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## RESEARCH ARTICLE

## Use of Conglomerates Mixed Crystals to Deracemize a Stable Racemic-Compound-Forming System

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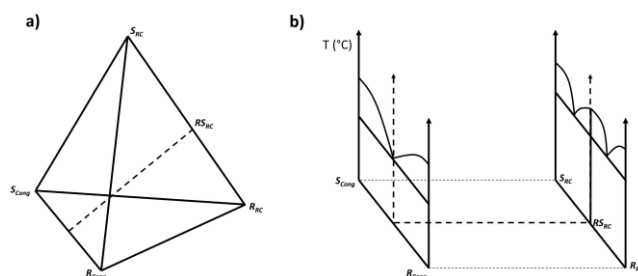
**Abstract:** Deracemization extended to racemic-compound-forming systems is demonstrated. We present here the first results of an alternative for the resolution of systems that exhibit a stable racemic compound but also a closely related conglomerate-forming system. If the couples of enantiomers forming the racemic compound and the enantiomers of the stable conglomerate can syncrystallize in mirror related partial solid solutions, it is possible to deracemize the racemic mixture of mixed crystals to access to a single handedness. The evidence of that possibility is given on three examples by using Temperature Cycling Induced Deracemization.

## Introduction

Since 2005, the seminal paper of Cristobal Viedma,<sup>[1]</sup> an intense research activity has been taking place in the domain of deracemization. By coupling racemization, and crystallization of a conglomerate in the same pot, numerous examples show that it is possible to direct the complete symmetry breaking towards 100% of the desired enantiomer.<sup>[2–5]</sup> Unfortunately, the two conditions: (i) full discrimination in the solid state (ii) fast racemization in solution appear to be difficult to fulfil at the same time. They represent severe limitations for the scope of application of this method as the number of chiral compounds crystallizing as conglomerates is estimated at only circa 5%. Nevertheless, large fluctuations from one series of molecules to another have been pointed out.<sup>[6–10]</sup> Hopefully, reaching chiral discrimination in the solid state for racemic-compound-forming systems remains possible. Several examples of conglomerate cocrystals, salts or solvates and their resulting chiral resolution are reported in the literature.<sup>[11–13]</sup> Moreover, enantiomeric systems can also present a partial miscibility in the solid state either for a conglomerate or a racemic compound. In the case of conglomerates, it prevents a total chiral discrimination and limits the effectiveness of chiral resolution methods by crystallization up

to the extreme composition of the partial solid solution in equilibrium. By contrast, it can be beneficial for racemic-compound-forming system as shown by the intriguing phenomenon of preferential enrichment.<sup>[14,15]</sup> The structural aspects of solid solutions in enantiomeric system were reviewed by Brandel et al.<sup>[16]</sup> and Rekis et al.<sup>[17]</sup> Solid solutions between resolving agents of the same handedness also improves the Pasteurian resolution. This improvement is known as: Dutch resolution.<sup>[18]</sup>

This work aims at identifying a new approach to reach chiral discrimination in the solid state for racemic-compound-forming systems by using the occurrence of solid solution between enantiomers of two chiral molecules.<sup>[19]</sup> To do so, the miscibility in the solid state between enantiomers of two chemically related chiral molecules; one crystallizing as a conglomerate and the other crystallizing as a racemic compound; was investigated.



**Figure 1.** (a) Tetrahedral and (b) extended binary representations of the studied systems. Racemic isoplethal section is represented in dotted line.

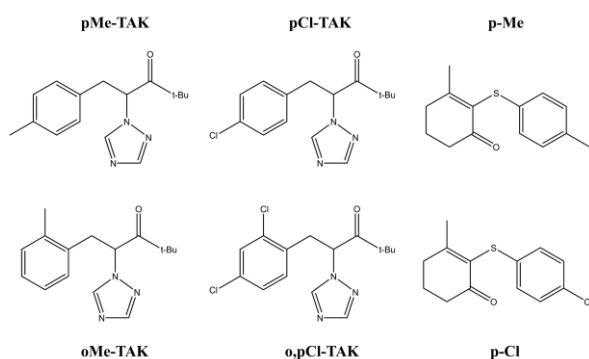
Thus, the phase equilibria investigated between the two racemic compositions is a binary isoplethal section of a quaternary system. This section is thermodynamically described by the classical isothermal tetrahedral representation (Figure 1a)

## RESEARCH ARTICLE

or by what is called the “extended binary” representation assuming that no diagonal equilibrium occurs (Figure 1b).<sup>[20]</sup>

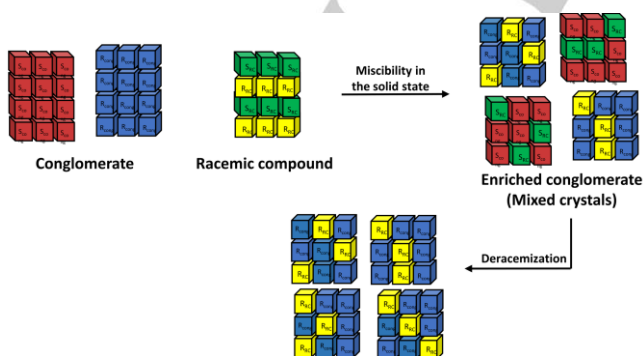
Three model compounds were studied. Two of them are racemic compounds (Figure 2 oMe-TAK; o,pCl-TAK) which belong to a family of conglomerate-forming compounds of Triazole Ketone (TAK) derivatives. Their respective chemically related conglomerate (Figure 2 pMe-TAK; pCl-TAK) were successfully deracemized by Temperature Cycling Induced Deracemization (TCID).<sup>[21,22]</sup> Furthermore, 44 cofomers were tried as a library approach in view to crystallize a conglomerate-forming cocrystal of o,pCl-TAK. However, no conglomerate cocrystal could be found.

The last model compound is an atropisomer crystallizing as a racemic compound (Figure 2 p-Cl).<sup>[23]</sup> The activation energy to switch from one configuration to the other is too high in the solid state. By contrast, the sulfur bond rotation is no more limited in the liquid state leading to a spontaneous and instantaneous racemization in solution. Therefore, its chemically related conglomerate (Figure 2 p-Me) is a good candidate for deracemization.



**Figure 2.** Racemic-compound-forming systems (bottom) and their chemically related conglomerate-forming system

The occurrence of partial solid solution on the three systems (i) pMe-TAK / oMe-TAK (ii) pCl-TAK / o,pCl-TAK (iii) p-Me / p-Cl was highlighted by the experimental determination of their racemic binary isopleth section. We show that enantiomers of the racemic-compound-forming system can fit into the conglomerate structure and thus, form mixed crystals which can be subsequently deracemized (Figure 3).



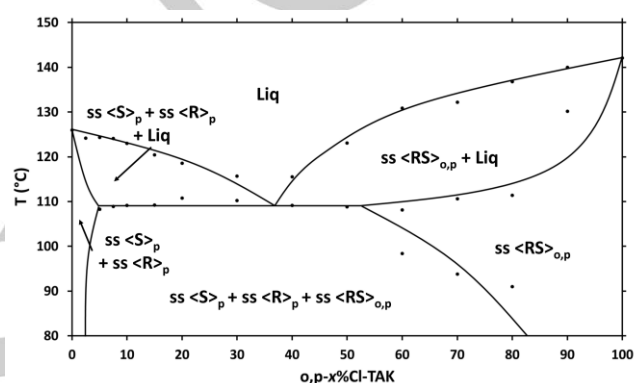
**Figure 3.** Illustration of the deracemization using conglomerate mixed crystals.

## Results and Discussion

## Racemic binary isopleth sections

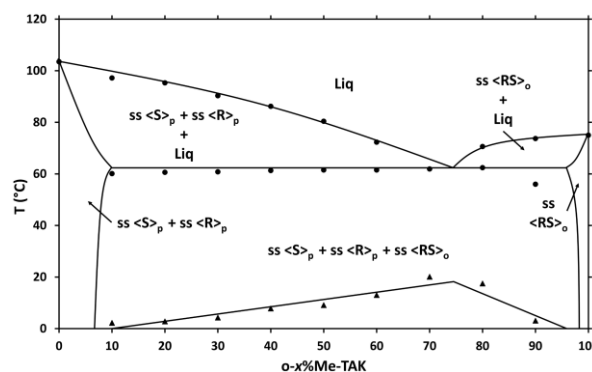
The systems pCl-TAK / o,pCl-TAK ; pMe-TAK / pCl-TAK ; p-Me / p-Cl will be described in mass fraction of the racemic compound-forming-systems o,p-x%Cl-TAK ; o-x%Me-TAK ; p-x%Cl respectively.

The racemic binary isopleth section of the system pCl-TAK / o,pCl-TAK was constructed by plotting the thermal data in the whole compositions range (Figure 4). This phase diagram shows that o,p-Cl-TAK is miscible in the solid state with p-Cl-TAK within a small composition range (i.e. less than 5%mol). By contrast, the miscibility of p-Cl-TAK in o,p-Cl-TAK, which is strongly temperature dependent, is much larger. One can note that the same behavior is obtained by high energy milling (Figure S3).



**Figure 4.** Racemic binary isopleth section o,pCl-TAK (o,p) / pCl-TAK (p). Bolded lines are for equilibria supported by the thermal data (guides for the eyes).

A second racemic binary isopleth section has been investigated: the system oMe-TAK / pMe-TAK. DSC measurements on the whole compositions range all presented two distinct phenomena (i) an endothermic invariant around 61 °C (ii) an endothermic signal varying between the melting point of pure components with a minimum around 0-70%Me-TAK (Figure S4). In this case, the widths of partial solid solutions were determined by plotting the enthalpy of the eutectic invariant for each composition. According to this Tammann graph, this system must be a eutectic invariant with a eutectic point at *circa* 0-76%Me-TAK and partial solid solution domains below 0-9%Me-TAK and above 0-96%Me-TAK (Figure 5).

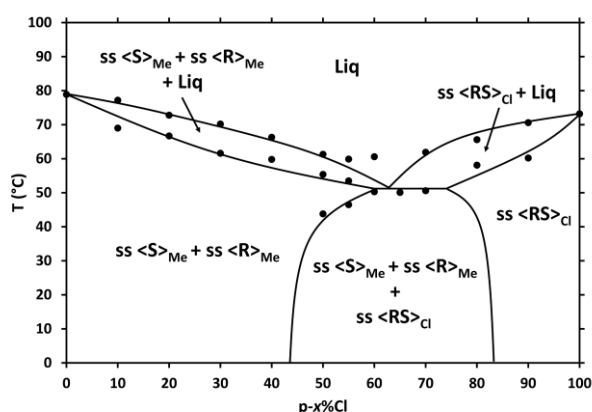


**Figure 5.** Racemic binary isopleth section oMe-TAK (o) / pMe-TAK (p). Bolded lines are for equilibria supported by the Tammann plot (▲) and the thermal data (guides for the eyes).

## RESEARCH ARTICLE

Interestingly, the solid solution on the conglomerate side can be extended up to circa o-30%Me-TAK by using high energy milling (Figure S5).[24,25] However, this metastable forced extension of the solid solution domain cannot be used under deracemization conditions.

The racemic binary isopleth section of the system p-Me / p-Cl can be drawn as in Figure 6 according to the DSC measurement of each composition and their corresponding crystallographic data. The equilibrium observed corresponds to partial solid solutions on each side with a eutectic invariant at circa 50°C between p-60%Cl and p-74%Cl compositions. The eutectic composition cannot be determined accurately but it may be approximated at circa p-67%Cl composition.



**Figure 6.** Racemic binary isopleth section p-Cl (Cl) / p-Me (Me). Bolded lines are for equilibria supported by the thermal data (guides for the eyes).

### Deracemization of TAK derivatives

Successful deracemization by temperature cycling (TCID) of pCl-TAK and pMe-TAK was already reported in the literature.<sup>[21,22]</sup> For both systems (pMe-TAK / oMe-TAK and pCl-TAK / o,pCl-TAK), a narrow domain of partial miscibility in the solid state could be highlighted. TCID experiment in those domains was performed using the same protocol as that reported by Suwannasang *et al.*<sup>[21]</sup>

The addition of the solvent adds one more dimension to the deracemized system. Therefore, compositions above the maximum miscibility were used to ensure the crystallization of the solid solution at its maximum composition. Thus, the solubilities of o,p-5%Cl-TAK and o-50%Me-TAK in various Methanol/Water mixtures were determined and summarized in Table 1.

**Table 1.** Solubilities of o,p-5%Cl-TAK and o-50%Me-TAK respectively in MeOH/H<sub>2</sub>O 85/15 (v/v) and 65/35 (v/v).

	o,p-5%Cl-TAK		o-50%Me-TAK	
T (°C)	20	30	20	30
Solubility (wt%)	4.66	5.15	9.43	12.11

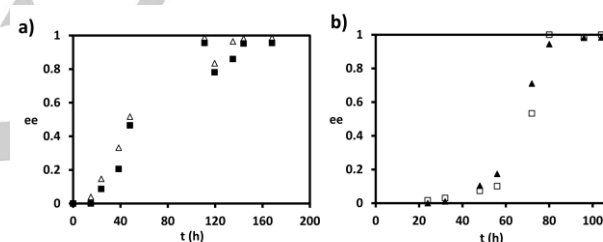
First, TCID experiment on o,p-5%Cl-TAK was carried out to give the proof-of-concept that the deracemization of a stable racemic compound through conglomerate mixed crystals was

possible. The increase in enantiomeric excess of pCl-TAK is followed by a similar increase in enantiomeric excess of o,pCl-TAK and a mixture of enantiopure p-CITAK and o,p-CITAK is obtained after 100 h of TCID (Figure 7a).

Actually, the final solid obtained was not composed of o,p-5%Cl-TAK. According to the calibration curve (Figure S9), the deracemized solid is an enantiopure o,p-2,5%Cl-TAK which is likely to be the stable limit of miscibility of o,pCl-TAK in pCl-TAK for the homochiral enantiomers.

Second, TCID experiment on o-50%Me-TAK was performed to conclude on a possible domino effect wherein more materials could be involved in the deracemization matrix and thus exceed the stable limit of solid solution. As for the previous one, the increase in enantiomeric excess of pMe-TAK is followed by a similar increase in enantiomeric excess of oMe-TAK and a mixture of enantiopure p-MeTAK and o-MeTAK is obtained after 80 h of TCID (Figure 7b).

According to the calibration curve (Figure S10), the deracemized solid is an enantiopure o-8,5%Cl-TAK which is close to the stable limit of the solid solution at the racemic composition highlighted by the experimental determination of its racemic binary isopleth section. Thus, no domino effect has been observed.



**Figure 7.** Evolution of the enantiomeric excess versus time of a) o,p-5%Cl-TAK ( $\Delta$ : pCl-TAK;  $\blacksquare$ : o,pCl-TAK) and b) o-50%Me-TAK ( $\blacktriangle$ : pMe-TAK;  $\square$ : oMe-TAK)

### Deracemization of p-Me / p-Cl

The system p-Me / p-Cl presents the largest domain of solid solution of this study. Therefore, it is the more favourable system for this deracemization method.

In this case, the deracemized composition was selected to be in the stable domain of the partial solid solution (*i.e.* p-45%Cl at 20°C). The solubility of p-40%Cl in *methyl tert-butyl ether* (MTBE) was determined and summarized in Table 2.

**Table 2.** Solubilities p-40%Cl in MTBE.

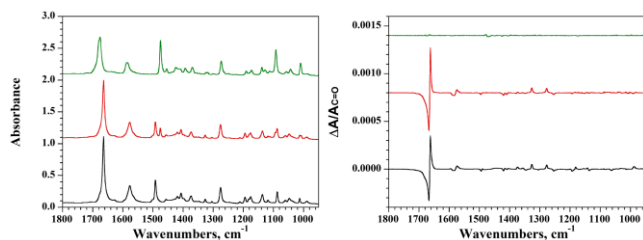
	p-40%Cl	
T (°C)	15	20
Solubility (wt%)	9.34	10.97

The spontaneous and instantaneous racemization in solvated media makes this system suitable for deracemization. However, the monitoring of the enantiomeric excess cannot be achieved in solvated media (*e.g.* HPLC, polarimetry). The efficiency of this experiment was determined within two different analysis (i)

## RESEARCH ARTICLE

Vibrational Circular Dichroism (VCD) to ensure the complete symmetry breaking (ii) HPLC analysis to quantify the composition of the deracemized mixture. VCD experiments were performed in the solid state using KBr pellets of powdered materials.<sup>[26]</sup>

VCD spectrum of the deracemized mixture is identical to the VCD spectrum of the deracemized pure p-Me (Figure 8). Thus, we can confirm that the complete symmetry breaking toward a pure enantiomer has been achieved. The HPLC analysis using HALO® columns of the deracemized solid shows that a mixture of *circa* p-25%Cl was deracemized during the TCID experiment.



**Figure 8.** IR spectra (left) and VCD spectra (right) of deracemized p-Me (black), deracemized p-40%Cl (red) and p-Cl samples (green).

## Conclusion

This work gives a proof-of-concept for the deracemization extended to stable racemic compounds using a deracemizable conglomerate host. More precisely, it is possible to direct the complete symmetry breaking toward a single handedness for a racemic-compound-forming system by using a solid solution with a chemically related racemizable conglomerate. Among the three successful examples, we could deracemized up to 25wt% of the racemic compound inside the conglomerate matrix. The effectiveness of this deracemization method does not seem to exceed the stable limit of solid solution. Indeed, a clear example of a forced extension of the solid solution domain under high energy milling has been characterized but, operative deracemization conditions cannot used this metastable equilibrium.

The effect demonstrated in this work renew the interest in the prediction of large domains of solid solutions for chemically related enantiomers easy to racemize. For non-racemizable enantiomers it is likely that preferential crystallization can be achieved.

## Experimental Section

### HPLC

Enantioselective HPLC measurements were performed on a Chiracel OD-H column (250 mm x 4.6 mm x 5 $\mu$ m) with a UV detection at a wavelength of 220nm using a mixture of isopropyl alcohol and n-heptane (3:97, v/v) as eluent at a flowrate of 1 mL.min<sup>-1</sup>.

HPLC measurements were performed on a Halo 90 Å phenyl-hexyl column (100 mm x 4.6 mm x 2.7 $\mu$ m) with a DAD detector at a wavelength of 254nm using a mixture of acetonitrile and water (1:1, v/v) as eluent at a flowrate of 1 mL.min<sup>-1</sup>.

### Differential Scanning Calorimetry (DSC)

DSC analyses were performed on a Netzsch DSC 214 Polyma apparatus. Each analysis was performed using circa 2 - 6 mg of sample in aluminium pans with pierced lid at a heating rate of 5 or 10 K.min<sup>-1</sup>. Atmosphere was regulated by a nitrogen flux (40mL.min<sup>-1</sup>). Proteus® Software were used for the processing data.

### X-Ray Powder Diffraction (XRPD)

XRPD analyses were performed at room temperature using a D8 Discover diffractometer (Bruker analytic X-ray Systems, Germany) with Bragg-Brentano geometry or on a D8 Advance (Bruker analytic X-ray Systems, Germany) with an inverted geometry ( $-\theta/-\theta$ ). The instrument is equipped with a copper anticathode (40 kV, 40 mA, K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ )), and a lynx eye linear detector. The diffraction patterns were recorded with a scan rate of 0.04° (2 $\theta$ ) in the angular range of 3-35° 2 $\theta$ , with a counting time of 0.5s per step. Eva® software was used for data processing.

### Vibrational circular dichroism

Vibrational circular dichroism (VCD) measurement of deracemized p-Me, deracemized p-40%Cl and p-Cl samples was performed using a ThermoNicolet Nexus 670 FTIR spectrometer equipped with a VCD optical bench. In this optical bench, the light beam was focused on the sample by a BaF<sub>2</sub> lens (191 mm focal length), passing an optical filter, a BaF<sub>2</sub> wire grid polarizer (Specac), and a ZnSe photoelastic modulator (Hinds Instruments, Type II/ZS50). The light was then focused by a ZnSe lens (38.1 mm focal length) onto a 1 x 1 mm<sup>2</sup> HgCdTe (ThermoNicolet, MCTA\* E6032) detector. The sample pellets were prepared by mixing p-Me, p-40%Cl and p-Cl materials (0.3-0.5 mg) with KBr (150 mg) powder and pressing at a pressure of 10 ton/cm<sup>2</sup> in vacuo. IR absorption and VCD spectra were recorded at a resolution of 4 cm<sup>-1</sup>, by coadding 50 scans and 24000 scans (8h acquisition time), respectively. Since the sample preparation may induce crystallite orientation, the KBr pellets of powdered materials were placed on a rotating sample holder and the VCD spectra were measured with the KBr pellets rotated at four angles around the light beam axis (0°, 45°, 90° and 135°). The final VCD spectra were obtained by averaging the four spectra. Baseline corrections of the VCD spectra were performed by subtracting the raw VCD spectrum of a racemic p-Me sample. The photoelastic modulator was adjusted for a maximum efficiency in the mid-IR region at 1400 cm<sup>-1</sup>. Calculations were performed via the standard ThermoNicolet software, using Happ and Genzel apodization, de-Haseth phase-correction and a zero-filling factor of one. Reproducible IR and VCD spectra were obtained for three samples independently prepared.

### Construction of racemic binary isopleth sections

Different compositions of systems pMe-TAK/oMe-TAK and pCl-TAK/o,pCl-TAK were prepared (i) by recrystallization in acetonitrile (ii) by high energy milling using Retsch Mixer Mill model MM400. Different compositions of system p-Me/p-Cl were prepared by recrystallization in diethyl ether. The recovered solids were analyzed by DSC and XRPD using NaCl as an internal standard.

### Solubility measurements

Solubilities were measured in triplicate in various solvent and temperature by using the standard gravimetric method. The suspensions were prepared in targeted solvents and stirred at fixed temperatures using a thermostated double-jacket glass vessels. After equilibration for at least 2 days, the suspension was filtered using a 13mm syringe filter (0.45  $\mu$ m PTFE membrane), the solid phase in equilibrium with the solution was identified by XRPD and the saturated solution was weighed before and after evaporation.

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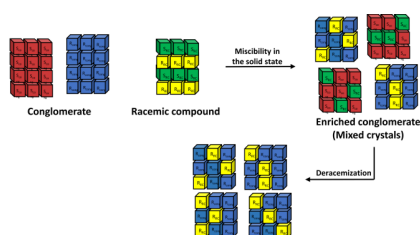
**Keywords:** Racemic Compound • Chiral Resolution • Deracemization • Solid Solution • Heterogeneous Equilibria

## References

- [1] C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504.
- [2] N. Uemura, S. Toyoda, W. Shimizu, Y. Yoshida, T. Mino, M. Sakamoto, *Symmetry* **2020**, *12*, 910.
- [3] W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg, D. G. Blackmond, *J. Am. Chem. Soc.* **2008**, *130*, 1158–1159.
- [4] C. Viedma, *Astrobiology* **2007**, *7*, 312–319.
- [5] L. Spix, H. Meekes, R. H. Blaauw, W. J. P. van Enckevort, E. Vlieg, *Crystal Growth & Design* **2012**, *12*, 5796–5799.
- [6] J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Krieger Publishing Company: Malabar, **1994**.
- [7] A. Otero-de-la-Roza, J. E. Hein, E. R. Johnson, *Crystal Growth & Design* **2016**, *16*, 6055–6059.
- [8] A. Otero-de-la-Roza, B. H. Cao, I. K. Price, J. E. Hein, E. R. Johnson, *Angew. Chem. Int. Ed.* **2014**, *53*, 7879–7882.
- [9] G. Coquerel, in *Advances in Organic Crystal Chemistry, Comprehensive Reviews*, Springer, **2015**, p. p 393-420, Chapter 20.
- [10] R. M. Kellogg, *Acc. Chem. Res.* **2017**, *50*, 905–914.
- [11] W. W. Li, L. Spix, S. C. A. de Reus, H. Meekes, H. J. M. Kramer, E. Vlieg, J. H. ter Horst, *Crystal Growth & Design* **2016**, *16*, 5563–5570.
- [12] R. Oketani, F. Marin, P. Tinnemans, M. Hoquante, A. Laurent, C. Brandel, P. Cardinael, H. Meekes, E. Vlieg, Y. Geerts, G. Coquerel, *Chem. Eur. J.* **2019**, *25*, 13890–13898.
- [13] M. Guillot, J. Meester, S. Huynen, L. Collard, K. Robeyns, O. Riant, T. Leyssens, *Angew. Chem.* **2020**, *132*, 11399–11402.
- [14] H. Takahashi, Y. Numao, J. Motokawa, S. Clevers, G. Coquerel, H. Tsue, R. Tamura, *Chem. Eur. J.* **2019**, *25*, 16405–16413.
- [15] R. Tamura, D. Fujimoto, Z. Lepp, K. Misaki, H. Miura, H. Takahashi, T. Ushio, T. Nakai, K. Hirotsu, *J. Am. Chem. Soc.* **2002**, *124*, 13139–13153.
- [16] C. Brandel, S. Petit, Y. Cartigny, G. Coquerel, *CPD* **2016**, *22*, 4929–4941.
- [17] T. Rekis, B. Agris, *CrystEngComm* **2018**, 6909–6918.
- [18] R. M. Kellogg, B. Kaptein, V. Ton R., Eds., in *Novel Optical Resolution Technologies*, Springer Berlin Heidelberg, Berlin, Heidelberg, **2007**, pp. 159–197.
- [19] B. Kaptein, H. Elsenberg, R. F. P. Grimbergen, Q. B. Broxterman, L. A. Hulshof, K. L. Pouwer, T. R. Vries, *Tetrahedron: Asymmetry* **2000**, *9*.
- [20] J. E. Ricci, in *The Phase Rule and Heterogeneous Equilibrium*, Dover, New York, **1951**, pp. 390–461.
- [21] K. Suwannasang, A. E. Flood, C. Rougeot, G. Coquerel, *Crystal Growth & Design* **2013**, *13*, 3498–3504.
- [22] K. Suwannasang, A. E. Flood, G. Coquerel, *Crystal Growth & Design* **2016**, *16*, 6461–6467.
- [23] V. Prelog, *Croat. Chem. Acta* **1975**, *9*.
- [24] L. Chaffron, Y. Le Bouar, G. Saint-Ayes, G. Martin, *Rev. Met. Paris* **2003**, *100*, 183–192.
- [25] P. Pochet, P. Bellon, L. Boulanger, L. Chaffron, G. Martin, *MSF* **1998**, *269–272*, 655–664.
- [26] T. Buffeteau, F. Lagugné-Labarhet, C. Sourisseau, *Appl Spectrosc* **2005**, *59*, 732–745.

## RESEARCH ARTICLE

## Entry for the Table of Contents



The deracemization of a racemic-compound-forming system by using the possibility of syncrystallization (i.e. formation of solid solution) with a chemically related conglomerate-forming system has been demonstrated. Based on phase diagram study, three model compounds crystallizing as racemic compound where deracemized this way giving the evidence of the concept.