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Cocrystallization-Induced Spontaneous Deracemization: A General Thermodynamic Approach to Deracemization**

Michael Guillot, Joséphine de Meester, Sarah Huynen, Laurent Collard, Koen Robeyns, Olivier Riant, and Tom Leyssens**

Abstract: *Processes leading to enantiomerically pure compounds are of utmost importance, in particular for the pharmaceutical industry. Starting from a racemic mixture, crystallization-induced diastereomeric transformation allows in theory for 100 % transformation of the desired enantiomer. However, this method has the inherent limiting requirement for the organic compound to form a salt. Herein, this limitation is lifted by introducing cocrystallization in the context of thermodynamic deracemization, with the process applied to a model chiral fungicide. We report a new general single thermodynamic deracemization process based on cocrystallization for the deracemization of (R,S)-4,4-dimethyl-1-(4-fluorophenyl)-2-(1H-1,2,4-triazol-1-yl)pentan-3-one. This study demonstrates the feasibility of this novel approach and paves the way to further development of such processes.*

With the increasing number of enantiomerically pure chiral drugs developed every year[1] and regulatory instances encouraging the development of enantiomerically pure compounds,[2] processes allowing access to such compounds are of utmost importance. In spite of significant advances in asymmetric synthesis (in particular, asymmetric catalysis), the most prominent way to synthesize enantiomerically pure drugs nowadays still involves the formation of a racemic compound[3] and separation of the unwanted enantiomer through a resolution process,[4–8] or its transformation into the desired enantiomer in a so-called deracemization process. Crystallization-based resolution processes are less costly than, for example, chromatographically based techniques and are therefore industrially widespread. Typical crystallization-based resolution processes are preferential crystallization[9–11] and diastereomeric resolution.[12–14] Going beyond separation, crystallization-based deracemization processes aim at transforming the unwanted enantiomer (distomer) into the desired enantiomer (eutomer). The kinetic processes of Viedma ripening (VR)[15,16] and dynamic preferential crystallization (DPC)[17] require a conglomerate-forming racemate and are therefore inherently limited to 5–10 % of all compounds. Crystallization-induced diastereomeric transformation (CIDT),[18,19] on the other hand, is a thermodynamic approach based on the differences in solubility between two diastereomeric salts and does therefore not require the formation of such a conglomerate.

As highlighted by a 2006 literature review, CIDT can only be performed on salt-forming compounds, with the vast majority of studied systems combining a carboxylic acid with an amine.[20] For nonsalifiable compounds, to the best of our knowledge, no thermodynamically based deracemization method has been reported, thus leaving no viable option for the deracemization of many racemizable compounds. Herein, we introduce such a method based on cocrystallization that expands the scope of thermodynamically based deracemization processes to all racemizable compounds (Scheme 1). Cocrystallization typically relies on strong intermolecular interactions, such as hydrogen and halogen bonding,[21] which are more universal. Cocrystallization has been explored by us and others in the context of chiral resolution to target several racemic drug systems.[22–25] On the basis of these methods, and drawing a parallelism to CIDT, we set out to go beyond chiral resolution, targeting a cocrystallization-induced spontaneous deracemization (CoISD) process. The industrially friendly thermodynamic process developed in this study is applicable to all compounds, whether they form salts or not, and to both conglomerate- and racemic-compound-forming systems, thereby making it a general process, in contrast to all other crystallization-based deracemization processes.

We used a model system to develop the CoISD process. The racemic target compound (*RS*)-4,4-dimethyl-1-(4-fluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)pentan-3-one [(*RS*)-BnFTP] belongs to a family of fungicidal compounds,[26] for which a conglomerate-forming system has already been successfully deracemized through the kinetic Viedma ripening procedure.[27,28] When BnFTP is combined with the chiral coformer (*S*)-3-phenylbutyric acid [(*S*)-PBA], a diastereomeric pair of cocrystals can be obtained. Each diastereomer crystallizes in a chiral space group with the asymmetric unit only containing one enantiomer of the target compound alongside (*S*)-PBA.[23,25,29] The diastereomers crystallize in the $P2_12_12_1$ and $P2_1$ space groups for [(*S*)-BnFTP–(*S*)-3-phenylbutyric acid] (Figure 1 A) and [(*R*)-BnFTP–(*S*)-3-phenylbutyric acid] (Figure 1 B), respectively. The former is referred to herein as the *S*,*S* cocrystal and is the energetically favored diastereomer.[30] As a consequence, this diastereomer has lower solubility as compared to the *R*,*S* cocrystal.

[*] M. Guillot, J. de Meester, S. Huynen, L. Collard, K. Robeyns, Prof. O. Riant, Prof. T. Leyssens
Department of Molecular Chemistry, Materials and Catalysis
Institute of Condensed Matter and Nanosciences
Université Catholique de Louvain
Place Louis Pasteur, 1 bte L4.01.06
BE-1348 Louvain-La-Neuve (Belgium)
E-mail: olivier.riant@uclouvain.be
tom.leyssens@uclouvain.be

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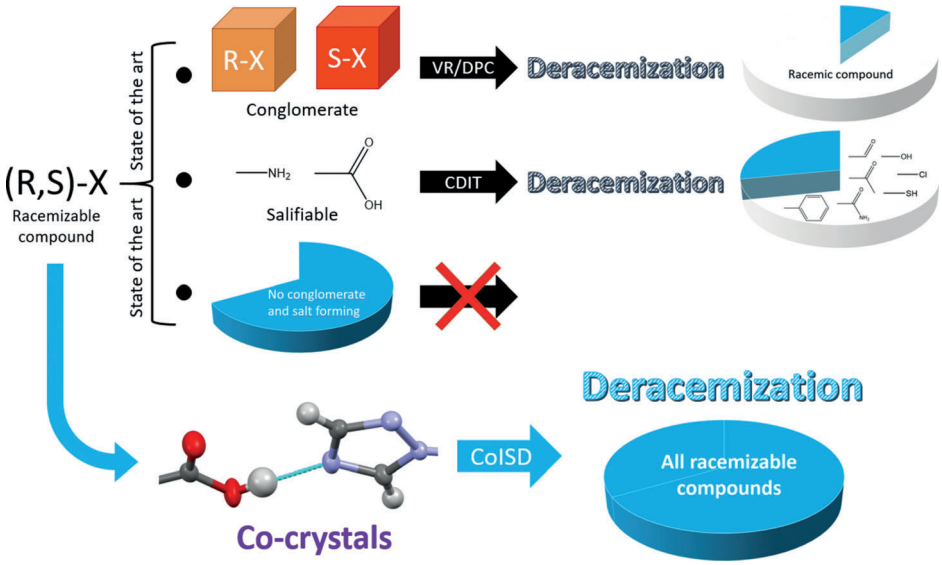


Scheme 1. State of the art regarding deracemization, and how CoISD redistributes the cards and opens new deracemization possibilities.

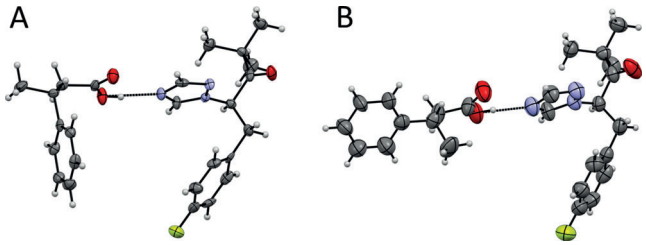
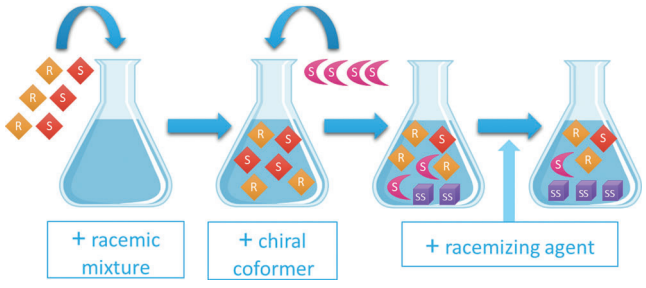


Figure 1. A) Asymmetric unit of the (*S*)-BnFTP–(*S*)-PBA cocrystal. B) Asymmetric unit of the (*R*)-BnFTP–(*S*)-PBA cocrystal. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen bonds are shown as black dashed lines. Disorder is left out for clarity.[40]

The principle behind CoISD (Scheme 2) taps into this solubility difference.[31] Given the right conditions, the addition of (*S*)-PBA (four pink crescents) to a racemic mixture of BnFTP (three orange squares for *R* and three red squares for *S*) will selectively lead to crystallization of only the *S*,*S* cocrystal (two purple cubes). This transformation induces a solution enantiomeric excess of (*R*)-BnFTP (three orange squares for only one red square in solution). The addition of a racemizing agent will pull the solution imbalance towards the racemic equilibrium once more, implying a net transformation in solution of (*R*)-BnFTP into (*S*)-BnFTP (number of squares are evened with two red and two orange). The associated concentration increase in (*S*)-BnFTP will lead to a solution that is supersaturated with respect to the *S*,*S* cocrystal,[32] which continues to crystallize as long as a sufficient amount of coformer is present in solution (one more purple cube appears). This process is purely thermodynamic and eventually leads to spontaneous full deracemization.[33] The main challenges in developing a CoISD process are comparable to those of kinetic deracemization processes and relate to the identification of a suitable chiral coformer and to the combination of crystallization and racemization conditions. The former often require low temperature to increase the yield, whereas the latter often require opposite conditions, as illustrated below.

Toluene was selected as the crystallization solvent, as the *S*,*S* cocrystal behaves congruently in this solvent and furthermore shows low solubility. This solvent also allows the BnFTP racemization reaction to occur without major difficulty. Moreover, there is a substantial solubility difference between the two diastereomers. Chiral resolution conditions in toluene (see the Supporting Information) enabled the *S*,*S* cocrystal to crystallize in 32% yield[34] with 98.6% *ee* (Figure 2) starting from the (*RS*)-BnFTP racemate. This process left a solution imbalance in favor of (*R*)-BnFTP (58.6% *ee*).

Besides induction of a solution enantiomeric imbalance, a racemization reaction is also a prerequisite for the development of a deracemization process. In our case, racemization is based on the keto–enol equilibrium of BnFTP with either a Brønsted acid or a Brønsted base.[35] BnFTP racemizes freely in the presence of weak bases but does not in the presence of weak or strong acids. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (DBU) was chosen as the racemizing agent, since the use of one equivalent of DBU at room



Scheme 2. Principle of the cocrystallization-induced spontaneous deracemization process.

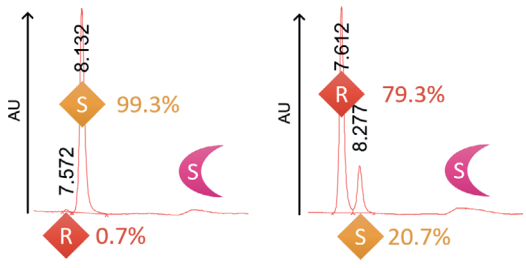


Figure 2. Chiral chromatography of a) the cake and b) the filtrate obtained from the (*RS*)-BnFTP chiral resolution process in toluene.

temperature led to full racemization in 30 min, whereas a 5 mol% catalytic amount of DBU was shown to induce complete racemization in 6 h (see the Supporting Information). Unfortunately, addition of the base to a solution containing both BnFTP and the coformer no longer led to racemization at this temperature. This result can be readily understood, as DBU (less than 1 equivalent with respect to BnFTP and the coformer) will deprotonate the carboxylic acid of the coformer, thus producing a much weaker carboxylate base. This latter is not strong enough to induce racemization under the initial conditions studied.

A similar situation is often encountered in CIDT processes, for which a temperature increase is typically required for the racemization to occur.[36,37] We therefore performed racemization in the presence of the coformer (and substoichiometric amounts of DBU) at higher temperatures. After 12 h at 110 °C, the filtrate obtained from the resolution had fully racemized, whereas partial racemization was observed after 2 h at 90 °C. The racemization kinetics are slower as compared to those typically observed for CIDT. For CIDT, however, one partner fulfills the role of the acid/base required for racemization, thus leading to the high kinetics observed. As DBU interacts with the acidic coformer, the quantity of base cannot be increased in the current system. For systems in which such an interaction does not occur, faster racemization can be achieved.

Temperature increases are usually counterproductive with respect to crystallization processes. To allow for a reasonable yield, we decided to physically separate the two processes by using a crystallization vessel at 10 °C and a racemization vessel at 90 °C.[38] The liquid from the crystallization vessel, with an enantiomeric imbalance in favor of the distomer, was continuously transferred to the racemization vessel, and the racemic solution from the racemization to the crystallization vessel (Figure 3).

Herein, we show the success of the CoISD process through three experiments (Table 1). Each experiment was performed using a 1:1 mixture of (*RS*)-BnFTP and the coformer and 7.5% mol of DBU. After each experiment, the solid in suspension was filtered, and the cake washed with toluene (see the Supporting Information). Tubing and reactor vessels were flushed with acetone, and solutions added to the filtrate. The resulting solution was evaporated, and the weights of the cake and solid recovered from the filtrate were determined. Both were further analyzed by HPLC on a chiral stationary phase to check the ratio of (*R*)- versus (*S*)-BnFTP. Combining these measurements allowed for a full mass balance.[39]

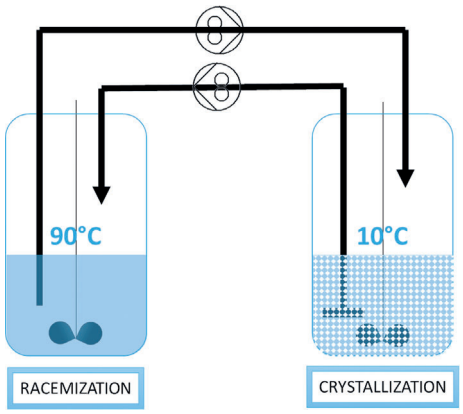


Figure 3. Sketch of the single deracemization process setup.

In all cases, the cake was found to be enantiomerically pure. As expected, starting with the *S* coformer led to crystallization of (*S*)-BnFTP, whereas the *R* enantiomer could be crystallized using the coformer of opposite handedness. Experiment 1 led to a recovered yield of over 50%, inherently implying that we went beyond mere resolution (maximum yield of 50%). The full mass balance showed deracemization to have occurred for all experiments, as observed from the total *R*/*S* ratio at the end of the experiments. In the case of experiment 2, the 50:50 *R*/*S* mixture was thermodynamically transformed into an 87:13 mixture. From the follow-up of experiment 2 (see the Supporting Information), racemization kinetics were shown to be faster than crystallization kinetics. For this reason, heating was decreased for the third experiment, with racemization becoming the limiting factor, yielding less deracemization over the same period of time.

With these three experiments, we have demonstrated that deracemization can be thermodynamically induced to yield an enantiomerically pure cocrystalline solid with high purity. Depending on the handedness of the coformer used, one can select the desired enantiomer. As for the kinetic Viedma ripening procedure, the process runs over multiple days. Process productivity is therefore not very high, as we are limited by the amount of DBU present. However, higher productivity is expected for systems that show a more suitable interplay between crystallization and racemization kinetics. The development of an optimized process is ongoing and requires a full understanding of all process parameters.

In conclusion, we report an innovative thermodynamic deracemization process coupling selective cocrystallization to a racemization reaction. We successfully deracemized (*RS*)-BnFTP, targeting either the *S* or *R* enantiomer according to the coformer handedness. Unlike kinetic processes, such as Viedma ripening or dynamic preferential crystallization, CoISD can target conglomerates as well as racemic compounds, and contrary to CIDT, CoISD can be used for those compounds that do not form salts. Overall, these features make CoISD

Table 1: Key parameters and results for the three deracemization experiments.[a]

Experiment	c(BnFTP–PBA) [mol L^{-1}]	V_{DBU} [µL] (mol%)	T_{rac} [°C]	t [days]	Yield [%][b] (cake)	ee_{cake} [%][c]	$ee_{filtrate}$ [%][c]	Ratio *R*/*S* total
1 ((*S*)-PBA)	0.20	203 (7.5)	90	4	50.7	0.999 (*S*)	0.276 (*S*)	18:82
2 ((*R*)-PBA)	0.25	254 (7.5)	90	5	44.6	1.00 (*R*)	0.54 (*R*)	87:13
3 ((*R*)-PBA)	0.30	305 (7.5)	75	5	38.7	0.97 (*R*)	0.246 (*S*)	38:62

[a] For each experiment, the same volume of toluene was used (90 mL). [b] The yield was calculated with respect to the total mass retrieved at the end of the experiment. [c] The enantiomer formed in excess is given in brackets.

a general deracemization process, which in the future we will most likely see applied to a multitude of compounds. Further studies are currently ongoing to optimize the process parameters and understand underlying racemization and crystallization kinetics.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: chiral resolution · cocrystallization · cocrystals · deracemization · thermodynamics

[1] H. Murakami, *Novel Optical Resolution Technologies*, Heidelberg, Springer, **2006**, pp. 274 – 278; available at: https://link.springer.com/content/pdf/10.1007%2F978-3-540-46320-7.pdf; accessed September 5, 2018.

[2] Administration F.D. **1992**; available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatorylnformation/Guidances/ucm122883.htm; accessed September 5, 2018.

[3] A. Calcaterra, I. D'Acquarica, *J. Pharm. Biomed. Anal.* **2018**, *147*, 323 – 340.

[4] R. Xie, L.-Y. Chu, J.-G. Deng, *Chem. Soc. Rev.* **2008**, *37*, 1243 – 1263.

[5] J. K. Whitesell, D. Reynolds, *J. Org. Chem.* **1983**, *48*, 3548 – 3551.

[6] S.-M. Xie, Z.-J. Zhang, Z.-Y. Wang, L.-M. Yuan, *J. Am. Chem. Soc.* **2011**, *133*, 11892 – 11895.

[7] W. L. Noorduin, P. van der Asdonk, H. Meekes, W. J. P. van Enckevort, B. Kaptein, M. Leeman, R. M. Kellogg, E. Vlieg, *Angew. Chem. Int. Ed.* **2009**, *48*, 3278 – 3280; *Angew. Chem.* **2009**, *121*, 3328 – 3330.

[8] Y. Okamoto, T. Ikai, *Chem. Soc. Rev.* **2008**, *37*, 2593 – 2608.

[9] G. Coquerel, *Novel Optical Resolution Technologies*, Heidelberg, Springer, **2006**, pp. 4 – 18; available at: https://link.springer.com/content/pdf/10.1007%2F978-3-540-46320-7.pdf; accessed September 5, 2018.

[10] G. Levilain, G. Coquerel, *CrystEngComm* **2010**, *12*, 1983 – 1992.

[11] C. Rougeot, J. E. Hein, *Org. Process Res. Dev.* **2015**, *19*, 1809 – 1819.

[12] D. Kozma, *CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation*, CRC, Boca Raton, **2001**.

[13] P. Marchand, F. Querniard, P. Cardinaël, G. Perez, J. J. Counioux, G. Coquerel, *Tetrahedron: Asymmetry* **2004**, *15*, 2455 – 2465.

[14] Q. He, Y. F. Peng, S. Rohani, *Chirality* **2010**, *22*, 16 – 23.

[15] L.-C. Sögütoglu, R. R. E. Steendam, H. Meekes, E. Vlieg, F. P. J. T. Rutjes, *Chem. Soc. Rev.* **2015**, *44*, 6723 – 6732.

[16] C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 3 – 6.

[17] M. Sakamoto, T. Mino in *Advances in Organic Crystal Chemistry* (Eds.: R. Tamura, M. Miyata), Tokyo, Springer, **2015**.

[18] F. Toda, K. Tanaka, *Chem. Lett.* **1983**, *12*, 661.

[19] N. A. Hassan, E. Bayer, J. C. Jochims, *J. Chem. Soc.* **1998**, 3747.

[20] K. M. J. Brands, A. J. Davies, *Chem. Rev.* **2006**, *106*, 2711 – 2733.

[21] A. D. Bond, *CrystEngComm* **2007**, *9*, 833 – 834.

[22] P. Thorey, P. Bombicz, I. M. Szilágyi, P. Molnár, G. Bánsághi, E. Székely, B. Simándi, L. Párkányi, G. Pokol, J. Madarász, *Thermochim. Acta* **2010**, *497*, 129 – 136.

[23] O. Sánchez-Guadarrama, F. Mendoza-Navarro, A. Cedillo-Cruz, H. Jung-Cook, J. I. Arenas-García, A. Delgado-Díaz, D. Herrera-Ruiz, H. Morales-Rojas, H. Höpfl, *Cryst. Growth Des.* **2016**, *16*, 307 – 314.

[24] G. Springuel, B. Norberg, K. Robeyns, J. Wouters, T. Leyssens, *Cryst. Growth Des.* **2012**, *12*, 475 – 484.

[25] G. Springuel, T. Leyssens, *Cryst. Growth Des.* **2012**, *12*, 3374 – 3378.

[26] "Fungicidal compounds": S. Balasubramanyan, US4243405A, **1981**.

[27] K. Suwannasang, A. E. Flood, C. Rougeot, G. Coquerel, *Cryst. Growth Des.* **2013**, *13*, 3498 – 3504.

[28] C. Rougeot, F. Guillen, J. C. Plaquevent, G. Coquerel, *Cryst. Growth Des.* **2015**, *15*, 2151 – 2155.

[29] M. Habgood, *Cryst. Growth Des.* **2013**, *13*, 4549 – 4558.

[30] When racemic (*RS*)-BnFTP was mixed with racemic (*RS*)-PBA, a mixture of the *R*,*R* and *S*,*S* cocrystals were formed instead of the *R*,*S*–*S*,*R* mixture, thus showing the higher stability of the *S*,*S* with respect to the *R*,*S* diastereomer.

[31] A. W. H. Lam, K. M. Ng, *AIChE J.* **2007**, *53*, 429 – 437.

[32] The cocrystal solubility product depends on the concentration of both components in solution, $K_{sp} = [(S)\text{-BnFTP}]^*[(S)\text{-PBA}]$.

[33] Full deracemization does not imply 100% transformation of *R* into *S*. The final solution still contains a mixture of (*R*)- and (*S*)-BnFTP. The lower the solubility of the cocrystal, the more effective the overall deracemization will be.

[34] The maximum yield for a resolution is 50%.

[35] W. Reusch, S. Farmer, **2015**. Available at: https://chem.libretexts.org/Textbook_Maps/Organic_Chemistry/Supplemental_Modules_(Organic Chemistry)/Reactions/Rearrangement_Reactions/Keto-Enol_Tautomerism. Accessed September 10, 2018.

[36] E. M. Davidson, E. E. Turner, *J. Chem. Soc.* **1945**, 843.

[37] T. Shiraiwa, T. Furukawa, S. Tsuchida, M. Sakata, M. Sunami, H. Kurokawa, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3729.

[38] For a process that does not require high temperatures, a one-pot method combining crystallization and racemization is fully achievable.

[39] Experiments 1 and 2 did not reach crystallization equilibrium before filtration, and thermodynamic yields are expected to be higher. Before filtration, it would be advisable to leave the process enough time to equilibrate.

[40] CCDC 1984002 and 1984003 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre

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Communications

Chiral Resolution

M. Guillot, J. de Meester, S. Huynen, L. Collard, K. Robeyns, O. Riant,* T. Leyssens* ———— ▮▮▮▮–▮▮▮▮

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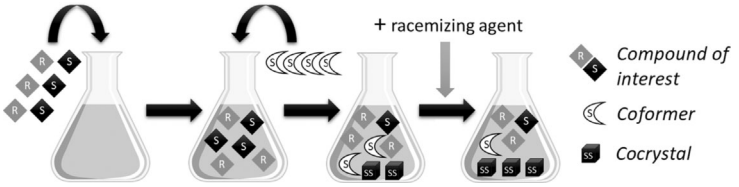

One model to fit all: As a general approach to deracemization, cocrystallization-induced spontaneous deracemization takes advantage of the universal dimension of cocrystallization to create a pair of diastereomers and combines it with a racemization reaction in solution (see picture). This model was successfully applied to a fungicide, the deracemization of which was not possible by established methods.