, 69.2 mmol) were suspended in acetic anhydride (50 mL). The mixture was refluxed for 3 h, quenched with an excess of water and filtered. The residue was triturated with acetone, the filtrate of which was evaporated *in vacuo*. Recrystallization from ethanol and drying *in vacuo* yielded yellow crystals (10.9 g, 41.4 mmol). The recrystallization filtrate was recrystallized from ethanol and water to obtain a second batch of yellow crystals (2.7 g, 10.1 mmol, combined yield 74 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.53 (C$\underline{H}_{arom}$, m, 2H), 7.50-7.39 (C$\underline{H}_{arom}$, m, 5H), 7.12-47.19 (C$\underline{H}_{arom}$, m, 2H), 2.40 (C$\underline{H}_3$, s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 164.9, 141.9, 138.2, 137.2, 130.9, 129.7, 129.6, 129.6, 128.9, 127.4, 124.3, 21.6.

Synthesis of *N*-isopropyl-3-phenyl-4-(4-methylphenyl)maleimide **2b**:

Compound **2a** (7.95 g, 30.1 mmol) was dissolved in toluene–DMF (3:1 v/v, 25 mL) and cooled to 0 °C. Isopropylamine (25 mL, 291 mmol) was added and the mixture was stirred for 1.5 h, after which excess isopropylamine was removed *in vacuo*. The mixture was refluxed for 4 h and subsequently evaporated and dried *in vacuo* to obtain yellow crystals (9.82 g, 32.2 mmol, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.44 (C$\underline{H}_{arom}$, m, 2H), 7.40-7.31 (C$\underline{H}_{arom}$, m, 5H), 7.17-7.12 (C$\underline{H}_{arom}$, m, 2H), 4.48 (C$\underline{H}$(CH_3)$_2$, septet, 1H, *J* = 6.9 Hz), 2.36 (C$\underline{H}_3$, s, 3H), 1.48 (C$\underline{H}_3$, d, 6H, *J* = 7.1Hz). ^{13}C

NMR (100 MHz, $CDCl_3$) δ 170.8, 170.8, 140.0, 136.0, 135.2, 129.8, 129.8, 129.5, 129.2, 129.0, 128.5, 125.8, 43.3, 21.5, 20.2.

Synthesis of *cis*-1-isopropyl-3-phenyl-4-(4-methylphenyl)pyrrolidine-2,5-dione (RS+SR-**2**):

Compound **2b** (12.0 g, 39 mmol) was dissolved in 20 mL ethyl acetate. After adding 500 mg Pd/C (10%), the suspension was stirred under 30 bar hydrogen pressure for 24 hours. After completion of the reaction (monitored by the change of a yellow to a colorless solution), the suspension was filtered over Celite to remove the Pd/C. After removal of the solvent, seed crystals were added to induce crystallization, after which *cis*-**2** was obtained as a colorless solid (initial crystals were obtained by pouring liquid nitrogen on the oil of *cis*-**2**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.05 (C$\underline{H}_{arom}$, m, 3H), 6.90-6.82 (C$\underline{H}_{arom}$, m, 4H), 6.72-6.68 (C$\underline{H}_{arom}$, m, 2H), 4.65 (C$\underline{H}(CH_3)_2$, septet, 1H, *J* = 7.0 Hz), 4.43-4.36 (C$\underline{H}$, m, 2H), 2.16 (C$\underline{H}_3$, s, 3H), 1.57 (C$\underline{H}_3$, d, 6H, *J* = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 177.2, 136.8, 134.2, 131.0, 129.2, 129.0, 128.9, 128.2, 127.2, 51.9, 52.2, 44.2, 21.0, 19.5.

Synthesis of rac *trans*-1-isopropyl-3-phenyl-4-(4-methylphenyl)pyrrolidine-2,5-dione (RR+SS-**2**):

The *trans* diastereomers could be easily prepared by dissolving *cis*-**2** in chloroform and adding catalytic amounts (2 mol%) of DBU. After stirring for one hour, the solvent was partially removed *in vacuo* and heptane was added, resulting in the crystallization of *trans*-**2** as colorless crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.29 (C$\underline{H}_{arom}$, m, 3H), 7.21-7.15 (C$\underline{H}_{arom}$, m, 4H), 7.10-7.05 (C$\underline{H}_{arom}$, m, 2H), 4.55 (C-$\underline{H}(CH_3)_2$, septet, 1H, *J* = 6.9 Hz), 3.98-3.92 (C$\underline{H}$, m, 2H), 2.35 (C$\underline{H}_3$, s, 3H), 1.57 (C$\underline{H}_3$, appears as a triplet, 6H, *J* = 7.1Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 176.7, 137.6, 137.0, 133.9, 129.7, 129.0, 127.7, 127.4, 127.2, 55.1, 54.8, 44.2, 20.9, 19.3, 19.1.

Compound **3** was synthesized, using a similar procedure as for the synthesis of **2**, now starting from 4-bilphenylacetic acid and phenylglyoxylic acid.

Synthesis of 3-phenyl-4-(4-biphenyl)maleic anhydride (**3a**):

4-Biphenylacetic acid (10.6 g, 50.0 mmol) and phenylglyoxylic acid (7.5 g, 50.0 mmol) were suspended in acetic anhydride (50 mL). The mixture was refluxed for

3 h, quenched with an excess of water and filtered. The residue was triturated with acetone, the filtrate of which was evaporated *in vacuo*. The obtained yellow solid was used in the next step without any further purification.

Synthesis of *N*-isopropyl-3-phenyl-4-(4-biphenyl)maleimide **3b**:
Compound **3a** was dissolved in toluene–DMF (3:1 v/v, 25 mL) and cooled to 0 °C. Isopropylamine (25 mL, 291 mmol) was added and the mixture was stirred for 1.5 h, after which excess isopropylamine was removed *in vacuo*. The mixture was refluxed for 4 h and subsequently evaporated and dried *in vacuo* to obtain yellow crystals (10.3 g, 27.9 mmol, 56% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.35 (C$\underline{H}_{arom}$, m, 14H), 4.52 (C$\underline{H}(CH_3)_2$, septet, 1H, *J* = 7.1 Hz), 1.51 (C$\underline{H}_3$, d, 6H, *J* = 6.8Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.6, 142.4, 140.2, 135.7, 135.5, 130.4, 129.9, 129.8, 129.7, 128.8, 128.5, 127.8, 127.6, 127.2, 127.1, 43.4, 20.2

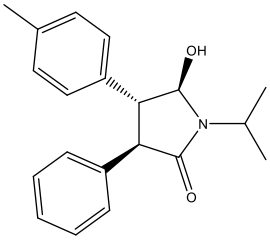
Synthesis of *cis*-1-isopropyl-3-phenyl-4-(4-biphenyl)pyrrolidine-2,5-dione (RS+SR-**3**):
Compound **3b** (10.3 g, 27.9 mmol) was dissolved in 20 mL ethyl acetate. After adding 500 mg Pd/C (10%), the suspension was stirred under 30 bar hydrogen pressure for 24 hours. After completion of the reaction (monitored by the change of a yellow to a colorless solution), the suspension was filtered over Celite to remove the Pd/C. After removal of the solvent, seed crystals were added to induce crystallization, after which *cis*-**3** was obtained as a colorless solid (initial crystals were obtained by pouring liquid nitrogen on the oil of *cis*-**3**). In contrast to the synthesis of cis-**2**, which yielded only the trans-diastereomer, the solid contained a 8:1 ratio of cis:trans-**3**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11-7.05 (C$\underline{H}_{arom}$, m, 3H), 6.90-6.82 (C$\underline{H}_{arom}$, m, 4H), 6.72-6.68 (C$\underline{H}_{arom}$, m, 2H), 4.65 (C$\underline{H}(CH_3)_2$, septet, 1H, *J* = 7.0 Hz), 4.43-4.36 (C$\underline{H}$, m, 2H), 1.59 (C$\underline{H}_3$, d, 6H, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1, 177.1, 140.0, 133.0, 129.8, 129.6, 129.1, 128.7, 128.3, 127.4, 127.3, 127.1, 126.9, 126.8, 52.3, 21.9, 44.4, 19.5, 19.4

Synthesis of rac *trans*-1-isopropyl-3-phenyl-4-(4-biphenyl)pyrrolidine-2,5-dione (RR+SS-**3**):
The *trans* diastereomers could be easily prepared by dissolving *cis*-**3** in chloroform and adding catalytic amounts (2 mol%) of DBU. After stirring for one hour, the

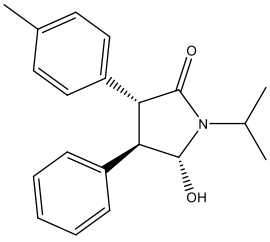
solvent was partially removed *in vacuo* and heptane was added, resulting in the crystallization of *trans*-**3** as colorless crystals.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.29 (C$\underline{H}_{arom}$, m, 7H), 7.11-7.04 (C$\underline{H}_{arom}$, m, 3H), 6.91-6.84 (C$\underline{H}_{arom}$, m, 4H), 4.67 (C$\underline{H}(CH_3)_2$, septet, 1H, *J* = 7.0 Hz), 4.05 (C$\underline{H}$, s, 2H), 1.53 (C$\underline{H}_3$, appears as a triplet, 6H, *J* = 6.8 Hz).
^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 176.6, 140.9, 140.4, 136.9, 135.8, 129.2, 128.8, 128.0, 127.9, 127.9, 127.5, 127.4, 127.0, 55.2, 55.0, 44.5, 19.5, 19.3

Synthesis of additives 5a-5d:
The synthesis of chiral additives **5a**-**5d** was based on the procedure described by Wijnberg et al.. Enantiopure compound **2** (0.5 g, 1.6 mmol) and $CeCl_3.7H_2O$ (0.6 g, 1.6 mmol) were added to 10 mL ethanol. The stirred solution was cooled on ice, after which 2 g $NaBH_4$ (50 mmol, 31 eq) was added over a period of two hours. After an additional 4 hours of stirring at 0°C, water was added to quench the reaction. The product was extracted using diethyl ether and was dried with Na_2SO_4. After removal of the solvent, a 5:5:1:1 mixture of **5a**:**5b**:**5c**:**5d** was obtained in quantitative yield. All additives were obtained in an enantiopure form, as could be derived from the comparison of the HPLC chromatograms of enantiopure and racemic products. To test whether the additives were resistant to racemization, a solution of the enantiopure additives in chloroform was exposed to 1 equivalent of DBU for 4 days. After this time, the additives remained enantiopure, according to chiral HPLC.

NMR spectra of **5a** + **5b (major):**
No distinction could be made between the NMR spectra of compounds **5a** and **5b**. For the ^{1}H spectrum, most peaks overlapped (with the exception of both CH_3 peaks). Assignment of the ^{1}H peaks to the corresponding protons was done based on COSY, HMBC and HSQC NMR experiments. For the ^{13}C spectrum, two separate peaks could be attributed to the combination of the two species. The chemical shifts of both peaks are given.



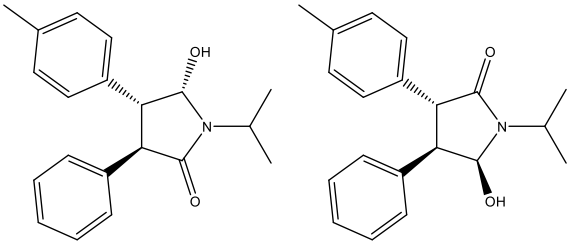
5a



5b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.03 (C<u>H</u>$_{arom}$, m, 9H), 5.22 (C<u>H</u>OH, ddd, J=7.4 Hz, J=5.1 Hz, J=3.5 Hz), 4.34 (C<u>H</u>$(CH_3)_2$, two septets, separated by 1.6 Hz, J=6.6 Hz), 3.68 (COC<u>H</u>, dd (appears as a triplet), J=7.0 Hz, J=7.0 Hz),), 3.26 (C<u>H</u>CHOH, ddd, J=10.6 Hz, 6.6 Hz, 3.5 Hz), 2.96 (dd, J=12.5 Hz, J=7.4 Hz), 2.33 (s, two peaks separated by 13.7 Hz), 1.35 (two doublets, separated by 17.6 Hz, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.2, 140.7, 139.0, 137.7, 137.0, 136.7, 135.9, 129.7, 129.5, 128.9, 128.0, 127.8, 127.0, 126.9, 87.6, 87.5, 57.3, 56.9, 55.9, 55.4, 44.4, 22.3, 21.1, 21.0, 19.2.

NMR spectra of **5c** + **5d (minor):**
No distinction could be made between the NMR spectra of compounds **5c** and **5d**. For the ^{1}H spectrum, all peaks overlapped (with the exception of the CH_3 peaks). Assignment of the ^{1}H peaks to the corresponding protons was done based on COSY, HMBC and HSQC NMR experiments. For the ^{13}C spectrum, two separate peaks could be attributed to the combination of the two species. The chemical shifts of both peaks are given.



5c **5d**

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.03 (C<u>H</u>$_{arom}$, m, 9H), 5.39 (ddd, J=9.0 Hz, J=5.1 Hz, J=3.9Hz), 4.34 (two septets, separated by 1.6 Hz, J=6.6 Hz), 4.18 (dd, J=10.9 Hz, J=3.5 Hz), 3.60 (ddd, J=11.3 Hz, 7.4 Hz, 5.1 Hz), 2.29 (s, two peaks separated by 24.2 Hz), 2.01 Hz, (dd, J=5.9 Hz, J=3.9 Hz), 1.35 (two doublets, separated by 17.6 Hz, J=7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 174.5, 137.5, 137.1, 136.7, 135.5, 133.9, 132.2, 129.6, 129.2, 128.8, 128.7, 128.5, 128.4, 128.3, 127.3, 127.1, 81.0, 81.1, 53.5, 53.8, 50.2, 49.8, 44.2, 44.2, 21.9, 21.8, 21.0, 20.1.

Temperature-dependent NMR experiments:

Calculation of the thermodynamic parameters of the racemization of compound **2**:

In these experiments, *trans*-**2** (0.1 g, 0.3 mmol) and DBU (2 µL, 0.013 mmol, 5 mol%) were dissolved in 0.8 mL deuterated chloroform. Then, the ^{1}H NMR

spectrum was recorded at several temperatures. At all these temperatures, the percentage *cis* diastereomer was determined, from which the equilibrium constant (*K*) could be calculated. Using the Van 't Hoff equation, the thermodynamic parameters of the equilibrium between *cis* and *trans* could be calculated:

$$\ln(K) = -\frac{\Delta H}{RT} + \frac{\Delta S}{R}$$

Δ*H* = 2.8 kcal/mol, Δ*S* = 1.2 cal/molK, Δ*G* = 2.5 kcal/mol (at RT)

In order to determine the energy barrier of racemization, temperature-dependent selective Exchange Spectroscopy (EXSY) experiments were performed. In these experiments, the NMR peaks of the protons at the chiral center of *cis*-**2** were excited and conversion into *trans*-**2** was observed after several mixing (waiting) times (figure S6.1). The rate constant of this process was determined at various temperatures (figure S1), from which the Eyring plot could be constructed (figure S6.2). Using the Eyring plot, the entropy, enthalpy and Gibbs free energy of the transition state could be determined:

$$\ln\left(\frac{k}{T}\right) = -\frac{\Delta H}{R} * \frac{1}{T} + \ln\left(\frac{k_b}{h}\right) + \frac{\Delta S}{R}$$

Δ*H* = 5.2 kcal/mol, Δ*S* = -168 cal/molK, Δ*G* = 17.0 kcal/mol (at RT)

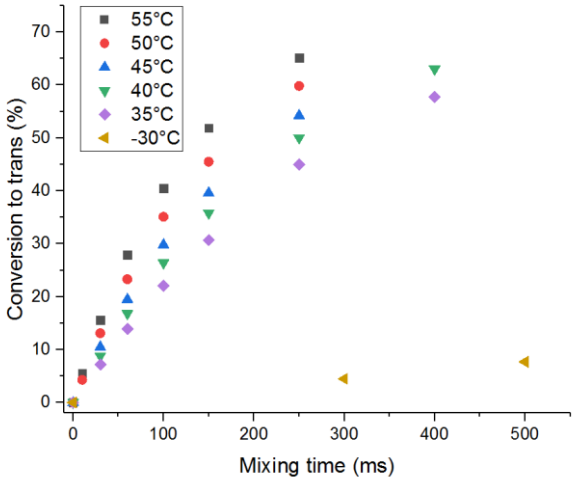


Figure S6.1: Conversion of *cis*-**2** into *trans*-**2** determined using temperature-dependent selective Exchange Spectroscopy Experiments.

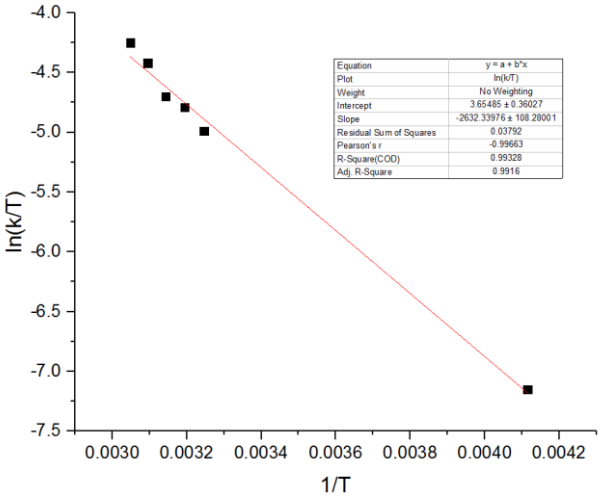


Figure S6.2: Eyring plot of the rate constant of the conversion of *cis* into *trans*-2.

Deracemization experiments:

Deracemization experiments starting from *cis*-RS+SR-**2**:

Cis-**2** (800 mg), glass beads (5 g, Ø ca. 2 mm VWR international) and an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm) were added to 7 mL heptane and 0.8 mL chloroform in a 15 mL vial. The suspension was stirred at 600 rpm for 1 hour to ensure homogenization of the crystal sizes. Next, 1 µL DBU was added. During the next 320 minutes samples were taken regularly to observe the

conversion of the RS+SR into the RR+SS diastereomers. Another 30 µL DBU was added, after which grinding was continued.

Deracemization experiments using chiral additives:
Cis or *trans*-**2** (450 mg), glass beads (4 g, Ø ca. 2 mm VWR international) and an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm) were added to 4 mL heptane and 0.5 mL chloroform in a 15 mL vial. When additives were used, a total of 20 mg enantiopure additive was added as well. The suspensions were stirred at 600 rpm for 1 hour to ensure homogenization of the crystal sizes. Next, 20 µL DBU was added, after which samples were taken regularly.

Sampling:
For sampling, 100 µL of the suspension was taken using a syringe. The crystals were filtered off on a P4 glass filter and were washed with 0.1 mL diethyl ether to remove the remaining DBU.

Deracemization experiments of compound 3:
Compound-**3** (800 mg), glass beads (5 g, Ø ca. 2 mm VWR international) and an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm) were added to 6 mL heptane and 3 mL chloroform in a 15 mL vial. The suspension was stirred at 600

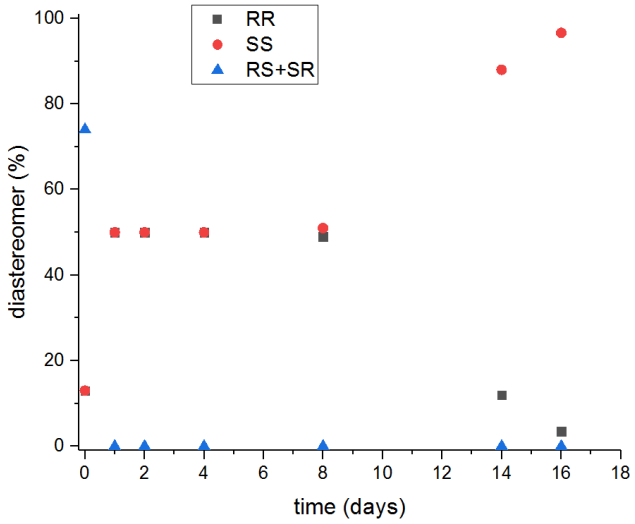


Figure S6.3: Deracemization curve of compound 3

rpm for 1 hour to ensure homogenization of the crystal sizes. Next, 30 µL DBU was added, after which grinding was continued. Samples were taken regularly during the experiment.

Powder Diffractograms:

All diffractograms were recorded using a Bruker D8 Advance Spectrometer using a VANTEX detector. Data was recorded using reflection mode with monochromatic Cu-Kα_1 radiation. The patterns based on the crystal structures were corrected for the different temperature at which they were recorded.

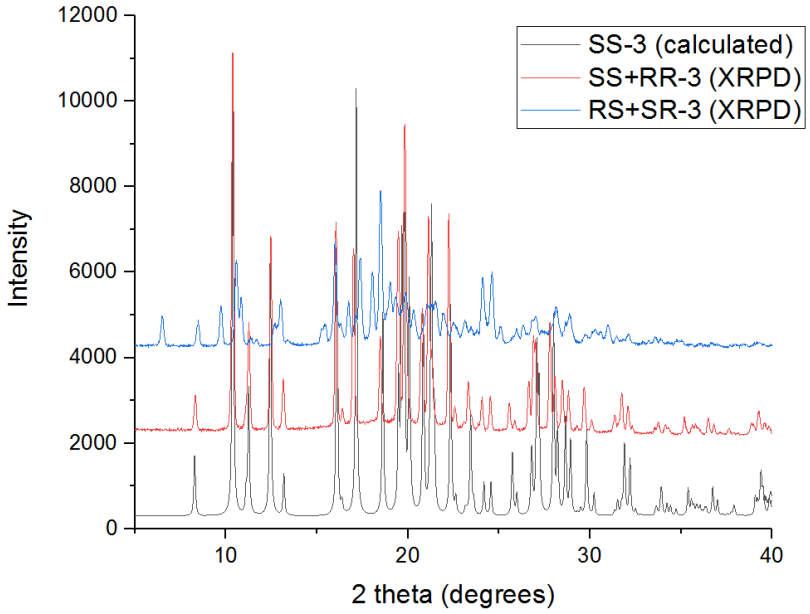


Figure S6.4: Powder diffractograms of the diastereomers of compound 3. For SS-3, the expected pattern based on the newly reported crystal structure is also given.

CD Spectra:

CD spectra were recorded on a JASCO J-815 CD spectrometer. Samples were dissolved (approximately 1mg/mL) in ethanol.

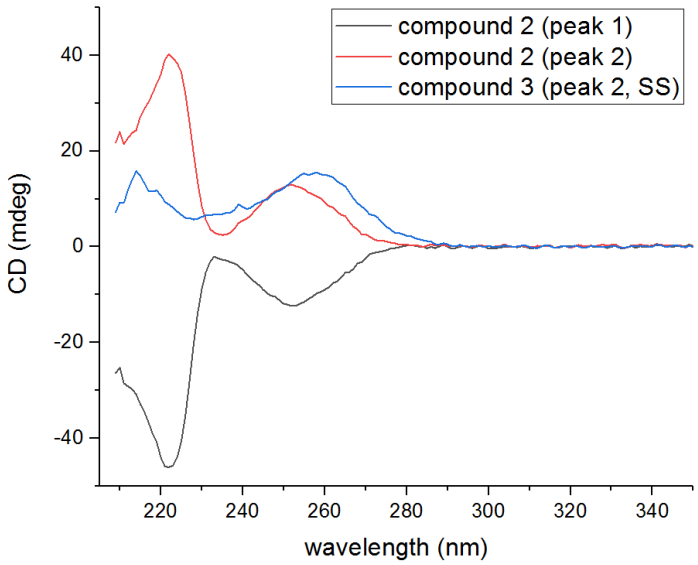


Figure S6.5: CD spectrums of compounds 2 and 3.

Determination of absolute configuration:

For compound **3**, the absolute configuration of the molecule was assigned based on the elucidation of the structure of a single crystal, which was consequently dissolved and run on the chiral HPLC. It was determined that the second peak corresponded to *SS*-enantiomer.

For compound **2**, the absolute configuration could not be determined using X-ray crystallography. By comparison of the CD spectra, which are near identical for compound **2** and **3**, the first HPLC peak was assigned to the *RR* and the second peak to the *SS*-enantiomer.

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Supplemental Information Chapter 7

Ostwald ripening experiments:

Preparation of racemic conglomerate of binaphthyl:

In order to prepare racemic conglomerate **1**, air was blown over a saturated solution of **1** in nonane at 110°C. The blowing of air was continued until all solvent had evaporated. Evaporation had to proceed rapidly to prevent spontaneous resolution.

Ostwald ripening experiments:

A total of 50 mg racemic compound **1**, 50 mg racemic conglomerate **1** and the required amount of additive (10%) were thoroughly mixed. The solid was then added to 1 mL nonane which was already at the required temperature. The resulting suspension was stirred at 300 rpm. After 30 minutes, 0.2 mL of the suspension was extracted using a syringe and was then rapidly filtered. XRPD analysis revealed that in all experiments, the solid contained both conglomerate and racemic compound (in approximately equal amounts). After two days, another sample was taken, which was analyzed by both XRPD and chiral SFC or HPLC.

Attrition enhanced deracemization experiments:

A total of 700 mg racemic compound, 5.5 g glass beads and 8 mL nonane were added to a 10 mL round bottom flask containing an oval PTFE-coated magnetic stirring bar (L 20 mm, Ø 10 mm). The suspension was heated to the required temperature for 30 minutes, after which a mixture of 100 mg racemic conglomerate and 100 or 20 mg additive were added. For sampling, 0.2 mL of the suspension was taken using a syringe and filtered off on a P4 glass filter. Due to the rapid cooling of the sample when extracted using the syringe, additional crystallization of both enantiomers occurred, lowering the observed *ee*.

HPLC analysis:

The *ee* of the samples was determined using chiral HPLC (ADH column, 1% IPA in heptane, flow 1 mL min^{-1}, retention times: (*S*)-(+)-binaphthyl 5.3 min, (*R*)-(-)-binaphthyl 6.7 min.

Racemization kinetics:

A total of 100 mg 97% *ee* (+)-binaphthyl was dissolved in 10 mL nonane. The solution was heated to 70 °C. Samples were taken and immediately cooled to room temperature (to stop racemization), after which the *ee* was analyzed. The racemization rate was calculated at 0.3 min^{-1}, resulting in a racemization half-life of $t_{1/2}$ = 2.3 min (figure S7.1). In a similar experiment, the racemization rate of binaphthyl at room temperature in heptane was determined to be 16 hours (figure S7.2).

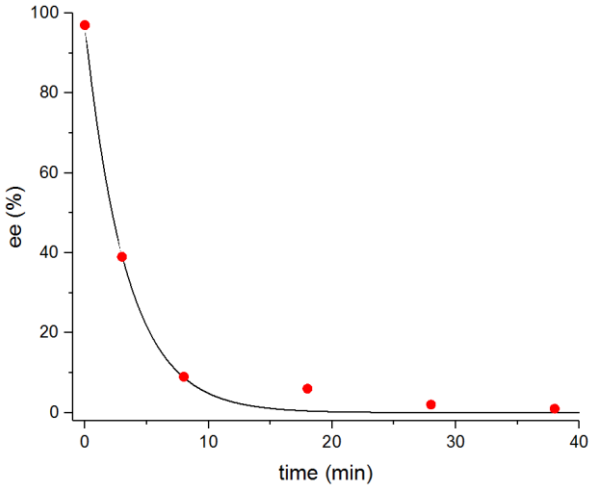

Figure S7.1: Racemization curve of Binaphtyl in nonane at 70°C.

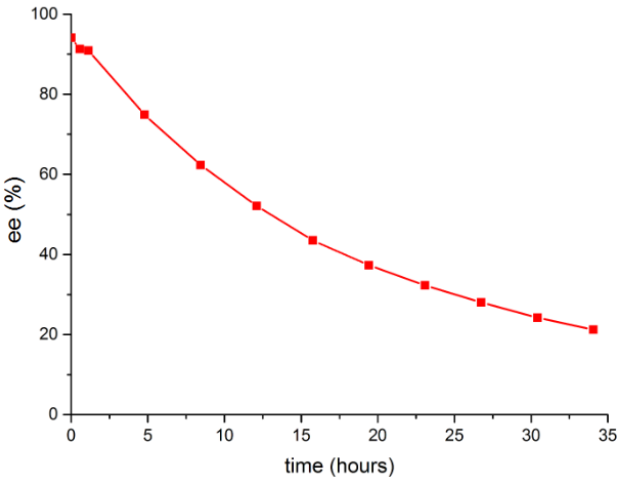

Figure S7.2: Racemization curve of Binaphtyl in heptane at 20°C.

Dankwoord

Ik heb de afgelopen vier jaar als een ontzettend leuke en stressvrije periode ervaren en dat is te danken aan alle mensen om mij heen.

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List of Publications

A. H. J. Engwerda, R. Maassen, P. Tinnemans, H. Meekes, F. P. J. T. Rutjes and E. Vlieg
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