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ARTICLE TYPE

The Racemate-to-Homochiral Approach to Crystal Engineering via Chiral Symmetry-Breaking

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The racemate-to-homochiral approach is to transform or separate the racemic mixture into homo chiral compounds. This protocol, if without an external chiral source, is categorized into chiral symmetry-breaking. The resolution processes without chiral induction are highly important for the investigation on the origin of homochirality in life, pharmaceutical synthesis, chemical industrial and material science. Besides the study on the models and mechanisms to explain the racemate-to-homochiral approach which may give the probable origin of homochirality in life, the recent developments in this field have been plotted towards the separation of enantiomers for the synthesis of pharmaceuticals, chiral chemicals. Direct synthesis of chiral metal-organic-framework (MOF) coordination polymers has been achieved as well. In this highlight, we will enclose comparison of spontaneous resolution and chiral symmetry-breaking resolution, are describing the evolution of models and mechanisms for chiral symmetry-breaking resolution and its applications in enantiomer resolution and material science.

1. Introduction

Since the days of Biot[1] and Pasteur (Figure 1),[2] chirality has become increasingly significant across a spectrum of disciplines among chemistry, material science, biology (especially the origin of the life) and the pharmaceutical industry. Chiral molecules consist of enantiomers which are stereoisomers. Enantiomers are nonsuperimposable mirror images and designated by classical notations as *d* or *l*, as *R* or *S*, or as (+) or (–).[3] As the experiments were carried out for the study of the chemical production of sugar and wines, chemist was encountered by the chiral molecules.[2] No answer is found for the question why life is essentially constructed *via* l-amino acids as building blocks. Numerous efforts have been devoted to solving such a fascinating problem.[4-7] There is tremendous interest in producing pure enantiomers for the food, agrochemical and pharmaceutical industries.[8-10] For enantiomers of the same substance, it has been proved to behave differently in the body or environment, or to be totally different metabolic products in the body being markers of different diseases. The physiological effect of the two enantiomers can be markedly different, and in many cases, the other enantiomer has no effect or is even harmful.[11-13] Regulators increasingly demand that chiral drugs are administered in an optically pure form.[14-15] The development of protocols for manufacturing chiral chemicals has been intensively stimulated in industrial and academic research. The developed approaches can be divided into two categories: (1) the asymmetric approach towards the synthesis of just one of the enantiomers; (2) the racemate-to-homochiral approach based on separating mixtures of the two enantiomers.

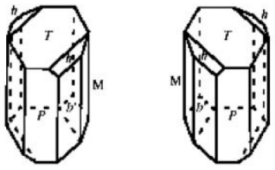


Fig. 1 Pasteur's simplified drawing of sodium ammonium tartrate.

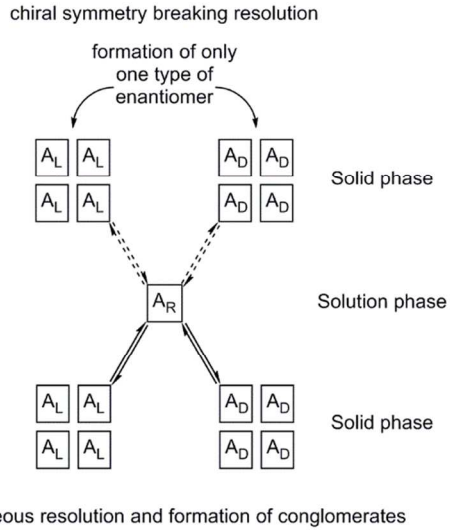
Among the approaches for enantiomer resolution, crystallization processes, as a racemate-to-homochiral approach for separation of enantiomers first reported in 1849,[2] have been widely investigated. Crystallization techniques generally are widely applicable, simple, and cost-efficient with the requirement of only standard equipment in the pharmaceutical and fine chemical industries. Despite a "low-tech-image" for crystallization processes in comparison to the asymmetric synthesis and chromatographic separations, it becomes apparent that the majority of drugs are produced by classical resolution, that is, crystallization, when reviewing manufacturing methods that are empolyed to provide pure enantiomer drugs,.[16]

The racemate-to-homochiral approach via crystallization are commonly sorted into four types: classical resolution, preferential crystallization, optically active solvent method and chiral symmetry-breaking resolution.[17] In a classical resolution of the racemate to be resolved is converted with a suitable enantiomerically pure resolving agent to provide two diastereomeric salts which are of different solubilities and, thus, are separable by crystallization. This technique has the advantage of being robust and simple to operate, but additional chiral sources are required. Similarly, another method by chiral sources assistance is the optically active solvent required. It was applied

in several cases to use the chiral solvents as the chiral induction source, resulting in the enantioselective crystallization.[18b, 19] To avoid external chiral sources for chiral induction, the challenging chiral symmetry-breaking resolution was developed. In this highlight, we are presenting the correlation between this chiral symmetry-breaking resolution and spontaneous resolution, evolution of its models and mechanisms, recent developments applying this protocol to the enantiomer separation and synthesis of chiral materials.

2. Spontaneous resolution, preferential crystallization and chiral symmetry-breaking resolution

Normally, when a racemic mixture is condensed it may form (i) a racemic compound, in which both enantiomers are present in the same single crystal; (ii) a conglomerate, in which the single crystals contain only one enantiomer, but the sample as a whole is racemic; and (iii) a solid solution, in which the condensate contains the two enantiomers in a non-ordered arrangement. Spontaneous resolution occurred when a conglomerate is condensed from the racemates (Scheme 1). However, only 5 to 10% of the chiral substances with known crystal structure belong to this type.[20] Both the preferential crystallization and the chiral symmetry-breaking resolution are based on such conglomerate formation behavior. The preferential crystallization of racemates is only feasible when the enantiomers in their mixtures form conglomerates, and two techniques of the resolution can be distinguished as the entrainment process and simultaneous crystallization.[18, 20a] For entrainment, seeding chiral pure enantiomer is required. Although the simultaneous crystallization can be achieved in Pasteur's way manually, the most of recent protocols involving preferential crystallization are carried out in the manners which requires seeding with pure chiral crystal of both enantiomers.



Scheme 1 Spontaneous resolution and chiral symmetry breaking resolution.

Notably, chiral symmetry-breaking resolution results in the crystallization of only one of the enantiomers from the racemates without any external chiral source. (Scheme 1). The requirement of conglomerate behavior for preferential crystallization and spontaneous resolution was accessible to the symmetry-breaking resolution as well. However, unlike the formation of the conglomerate, the formation of single enantiomer from one batch is the typical character for such process.

3. Evolution of models and mechanisms

Chiral symmetry breaking, as a concept, is coined to represent that a physical or chemical process, with no preference for the production of one enantiomer or the other, spontaneously generates a large excess of single enantiomers: left-handed (L) or right handed (D). Chiral symmetry-breaking resolution has been connected to a "parity-violating difference" between enantiomers. During the course of investigating the life origin and the homochirality in the life materials, pioneer works on chiral symmetry-breaking resolution of organic molecule were reported in 1950s.[21] However, the mechanism remained unclear for the resolution until the landmark work by Kondepudi in the field which disclosed that chiral crystals might randomly crystallize in a homochiral phase macroscopically through a chiral symmetry-breaking resolution.[22] A mechanism involving autocatalysis with secondary nucleation was proposed and statistical bimodal distribution was characterized as the feature of the process. In this section, we are describing the evolution of the mechanism explanation for symmetry-breaking resolution by the discussion of the inherent origin, Frank model, Kondepudi model (nonequilibrium system, secondary nucleation and suppression) and Viedma ripening. Although several mechanisms or models are concluded from the investigation of achiral compounds, it can be directly applied in the resolution of chiral enantiomers.

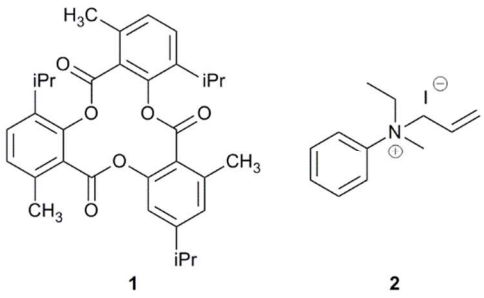
3.1 Debates on the basic level of chiral symmetry-breaking

Before we go any further, a few comments about the inherent handedness of matter are unavoidable. Up to now, electromagnetic, gravitational, strong and weak interactions are believed to be the only basic forces in nature. Although the fact that biologically relevant molecules exist only as one of two enantiomers has been recognized as the fascinating example of complete symmetry breaking in chirality, the chiral symmetry breaking, in early days, was believed not to happen in elementary particles and it was thought that nature was symmetric at the atomic level. However, parity violation, namely, a different probability for the occurrence of a process and its mirror image, proposed by Lee and Yang in 1956,[23] was discovered in the weak nuclear force in next year.[24] L-electrons are preferentially formed relative to D-electrons during the β-particles decay of ^{60}Co, which indicates that selective chirality exists at the level of elementary particles.[24] Till late 1960s, it was assumed that such parity violation was confined to nuclear reactions. Later on, another breakthrough was disclosed in the fundamental physics known as the theory which unified the weak and electromagnetic forces.[25] By the foundation of such a theory, the scope of parity violation for the symmetry breaking was extended to the molecule level, concluding that a chiral molecule exists in a lower or higher energy state relative to its enantiomer. The direct implication of these interactions is that there is a parity-violating energy difference between two enantiomers and the parity violation was assumed to be originated from an energy difference between two

species of L- and D-enantiomers. The energy difference between two enantiomers was first suggested by Yamagata as parity-violating energy difference (PVED).[26] In the proposal, it was postulated that a small reaction rate or binding energies differences between enantiomers caused by PVED could lead to almost complete selection of one enantiomer during millions of years of evolution.[26] Unfortunately, the magnitude of the PVED between enantiomers is too small to be measured experimentally, and numerous efforts have been carried out to estimate this magnitude theoretically. The values have ranged from 10^{-5} to 10^{-10} for the crystal lattice energies[27, 28] and 10^{-14} for amino acids.[29] Further experiments on atomic level showed the optical rotations of a few atoms .[30, 31] Amplification mechanisms by factors of about 10^{14} were suggested to explain the observed homochirality of molecules and theoretical bases are built up for the chiral symmetry-breaking.[32] Despite the support from the theoretical and preliminary experiments, precise experiments are still on demand to end the debate.

3.2 Early study of life and homochirality origin and Frank model

Even before debating and investigating the chiral symmetry breaking of elementary level in 1956,[23, 24] the study on molecule level was already performed both experimentally and theoretically.[21] As the condensation of the solution of organic molecule trithymotide **1**[21b] or the chiral quaternary ammonium salt **2**,[21c-21f] one could randomly obtained homochiral crystals from single batch (Structures see Scheme 2). As in later cases, the chiral quaternary ammonium salt **2** was preferentially obtained in (+)-crystal form rather than (–). Such a racemate-to-homochiral process was not induced by any chiral sources and attention was attracted that this might be a path for origin of the chirality in the life.



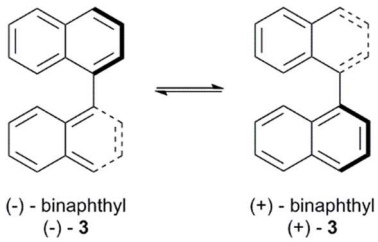
Scheme 2 trithymotide **1** and chiral quaternary ammonium salt **2**

In 1953, to settle a debate on the asymmetric synthesis giving rise to the chirality of living matter, Frank proposed the model chiral amplification via autocatalysis.[21c] Frank started with a simple life model containing only two sets of autocatalysis for two enantiomers. Two sets of reaction rate equation could be built up and the transformation of the mathematic equations afford Frank's idealized model. The assumed conditions for the model corresponded to a well-mixed system, such as a laboratory flask. The autocatalysis of each enantiomer catalyzed its own production, while suppressing that of its mirror image. Such nonlinear dynamics was concluded to originate the amplification of small initial fluctuations in the concentrations of the enantiomers. When applied in a large imperfectly mixed system, like an ocean, by considering formation of colonies for each enantiomers, diffusion at the boundary surfaces between the colonies, and several other effects, Frank proposed that the principles considered above should generally apply as well. Frank concluded that spontaneous asymmetric synthesis is a natural property of life *via* simpler autocatalytic systems and a laboratory demonstration may not be impossible. Although Frank's model might be too idealized for the origin of life, the racemate-to-homochiral approach *via* chiral symmetry-breaking crystallization at lab scale would benefit from such autocatalysis.

3.3 Primary nucleation, secondary nucleation, suppression and nonequilibrium system

Although already equipped with Frank's autocatalysis, the most results in crystallization of racemic mixture produce a racemate or a conglomerate. This phenomenon can be attributed to the following theory.

Crystal growth takes advantage of the statistical fluctuations in a system where crystallization of a left-handed crystal acts as a seed and causes other crystals nearby to be left-handed also. This chiral primary nucleation is the origin of the spontaneous resolutions.[33] However, the crystals with both left and right handness will precipitate simultaneously, if without any suppression. Such a chiral primary nucleation would at most result in a resolution of racemate into a conglomerate. Therefore, the occasional symmetric breaking was rationalized by the statistical fluctuations.



Scheme 3 Racemization of 1,1'-binaphthyl **3**

In 1971, the careful statistical study on 1,1'- binaphthyl **3** by Pincock et al. showed a distribution that is close to a Gaussian with a mean of 50% (Figure 2).[34] The results proved chiral primary nucleation for the crystallization. Upon the melting temperature, 1,1'-binaphthyl racemized quickly (Scheme 3). The process gave different rotation value per batch. These experiments clearly showed that the two enantiomorphs will be found in equal proportion; any deviation from chiral symmetry is a result of statistical fluctuation (Figure 2). Although further investigation revealed a preferential crystallization process towards random single enantiomer, careful examination of the probability distribution was not carried out afterwards.[35] The experiments by Richard E. Pincock's group revealed that racemic binaphthyl may be resolved spontaneously into crystals with different enantiopurity level and there are no confidential evidence that the chiral symmetry-breaking occurred in their experiments. Regrettably they got the chiral symmetry-breaking results in the later cases but no further examination was carried out. It could be attributed to the fact that there were still a big gap between the connection of theory and experiment concerning chiral symmetry-breaking resolution till that moment.

Following the path of Frank's model, the efforts have been made to revel a clear picture of how a chirality symmetry-breaking occurs by Kondepudi et al.[36] In 1990, a landmark work on the chiral symmetric breaking resolution was reported by Kondepudi et al. [22] A systematic probability distribution scheme was investigated as well (Figure 3). The intrinsically achiral $NaClO_3$ crystallizes in the chiral space group $P2_13$ and forms a conglomerate. A statistically equal number of (+)- and (–)-$NaClO_3$ crystals are obtained from an unstirred solution, however, instead of crystallization from stagnant or gently agitated solution, in their case efficient stirring resulted in the formation of an enantiomerically pure solid phase of random absolute configuration. A bimodal probability distribution is obtained as B-type column distribution shown in Figure 3 rather than the Gaussian of A-type column one in the Figure 3. A plausible mechanism was proposed by Kondepudi et al. for this symmetry-breaking resolution as below.

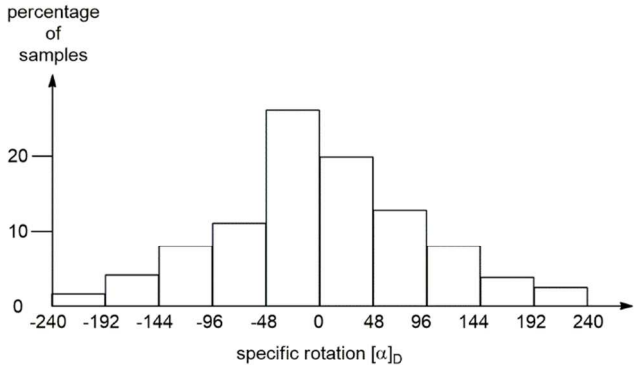


Fig. 2 The Gaussian type distribution of rotation value for resolution of 1,1'-binaphthyl.

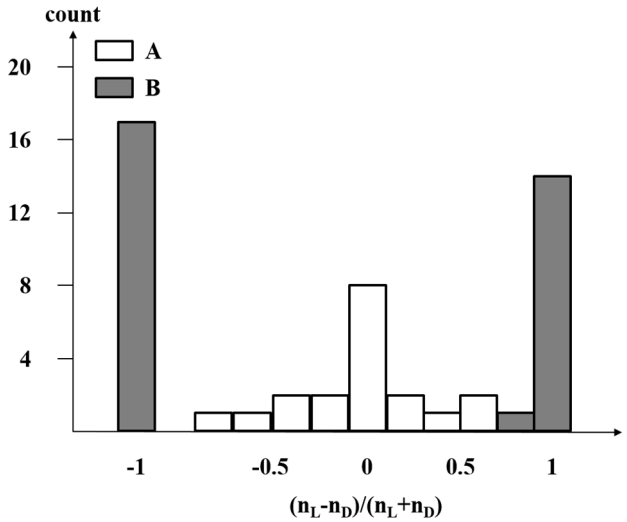


Fig. 3 Ddistribution of rotation value. Frequency distribution for crystal enantiomeric excess shown in A-type column for the unstirred and in B-type column for the stirred experiments; n_L and n_D, are the number of L- and D-crystals, respectively, in a particular experiment.

As we discussed above, the chiral primary nucleation without suppression results at most in a racemate-to-conglomerate approach. The previous preferential crystallization to give homochiral crystals is induced by external chiral sources. In Kondepudi's case, they proposed autocatalytic secondary nucleation with suppression. The rapid production of secondary nuclei from a primary nucleus in stirred systems was assumed to be involved and the process was proposed to be chirally autocatalytic. Additionally, the suppression of nucleation of crystals of the opposite handedness is also required for the resolution to assist the secondary nucleation. A non-stirring experiment was carried out to test the effect of suppression. The primary nucleation produced crystals of both kinds in crystallization performed without stirring in 4 to 5 days. They proposed that the depletion of the solute from the solution results from the growth of the primary nucleus and the secondary nuclei that were rapidly generated from it could reduce the concentration to a level at which the rate of primary nucleation is virtually zero. As a result, the growth of single handness crystal suppressed all primary nucleation and the formation of the nuclei of the opposite handedness. Thus, the only nuclei that grow are the initial nucleus of certain handedness. Furthermore the resulting whole batch of the crystals bears the same chirality of the initial nucleus through the secondary nucleation and suppression.

Their experiment was reproducible and could even be videotaped.[37] In the videotape, one could note that the process began with a single crystal and massive crystallization took place when the single crystal first contacted the stirring bar. In the later research by Kondepudi and cowokers, both the stirring rate and the size of the nucleating crystal were found to be crucial for the distribution of enantiomeric excess.[38]

In 1997, a theory on mechanism of secondary nucleation was proposed by Qian and Botsaris.[39] Noting that forces between clusters and surfaces of crystals can lead to higher nucleation rates, they proposed that high chiral selectivity at a low supersaturation and lower selectivity at higher supersaturation might be attributed to a shift in the nucleation rates in the vicinity of a chiral surface. Chiral selectivity arose because L and D nucleation rates shifted by different amounts. They believed that there should be a supersaturation range in which only the L nuclei are produced in the vicinity of an L crystal surface, but both L and D nuclei are generated at higher supersaturation.

Further concise picture of the chiral symmetry-breaking resolution of $NaClO_3$ was discussed in a review by Kondepudi and Asakura.[40] At thermodynamic equilibrium, there can be no symmetry-breaking of chirality, however, in nonequilibrium systems a state of nonzero enantiomeric excess (ee) can spontaneously arise from an achiral or a racemic state through a chiral-symmetry-breaking transition. They concluded that the chiral symmetry-breaking resolution might occur if the racemic system would form a conglomerate and the bimodal probability distribution (B-type column distribution as shown in Figure 3) is a clear signature of a symmetry-breaking resolution.

3.4 Viedma ripening

Besides Kondepudi's landmark work on direct crystallization of $NaClO_3$, complete symmetry breaking and chiral purity was achieved from an initial system where crystals of both enantiomers were present since the beginning from racemate crystal to homochiral crystal phase.[41] Such a process, reported by Viedma, was named as attrition-enhanced deracemization or Viedma ripening. Experiments have showed how a solution of $NaClO_3$ with a large population of L- and D-crystals moved into

complete chiral purity: instead of stirring, another mechanical force, abrasive grinding with glass beads, yielded the random dissolution of the crystals for single enantiomers. The distribution of the probability to obtain homochiral crystals was bimodal type one, which indicated that a symmetric breaking event occurred in the abrasive grinding. Viedma concluded that (i) any small initial crystal enantio excess (ee) eventually gives rise to total crystal purity with the less abundant enantiomer disappearing; (ii) "symmetric" proportion of both enantiomeric crystals (a 50-50 mix of chiral crystals) gives rise to total symmetry breaking and crystal purity with one of the two enantiomers disappearing randomly. Instead of Kondepudi's solution-to-homochiral crystal process, Viedma presented a new process of chiral symmetry-breaking resolution from conglomerate to homochiral crystal form.

During the further investigation on preferential condensation by Viedma, both stochastic and non-random cases were found at Viedma ripening. After a careful examination, conclusion was drawn that the selective chiral symmetry breaking on a macroscopic level was attributed to the cryptochiral environmental impurity.[42] As previously reports on the chiral amplification were numerous,[43a-f] Viedma argued that during the process, any small initial crystal enantio excess (ee) will eventually gave rise to total crystal purity with the less abundant enantiomer disappearing which was named as the "cryptochiral environmental impurity".[43g]

A more clear picture of chiral symmetry-breaking resolution would be drawn from the investigation of the Viedma ripening by Viedma, Blackmond, Vlieg and Kellogg et al.[41, 42, 43c-43f] Employing Kondepudi's and Viedma's model, it should be a dynamic process of crystal dissolution and growth enhanced by attrition or stirring. According to the Gibbs−Thomson rule, smaller crystals dissolve more readily than larger ones. Thus, the large crystals grow at the cost of smaller ones regardless of their handedness in a saturated solution. A small imbalance in the handedness of large compared to small crystals may occur because of a small initial enantiomeric excess or may be induced by minute amounts of chiral species present in the solution. The continued fragmentation of crystals by attrition or stirring also provides a relative increase in the surface area of the hand that has established an excess. The continuous grinding or stirring of the solid enantiomorphs creates the essential solubility gradient for the dissolution and recrystallization processes that drive the system until all the solid material of one enantiomer is converted to the solid of the opposite hand. Once a state of single chirality is achieved, the system is "locked", because primary nucleation to form and sustain new crystals from the opposite enantiomer in the racemizing solution is kinetically prohibited under the conditions of the experiments (In Viedma ripening).

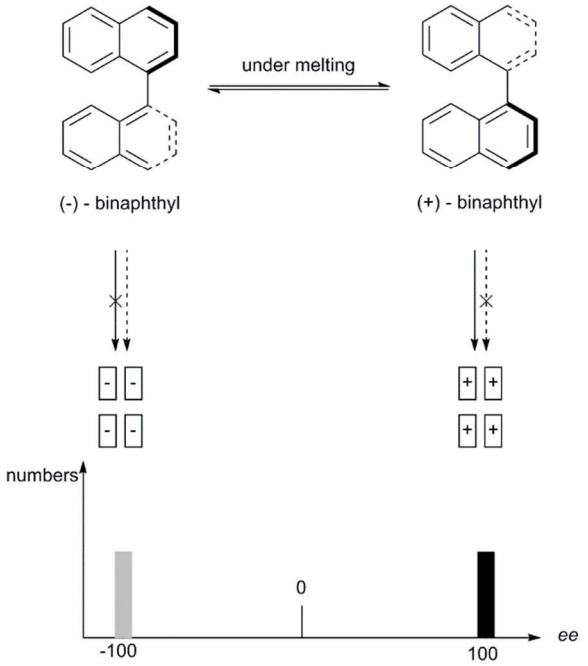
4 Applications

Although the discussion in section 3 are mainly focused on the achiral to chiral crystal phase, all the models and mechanisms, such as autocatalysis, secondary nucleation, nonequilibrium system, bimodal probability distribution and Viedma ripening, can be applied to racemate-homochiral approach with chiral symmetry-breaking. With this special racemate-to-homochiral approach, one can separate the enantiomers efficiently or even, with racemization process, obtain the 100% homochiral enantiomer from racemates. (See section **4.1**) As for the material science, the homochiral metal organic frameworks (HMOF) can be direct synthesis by crystallization from the racemic mixture. (See section **4.2**)

4.1 Racemate-to-homochiral approach for separation of the enantiomers *via* chiral symmetry-breaking

Intriguing by Kondepudi and Viedma, chemists have achieved great developments for racemate-to-homochiral approach *via* chiral symmetry breaking resolution of racemates to enantiomer.

In section 3.2, we have already mentioned that trithymotide **1** and chiral quaternary ammonium salt **2** can be separated *via* chiral symmetry-breaking resolution. These early work can be dated back to 1950s.[21] However, up to now, there are still few reports on the chiral symmetry-breaking resolution of enantiomers and newly reported systems can be summarized as axially chiral systems,[34, 35, 45] acids with chiral stereogenic center at α-position,[46-49] and isoindolinones[50-51].



Scheme 4 Racemization of 1,1'-binaphthyl and its distribution of ee in the complete resolution.

The first example of resolution for axially chiral systems was reported by Pincock et al. in 1970s (Scheme 3).[34] Although series of work on this resolution of 1,1'-binaphthyl **3** have been carried out to present that the chiral resolution occurred,[34, 35], a systematic investigation of 1,1'-binaphthyl has not carried out by Kondepudi utill 1999 (Scheme 4).[44] As a supercooled melt at 150 ^{o}C, the chiral compound 1,1'-binaphthyl racemizes rapidly, and solidifies as a conglomerate of crystals. This melt to conglomerate process and in situ racemization indicate the possibility of chiral symmetry-breaking to afford single enantiomer from racemates through crystallization (Scheme 4). Kondepudi and coworkers revealed that crystallization performed with a 2.00 g sample with *constant stirring* produced a large enantiomeric excess (mean 77%) in almost all crystallization. The effects of stirring, as reported in case of $NaClO_3$,[22] became more

significant for larger samples of 1,1'-binaphthyl and was crucial for this racemate-to-homochiral approach. The predominance of *R*-(-) or *S*-(+) was random as depicted in Scheme 4. As illustrated in Pincock's work,[34, 35] unstirred 2.00 g samples of binaphthyl produce a much lower enantiomeric excess (mean 20%) with Gaussian type distribution of optical activity. (Figure 3A) They concluded that chiral symmetry breaking resolution of 1,1'-binaphthyl could be realized in crystallization from a melt by the mere act of stirring.

In 2010, a similar axially chiral systems, chiral amidoamine **4**, was found to undergo this racemate-to-homochiral approach *via* chiral symmetry breaking resolution as well.[45] Racemic **4**·TFA was synthesized (Scheme 5) and crystallized *via* spontaneous resolution to form a conglomerate (Figure 4). Thus, rather than under melting condition, the process was carried out in an ethanol solution of **4**·TFA and up to >99% ee at ≤15% crystallization was obtained with or without stirring. This might be one of the few cases in which chiral symmetry breaking occurred without stirring. However, a significantly higher median ee was observed with stirring as compared to without it (44% vs. 14%, respectively), which met a Kondepudi's model that an autocatalytic secondary nucleation process suppress further primary nucleation. The produced chiral amidoamine **4** was subjected to catalyze the aldol reaction between substituted benzaldehydes and acetone in a limited stereoselective control.

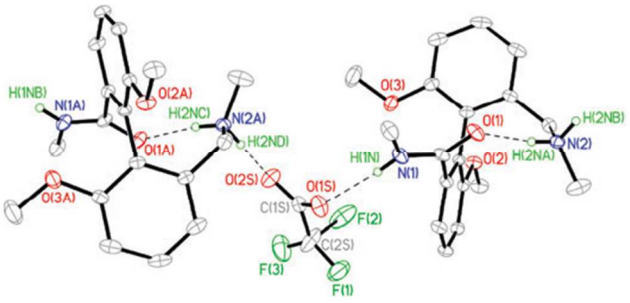
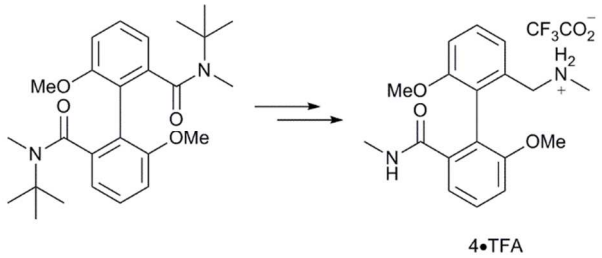


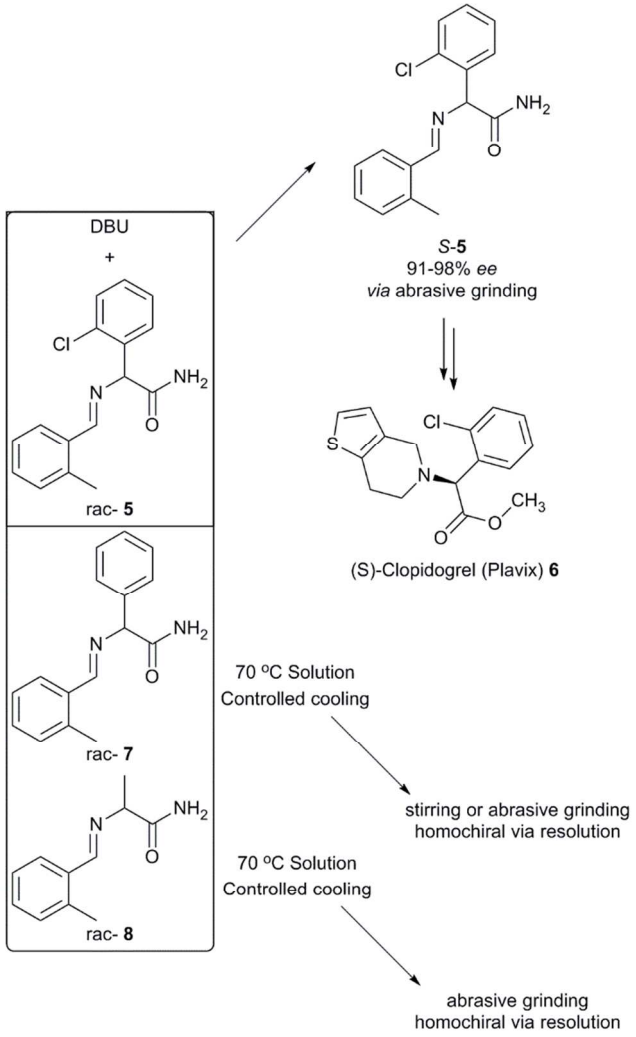
Fig. 4 ORTEP diagram for amidoamine **4**·TFA conglomerate showing a bridging trifluoroacetate anion between two homochiral biaryl cation units. 50% probability ellipsoids are plotted for non-hydrogen atoms. Reprinted with permission from ref. 45. Copyright 2010 the Royal Society of Chemistry.



Scheme 5 Synthesis of chiral amidoamine **4**·TFA.

This racemate-to-homochiral approach via chiral symmetry-breaking, when applied in the separation of enantiomers, required the formation of conglomerate from racemates. By variation of different substitutions, the conglomerate behavior can be modulated and the formation of conglomerate can be achieved. It is, now, a technique for the design of molecules that undergo chiral symmetry-breaking resolution and several examples will be presented in this aspect.

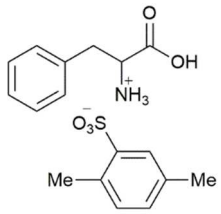
Several amino acid derivatives can be resolved *via* chiral symmetry-breaking resolution as well.[46-48] In 2009, a racemate-to-homo approach towards synthesis of the blockbuster drug, Clopidogrel (Plavix) **6**,[46a] has been reported which originated from the previous investigation on chiral amplification of the same and similar systems[43c-43d] (Scheme 6). A systematic examination was carried out to study the conglomerate behavior of different imine type derivatives of 2-chlorophenyl glycine *via* second harmonic generation measurement. Only imine type derivative **5** crystallized in chiral space group $P2_12_12_1$ and showed conglomerate behavior.



Scheme 6 Amino acid derivatives **5** and **6** and the procedure for their complete resolution.

Imine **5** was racemized by 10mol% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol with $t_{1/2}$ < 2 min. Thus, an in situ racemization with racemate-to-homochiral resolution was planned. The abrasive grinding, known as Viedma ripening, with and without seeding of the enantiopure compounds gave a complete conversion of the racemate of imine **5** into *S*-**5** and the (*S*)-enantiomer was obtained five times from five experiments. Consequently, complete resolution of amino acid derivative **7** was achieved from racemates by Kellogg and coworkers (Scheme 6).[46b] Controlled cooling and abrasive

grinding were combined during the crystallization of conglomerate **7** under racemization conditions starting from a homogenous solution. Racemization in solution was catalyzed by DBU and complete resolution occurred either with abrasive grinding or stirring. By carefully controlling cooling rates, the *ee* of **7** can be achieved as high as >99%. Similar protocol with cooling rate at 0.05 $^{o}C{\cdot}min^{-1}$ and abrasive grinding afforded the alanine derivative **8** in >99% *ee* as well. The protocol gave an access to provide the intermediate for the blockbuster drug, Clopidogrel (Plavix) as well. Following studies on non-random cases for resolution of **7**, like example of **5**, [46a] have been attributed to the chiral impurity effect. [47]



Scheme 7 Structure of amino acid salt **9**

Instead of the imine type derivatives, Vlieg et al. disclosed that amino acid salts **9**, phenyl alainine 2,5-xylenesulfonate (Phe-XSA, structure see Scheme 7), would undergo a complete resolution offering the enantiomer.[48] Different amino acid sulfonates were examined for their conglomerate behavior. Phe-XSA crystals were grown from racemic phenylalanine and the structure was determined using single crystal X-ray diffraction (Figure 5). The structure exhibits the typical double layers containing hydrophilic H-bonds and hydrophobic van der Waals interaction between the benzene rings (see Figure 2). Phe- XSA has a monoclinic space group. (C_2, a = 21.6898(3) Å, b = 5.2152(9) Å, c = 18.2370(15) Å, β = 125.000(6)°) In their experiments for Phe-XSA, all 10 racemically started experiments resulted in a left-handed final state and they rationalized this phenomena to the very small amount of chiral impurity induction as suggested by Viedma.

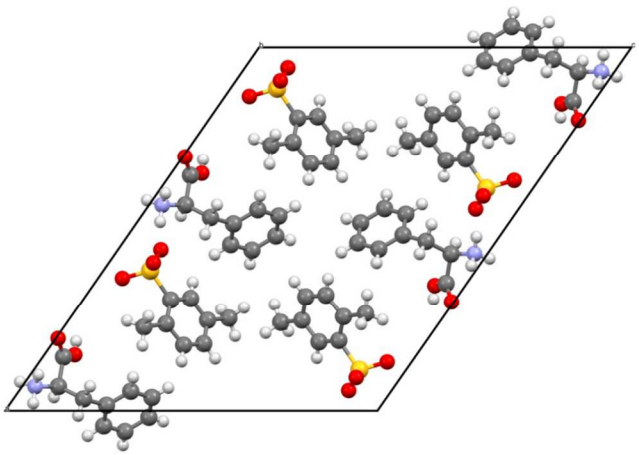
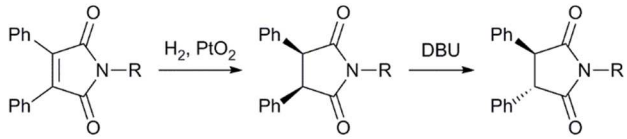


Fig. 5 Single crystal X-ray diffraction structure of phenylalanine-pxylenesulfonate **9** viewed along the b-axis. Reprinted with permission from ref. 48. Copyright 2014 American Chemical Society.

Another example of acids with chiral stereogenic center at α-position had been reported by Sakamoto et al. in 2013.[49] 11 derivatives of achiral *trans*-3,4-diphenylsuccinimides **12** were synthesized in which only 3 of them, **12d**, **12e** and **12i** could form conglomerates *via* spontaneous resolution. As a result, **11d** and **11e** were tested in situ isomerized and racemized by DBU that optically active *trans*-3,4-diphenylsuccinimides were obtained by dynamic crystallization. (up to 97% ee) As **11i**, upon formation during the reduction, it was transformed into **12i**, and the latter was further direct subjected to the crystallization conditions above, giving the homochiral *trans*-3,4-diphenylsuccinimides in up to 98% ee. In the above protocols, resolution with deracemization yielded single enantiomers. This general protocol of complete resolution with deracemization is efficient to provide the enantiopure form of chiral compounds and the in situ racemization was thought to be another force that promoted the racemate to homochiral approach *via* chiral symmetry-breaking.[43c-43e]



10 **11** **12**

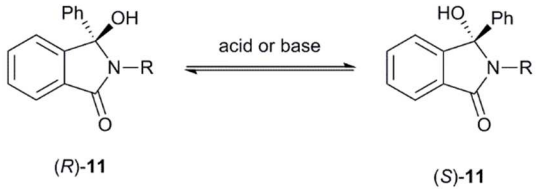
a: R=H; b: R=Me; c: R= Et; d: R= Pr; e: R= *i*-Pr; f: R=CH_2Ph; g: R=CH_2CH_2Ph; h: R=Ph; i: R= 2-MePh; j: R= 3-MePh; k: R=4-MePh

Scheme 8 Synthesis of *trans*-**12** from **10**

Total spontaneous resolution by deracemization of isoindolinones **13** have been achieved by Sakamoto et al. as well. [50] By variation of the substitution on the *N*-atom of amide, the conglomerate behavior of 6 derivatives was tested. The crystal structure of **11c** was reported with the chiral space group $P2_12_12_1$.[51] Recrystallization of the other isoindolinones in a chloroform–hexane solution afforded **11d** and **11f** in the chiral space group $P2_12_12_1$. By controlling the rates of racemization and crystallization, the optimized conditions of the concentration of **11** and the catalyst for the resolution were set up. Each compound of **11c**, **11d** and **11f** was efficiently racemized in the presence of DBU, and the enantiomer was obtained in quantitative recovery rates and with excellent *ee* values. In their work, only stirring is required for the chiral resolution and attrition-enhanced deracemization didn't work well under their conditions due to the inefficient deracemization. Further work by Vlieg, Rutjes and coworkers demonstrated that deracemization of isoindolinones using Viedma ripening was possible starting from a racemic mixture of conglomerate crystals.[52] Thus, a complete resolution through Viedma ripening was achieved on this isoindolinones system. These protocols may access a new methodology towards the synthesis of this key building block of the nature products.

Table 1 Space groups of 3-hydroxy-3-phenylisoindolin-1-ones **11a–f**

Isoindolinone	R	Space group
11a	Me	*C*2/c
11b	Et	racemic
11c	Pr	$P2_12_12_1$
11d	*i*-Pr	$P2_12_12_1$
11e	$PhCH_2$	$P\bar{1}$
11f	$PhCH_2CH_2$	$P2_12_12_1$



(*R*)-**11** (*S*)-**11**

Scheme 9 Racemization of **11**.

4.2 Racemate-to-homochiral approach for synthesis of chiral MOF materials *via* chiral symmetry-breaking

In addition to the separation of the enantiomers for the pharmaceutical and chemical industries, direct synthesis of chiral materials to study their nonlinear properties is of great importance as well. This direct synthesis of chiral materials through racemate-to-homochiral protocol without external chiral sources would result in a very efficient manner, because the chiral sources of the compounds are costly and rare. However, scarce examples have been reported on this type of synthesis.[53,54] Below are some examples which have been reported recently.

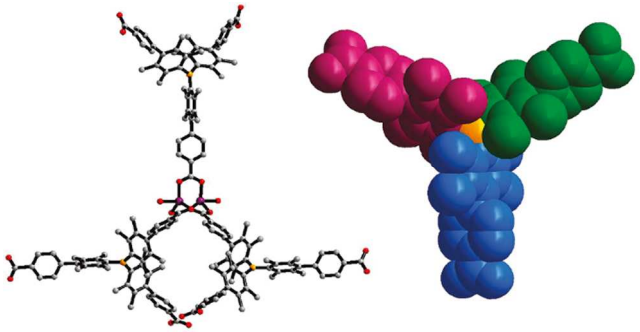


Fig. 6 (left) $[Co_2L(OH)(MeOH)]$ building block in **13a**. The disordered CH_3 group of methanol has been omitted for clarity. Color code: Co, purple; B, yellow; O, red; C, gray. (right) Space-filling model of the L ligand. Reprinted with permission from ref. 53. Copyright 2009 American Chemical Society.

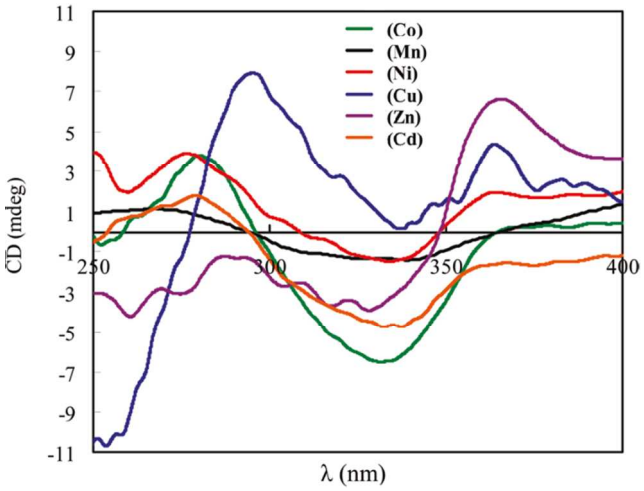
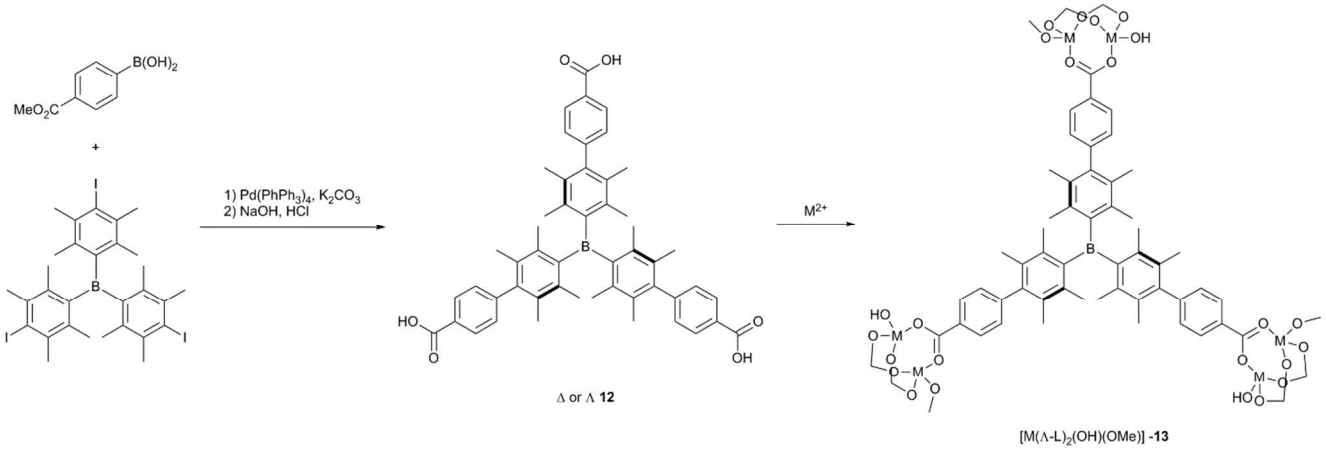


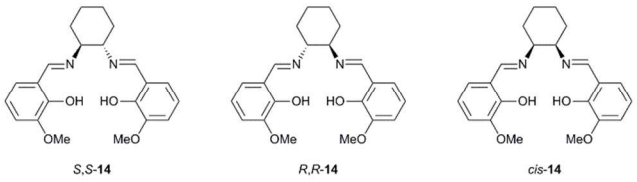
Fig. 7 Solid-state CD spectra of **13a-13f**. Reprinted with permission from ref. 53. Copyright 2009 American Chemical Society.



Scheme 10

In 2009, Cui et al. reported the synthesis of a series of homochiral octupolar metal-organoboron frameworks **13** with the general formula $[M_2L(OH)(MeOH)]_3 \cdot 3H_2O$ [M = Co (**13a**), Mn (**13b**), Ni (**13c**), Cu (**13d**), Zn (**13e**), Cd (**13f**)] (Scheme 10).[53] The MOF **13** was constructed from racemic C_3-symmetric tris(4-benzoic acid)tridurylborane and the divalent metal ions *via* solvothermal manner. Complexes **13a-13f** are isostructural and crystallize in the chiral cubic space group F432. By adopting an eightfold-interpenetrating (10,3)-a network formed by linking bimetal building blocks with three bidentate carboxylate groups

of bridging Λ-L ligands, they underwent a symmetry-breaking event to involve only Λ-type ligands in the structure (Co complex **13a** as an example in Figure 6). To ensure that the bulk crystals of each of the six compounds are not a racemic mixture, the solid-state circular dichroism (CD) were tested, indicating the homochirality of each complex. Consistent with their polar structures, the colorless complexes **13e** and **13f** exhibit powder second harmonic generation intensities 3-4 times higher than that of potassium dihydrogen phosphate, making them the first two examples of NLO-active, homochiral octupolar metal-organic solids.



Scheme 11 Structures of different isomers of **14**

A classic chiral ligands, salen **14**, was accessible to the complete resolution *via* direct crystallization and the separation of enantiomers and diastereomers by metal organic framework (MOF) have been reported recently by Li, Yan and coworkers (Scheme 11).[54] By introducing NH_4PF_6 as counterions, a homochiral complex **15**, $\{[Ce(H_2L)_2(NO_3)_2]\cdot(PF_6)\cdot 2CH_3CN\}_n$, with unique quartz 3D topological structure has been isolated *via* the conventional diffusion method (Figure 8 and Figure 9).[54a] The complex crystallizes in space group *P6₄22*. In this complex, each Ce(III) ion connects four neighboring Ce(III) ions via four salen type ligands with the Ce⋯Ce distance of 10.2848(2) with all salens as *SS*-configuration (Figure 8). While each salen type ligand adopts only a monodentate bridging coordination mode and coordinates to two neighboring Ce(III) ions by its phenol O atom, acting as a bridging ligand. By this linking mode, the structure displays the 3D frameworks. Interesting that in this complex, the structure is constructed by single chiral ligand from racemates, which resulting in the final homochiral frameworks (Figure 9).

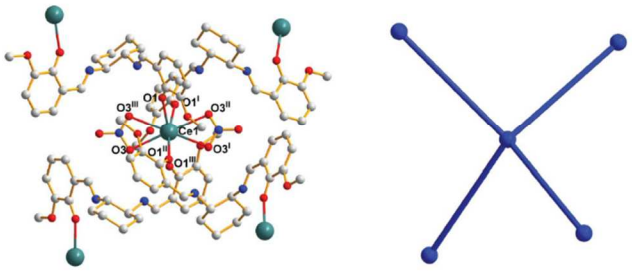


Fig. 8 The coordination environment of Ce(III) ion (left) and the simplified ball-and-stick model (right, the blue lines represent the salen type ligand) in **15** (hydrogen atoms, free PF_6^- ions and crystalline molecules are omitted for clarity). Reprinted with permission from ref. 54a. Copyright 2013 the Royal Society of Chemistry.

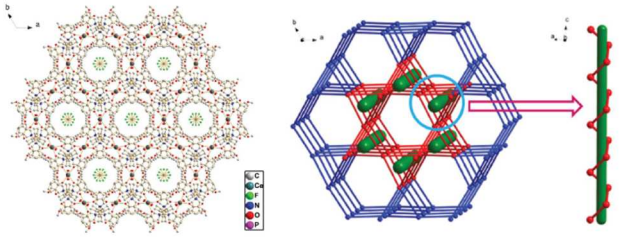


Fig. 9 3D coordination structure of **15** along the c axis (left) and schematic illustration of quartz topology with the Schläfli symbol $\{6^4\cdot 8^2\}$ along the c axis (right, the free PF_6^- ions are omitted for clarity).. Reprinted with permission from ref. 54a. Copyright 2013 the Royal Society of Chemistry.

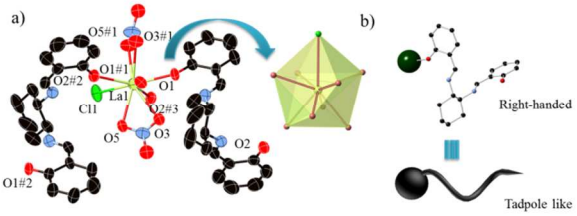


Fig. 10 The crystal structure of **17**: a) the structural unit, #1 y, x, 2-z; #2 0.5-x, -0.5+y, 1.75-z; #3 -0.5+y, 0.5-x, 0.25+z; b) tadpole-like metal-organic subunit. Reprinted with permission from ref. 54b. Copyright 2014 American Chemical Society.

Subsequent careful investigation of similar chiral salen **16** (*N*,*N*'-bis(salicylidene)-cyclohexanediamine) in the synthesis of chiral lanthanide complexes afforded a series of homochiral lanthanide-organic frameworks.[54b] Three homochiral lanthanide-organic frameworks **17**, $\{[Ln(H_2L_{SS})(NO_3)_2Cl]\cdot 2CH_2Cl_2\}_n$ [Ln = La, Ce and Nd, H_2L_{SS}= *trans*-*N*,*N*'-bis(salicylidene)-(1*S*,2*S*)-cyclohexanediamine] have been prepared from racemic salen-type ligand and mixed lanthanide salts by the diffusion method. (Figure 10 and Figure 11). Interestingly, normally reaction conditions without strong mechanical forces would result in a poor resolution result. However, in this case, homochiral complexes were obtained without any stirring or grinding. These complexes are isostructural, crystallizing in the chiral tetragonal space group *P4₃2₁2* adopting an individual *dia* network formed by lanthanide ions and bridging ligand H_2L_{SS}. Additionally, the homochirity of the lanthanide-organic frameworks results in the SHG effects (0.6, 0.56 and 0.56 times compare to KDP).

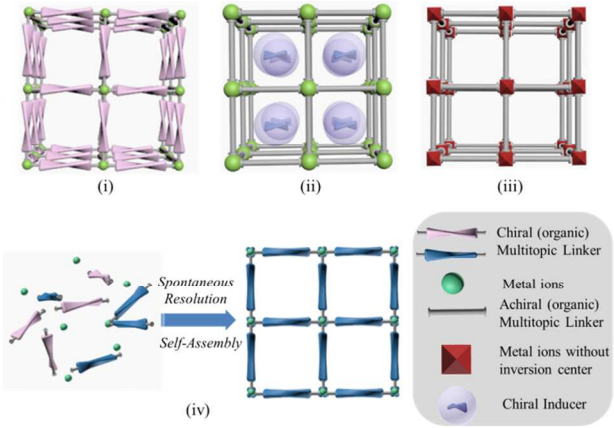


Fig. 11 Prime Methodologies for Assembling HMOFs. Reprinted with permission from ref. 54b. Copyright 2014 American Chemical Society.

In addition to the enantiomer resolution and chiral material synthesis, numerous efforts have been devoted to resolving the homochiral crystal structure from achiral sources, and these results will not be discussed here.[55]

5 Conclusions and outlook

We have highlighted recent developments for the racemate-to-homochiral approach via symmetry-breaking resolution in crystal engineering field.[56] With no external chiral sources, such a resolution occurred to afford homochiral compounds per batch, which required no manual separation in Pasteur's method. The most charming character of this approach would be avoiding the usage of the expensive and rare chiral sources. Generally, a racemate, which may form a conglomerate, is potential system to undergo a chiral symmetry-breaking resolution. Mechanical forces, such as stirring, grinding or even refluxing of the solvothermal manner, would promote the resolution towards producing of single enantiomer per batch. A nonequilibrium system would be maintained by mechanical forces,the secondary nucleation and autocatalysis that removes the small crystals from one handness to another enantiomer. For organic compounds, such racemate-to-homochiral approach *via* symmetry-breaking resolution provided a new path for the racemate resolution and, combing with an in situ racemization or isomerization, over 50% conversion of racemates can be obtained rather than classical resolution or preferential crystallization. Furthermore, the racemate-to-homochiral approach can also be applied in the synthesis of homochiral complexes, for example: metal-organic framework (MOF), from racemate ligands. These resolutions can be proceed either by solvothermal protocol or by the conventional diffusion method. The limitation of this protocol would be the low conglomerate ratios of known crystal structures. However, to control the racemate's conglomerate behaviour, one could synthesize different derivatives of the organic compounds or ligands. Switching certain function groups or branches on the compounds would result in the formation of conglomerate system, which is potential chiral symmetry-breaking precursor. Although the basic mechanism of this field is clear, however, only several reports have been published. It is no doubt that more work on the direct synthesis of chiral materials or drugs in future would be performed in the efficient symmetry-breaking manner from the racemates, and more systems, which can undergo racemate-to-homochiral crystallization, will be disclosed.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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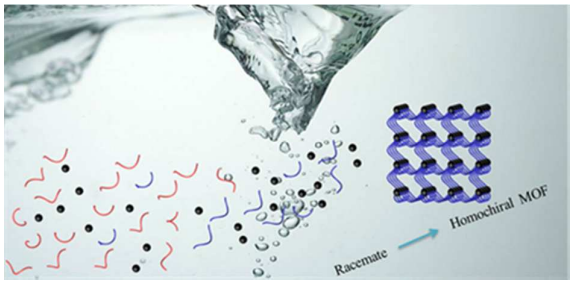

The racemate-to-homochiral crystallization was highlighted for symmetry breaking phenomena by showing clear pictures of mechanism and development history.