*Supporting information*

# Shaking things up: exploiting the potential of mechanochemistry to enhance deracemization of racemic compounds

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# Experimental Details

## I. Materials & methods

### I.1 Chemicals

All solvents used in this study (n-heptane, 2-propanol, methanol) were HPLC grade (≥ 99%) and obtained from VWR chemicals. Sodium hydroxide and sodium chloride were purchased from VWR (≥ 95 %), stored in glovebags under nitrogen atmosphere during at least 1 week before used to limit the moisture exposition and used without further purifications. Racemic starting material of o-MeTAK and p-MeTAK was obtained over the course of previous research.[1]

### I.2 Chiral HPLC

Chiral HPLC analyses were performed using an Ultimate 3000 HPLC (ThermoFisher Scientific). For the determination of the enantiomeric composition of samples o-x%MeTAK, a cHPLC method was used involving a Chiracel OD-H and Chiralpak AD-H columns (250 mm ×4.6mm×5 µm) with a UV detection at a wavelength of 220 nm using a mixture of 2-propanol / n-heptane / TFA (95:5:0.1, v/v/v) as eluent at a flow rate of 1 mL.min$^{-1}$. Each run had a total time of 60 minutes (Figure S1). The initial and final solid compositions were determined using the calibration curve in figure S2, relating the solid composition to the HPLC percentage surface area of o-x%MeTAK.

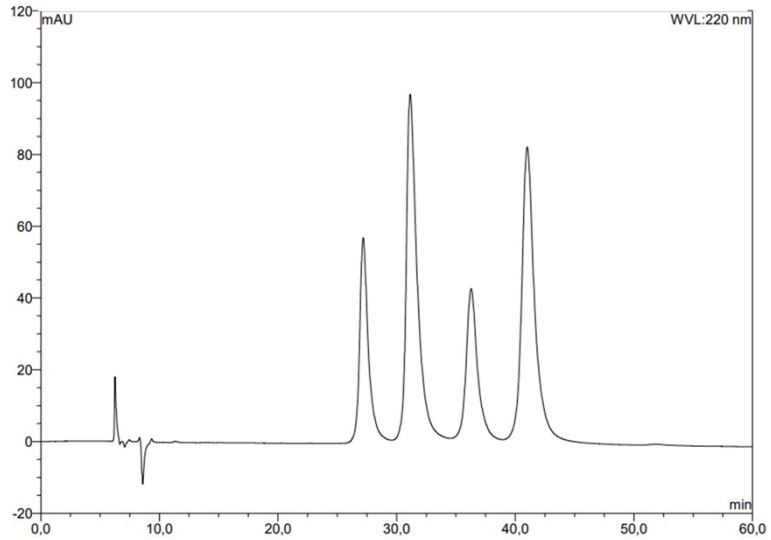


**Figure S1. Typical chromatogram obtained for racemic o-*x*%MeTAK samples. Retention time (min) for (*R*)-p-MeTAK: 30.55 (*S*)-p-MeTAK: 39.27 (*R*)-o-MeTAK: 28.02 (*S*)-o-MeTAK: 35.87.**

[1] C. Pinètre, F. Gendron, R. Kuroda, R. Oketani, C. Aupetit, T. Buffeteau, G. Coquerel, *Chemistry A European J* **2023**, e202300441.

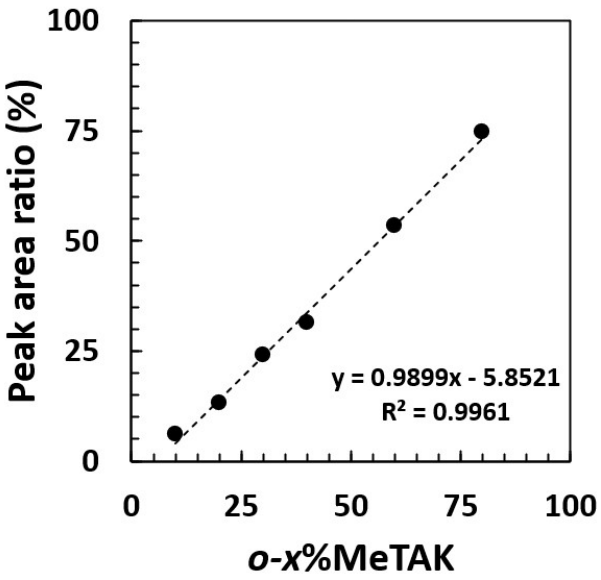


**Figure S2. Calibration curve relating the solid composition to the HPLC percentage surface area of o-*x*%MeTAK.**

### I.3 XRPD analyses

XRPD analyses were performed at 25 °C using a D8 Discover diffractometer (Bruker analytic X-ray Systems, Germany) with a Bragg-Brentano geometry. The instrument is equipped with a copper anticathode (40 kV, 40 mA, Kα radiation, λ =1.5418 Å), and a Lynx-Eye linear detector. The diffraction patterns were recorded with a scan rate of 0.04° (2θ) in the angular range of 3-30° 2θ, with a counting time of 0.5s per step. The Eva software was used for data processing.

### I.4 High energy milling

Milling experiments were all conducted with a Mixer Mill MM400 equipped with two 10mL-jars. They are composed of $ZrO_2$ as well as the 10mm diameter bead used to ensure milling. In all mixed crystal deracemization experiments, ca. 100 mg of model compounds was ground with around 7 mg of NaOH (0.5eq) and 50 mg of NaCl. All jars were filled in glove bags under nitrogen atmosphere. The mixtures were ground at 30 Hz for six consecutive hours. The maximum of the ground material was removed and washed with a sufficient amount of water to remove any trace of base before cHPLC analyses.

For mixtures exceeding the metastable solid-state miscibility limit (*i.e.* o-40%MeTAK and o-50%MeTAK), we observed complete enantioconversion of p-MeTAK (>98 %ee) while the deracemization of o-MeTAK remained partial, exhibiting an enantiomeric excess of 67 and 38 %*e.e.*, respectively. Here, the host conglomerate mixed crystal reaches saturation, the excess of o-MeTAK remains as racemic crystals, thus explaining the lower optical purities. Considering the final solids to be composed of enantiopure o-*x*%MeTAK mixed crystals and racemic crystals of o-MeTAK, the final enantiopure mixed crystals consistently exhibit a composition of ca. o-27%MeTAK (Table S1). This maximum enantiopure mixed crystals composition must reflect the metastable solid-state miscibility limit under non-equilibrium conditions, which is in line with the solid-state miscibility estimated based on the thermochemical and crystallographic data[1]

**Table S1. Peak area collected by cHPLC after complete deracemization under high energy milling of different *x*%-1d mixtures. The composition of the racemic crystals is estimated considering the non-deracemized solids to be part of a racemic phase (either racemic conglomerate or racemic compound). The composition of the enantiopure crystals is therefore estimated by considering the deracemized solids to be part of an enantiopure mixed crystal phase.**

| Initial o-*x*%MeTAK | | | o-40%MeTAK | o-50%MeTAK |
|---|---|---|---|---|
| p-MeTAK | Area (*a.u.*) | R | 3.4 | 6.8 |
| | | S | 236.7 | 250.1 |
| | Area racemic mixture (*a.u.*) | | 6.8 | 13.6 |
| | Area enantiopure crystal (*a.u.*) | | 233.3 | 250. |
| o-MeTAK | Area (*a.u.*) | R | 16.2 | 51.5 |
| | | S | 79.4 | 114.3 |
| | Area racemic mixture (*a.u.*) | | 32.3 | 103.0 |
| | Area enantiopure crystal (*a.u.*) | | 63.3 | 62.8 |
| Peak area ratio of enantiopure crystals (%) | | | 21.4 | 20.5 |
| Recovered enantiopure mixed crystals o-*x*%MeTAK (%) | | | 27.5 | 26.6 |

## I.5 Temperature cycling induced deracemization (TCID)

TCID experiments were carried out in a 50 mL one-neck round-bottom thermostated flask connected to a circulating cryostat (F34-HE, Julabo). The neck is closed with a septum to allow sampling during the solvent cycling process. The different o-*x*%MeTAK (*i.e.* 20, 30, 40) mixtures were loaded in the 50 mL one-neck round-bottom thermostated flask and partially dissolved in a MeOH/$H_2O$ (65/35, v/v) solvent mixture. The quantity of initial racemic solids consistently represented 13 %wt of the total mixtures. The resulting slurries were stirred using an oval PTFE magnetic stirring bar (#BRND137307, VWR) and submitted to temperature variation according to the temperature program reported by Suwannasang *et al.*.[2]

The evolution of the *e.e.*% were monitored by sampling ~ 0.5 mL of the slurry from the 50 mL one-neck round-bottom thermostated flask using a single channel mechanical pipettor (613-0155, VWR). The solid phases were isolated from the collected suspension by casting it on top of filter paper laid down on glass filter connected to a vacuum filtration setup and washed with a sufficient amount of water to remove any trace of base before cHPLC analyses.

[2] K. Suwannasang, A. E. Flood, C. Rougeot, G. Coquerel, *Crystal Growth & Design* **2013**, *13*, 3498–3504.