Supporting information

1. Material and methods

1. Method

i. Milling procedure

All milling experiments are performed with a Mixer Mill 400 from Retsch. The material to be milled was loaded in a 10mL-jar containing one 12mm diameter ZrO_2 bead. Milling was performed with a frequency of 30Hz during $t_{milling}$.

For experiments with controlled humidity, jar preparation was entirely performed within a glove bag in which relative humidity (RH) is lower than 20%. The materials (i.e. *(S)*-ETI, NaOH and NaCl) are all stored inside a desiccator under P_2O_5. This desiccator is also stored inside the glove bag. The jar was sealed with a parafilm prior to milling. Once the milling stops, the powder was analyzed by cHPLC.

ii. cHPLC

cHPLC analyses were performed on a Ultimate 3000 system, with a UV detection at 210 nm. Milled material is dissolved in a mixture of Heptane/IPA/TFA (80/20/0.1, v/v/v) The mobile phase is a heptane/IPA (90/10 v/v) mixture with a 1mL/min flow rate. The stationary phase is a Chiralcel OD-H 5µm 250x4.6mm column from Daicel. The retention time are at 16.3 and 20.1min for the *(R)* and the *(S)* enantiomers respectively.

iii. PXRD analyses

PXRD analyses were performed at room temperature using a D8 Discover diffractometer (Bruker analytic X-ray Systems, Germany) with Bragg–Brentano geometry. The instrument is equipped with a copper anticathode (40kV, 40mA, K_α radiation (λ = 1.5418 Å)) and a LynxEye linear detector. Routine PXRD measurement involved recording with a scan rate of 0.04° (2θ) in the angular range 3–30° 2θ, with a counting time of 0.5s per step.

iv. IR Analyses

Infrared spectra were obtained with an Alpha Platinum ATR spectrometer from Bruker. The program Opus was used for the data treatment. An atmospheric compensation for the potential H_2O and CO_2 interferences and a baseline correction were applied to the raw data.

2. Materials

Table S1 : Supplier and purity of the used bases

Material	**Supplier**	**Purity minimum(%)**
(S)-2-(2-oxopyrrolidin-1-yl)butanamide	Xiamen Top Health Biochem. Tech. Co., Ltd.	98
Sodium chloride	VWR	99.5
	Base	
Sodium hydroxide	Alfa Aesar	97
Sodium methoxide	Alfa Aesar	25/30%v (solution in MeOH)
Calcium hydroxide	Fisher	95
Calcium carbonate	Prolabo	95
Magnesium hydroxide	Fisher	95
1,8-Diazabicyclo(5.4.0)undéc-7-ène (DBU)	Sigma	98
Magnesium carbonate	Prolabo	95
Potassium carbonate	Acros organics	99
Lithium hydroxide	Merck	98
	Solvent	

Methanol	VWR	99.8
Acetonitirile	VWR	99.5
Heptane	VWR	99

2. Using sodium methoxide as racemizing agent

1. Milling experiments

Results of the milling experiments using MeONa as racemization agent are given in the following table (**Table S2**).

Table S2 : Results of the milling experiments using MeONa as racemizing agent. (30Hz)

$m_{((S)\text{-ETI})}$ (g)	$m_{(MeONa)}$ (g)	$V_{(MeOH)}$ (µL)	Eq.	Time (min)	*e.e.* (%)	*Mean*	*Standard deviation*
0.205	0.0063	19	0.10	10	77.1	76.7	0.38
0.206	0.0060	18	0.09		76.4		
0.203	0.0057	17	0.09	15	43.0	64.4	21.4
0.200	0.0084	25	0.13		69.3		
0.201	0.0063	19	0.10		71.2		
0.202	0.0063	19	0.10		73.9		
0.204	0.0051	15	0.08	30	59.3	56.9	2.7
0.204	0.0048	14	0.07		59.6		
0.199	0.0057	17	0.09		54.3		
0.205	0.0057	17	0.09		54.2		
0.204	0.0054	16	0.08	45	3.6	5.2	1.6
0.199	0.0084	25	0.13		3.7		
0.203	0.0060	18	0.09		7.4		
0.204	0.0060	18	0.09		6.1		

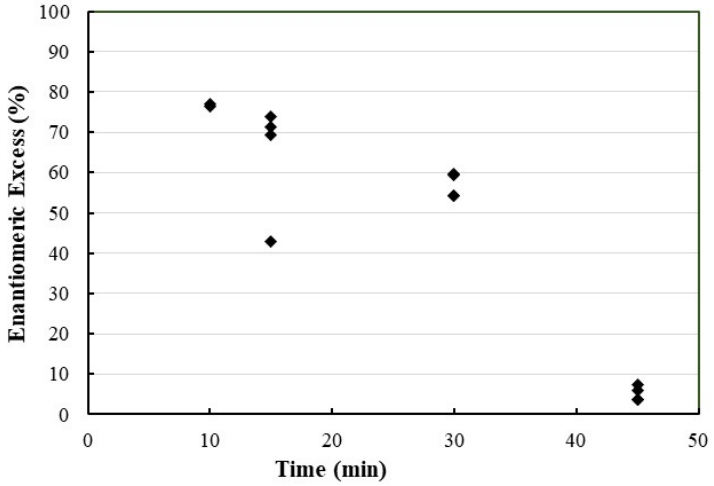


Figure S1 : Graphical representation of the mechanochemical racemization experiments using MeONa as a racemizing agent (30Hz)

2. Solution-based experiments

i. Performed at reflux

The reflux has been performed by dissolving 199.8mg of ***(S)*-ETI** in 10mL of methanol. 30µL of a 30%v solution of MeONa in methanol are added to the system once the reflux begins. It represents an equivalence of 0.14. Enantiomeric excess of the sampling are given in the following table (**Table S3**).

Table S3 : Racemization performed at reflux by using MeONa as racemizing agent.

Time (min)	*e.e.* (%)
0	100
230	87.76
395	78.28

ii. Performed at room temperature

Three racemization kinetics follow ups are performed at room temperature using 10mL of methanol for each. Results are given in the following table (**Table S4**).

Table S4 : Racemization performed at ambient temperature by using MeONa as racemizing agent.

$m_{((S)\text{-ETI})}$ (g)	0.202	0.201	0.205		
Eq. MeONa	0.14	0.14	0.13		
Time (min)	***e.e.* (%)**			**Mean**	**Standard deviation**
240	100	100	100	100	0
430	100	100	100	100	0
1455	99.5	99.6	99.3	99.5	0.1
4355	98.0	98.4	97.3	97.9	0.5

3. Using sodium hydroxide as racemizing agent

1. Kinetics study

Table S5 : Mechanochemical kinetics of racemization performed using NaOH as racemizing agent (30Hz).

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (g)	Time (min)	Eq.	*e.e.* (%)	*Mean*	*Standard deviation*
0.200	0.005	15	0.11	66.0	79.2	12.9
0.201	0.005		0.11	70.9		
0.202	0.004		0.08	76.0		
0.199	0.003		0.06	72.5		
0.198	0.006		0.13	89.8		
0.196	0.007		0.15	99.7		
0.199	0.009	30	0.19	32.9	48.6	38.2
0.196	0.003		0.07	51.4		
0.201	0.005		0.11	27.2		
0.201	0.005		0.11	3.8		
0.197	0.008		0.17	67.1		
0.198	0.009		0.19	94.2		
0.200	0.006		0.13	92.5		
0.202	0.006		0.13	95.0		
0.200	0.005		0.11	97.5		
0.202	0.007		0.15	1.3		
0.200	0.007		0.15	25.6		
0.198	0.007		0.15	87.8		
0.201	0.008		0.17	1.6		
0.203	0.006	45	0.13	4.1	34.3	39.1
0.202	0.005		0.11	22.4		

0.202	0.003		0.06	60.1	
0.199	0.004		0.09	0.5	
0.201	0.008		0.17	7.5	
0.202	0.008		0.17	1.4	
0.202	0.006		0.13	89.0	
0.201	0.007		0.15	89.6	
0.194	0.006		0.13	0.8	
0.194	0.006		0.13	2.8	
0.203	0.008		0.17	45.1	
0.200	0.006	60	0.13	94.7	48.6
0.200	0.007		0.15	96.7	
0.199	0.006		0.13	0.4	
0.199	0.006		0.13	75.5	
0.200	0.005		0.11	72.6	

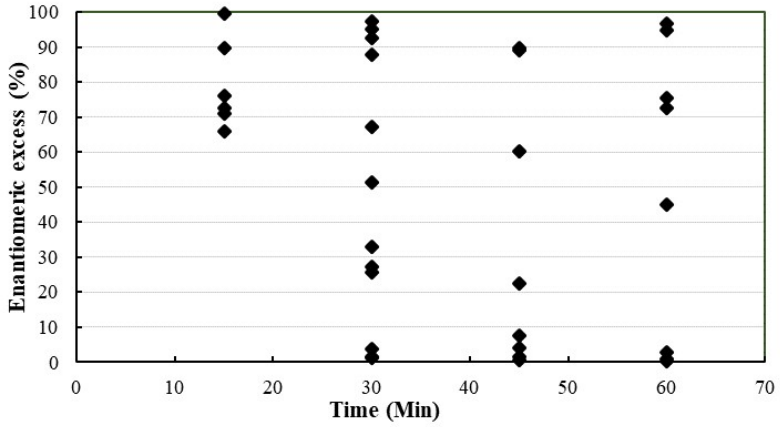


Figure S2 : Graphical representation of the mechanochemical kinetics of racemization performed using NaOH as racemizing agent (30Hz).

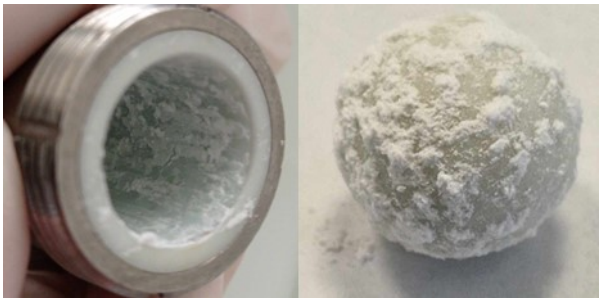


Figure S3 : Picture of the bead and milling jar after 60minutes of milling by using NaOH as racemizing agent.

2. Ex-Situ analyses

i. Powder X-ray diffraction (PXRD)

PXRD analyzes are performed on the ground product after 60 minutes of milling. The following figure (**Figure S4**) is an example of PXRD of a 60min milling without solvent

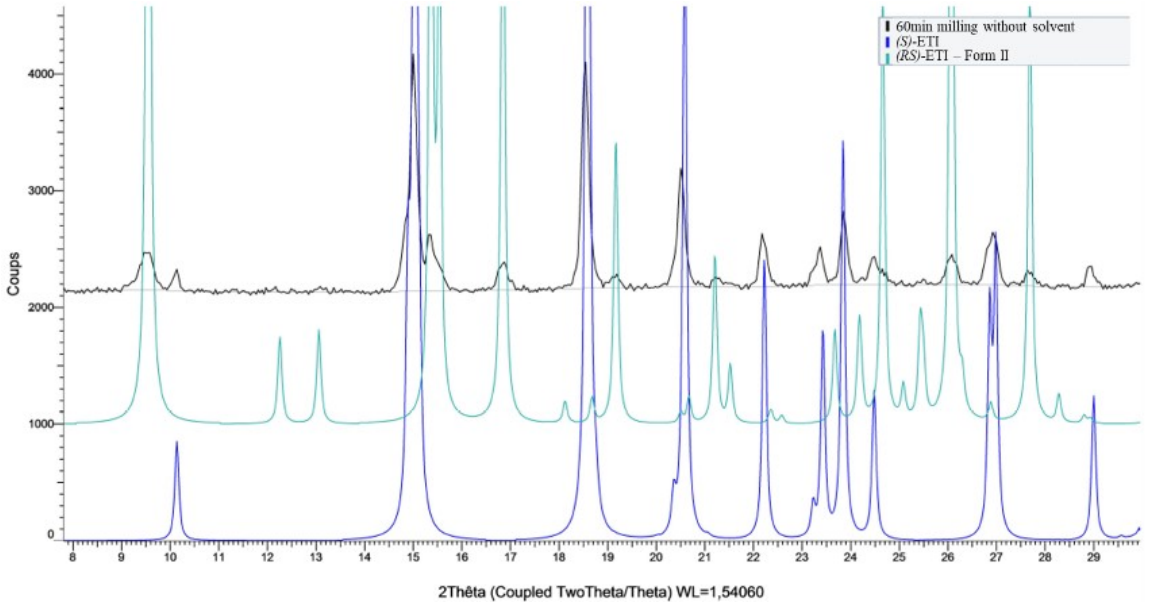


Figure S4 : PXRD pattern of the ground product (NaOH, 60min, 30Hz, in black) compared to the pattern of the enantiopure reference (dark blue) and the racemic one (light blue).

ii. ^{1}H Nuclear magnetic resonance (^{1}H NMR)

^{1}H NMR analyzes are performed on the ground product after 60 minutes of milling. Corresponding NMR spectra is found in the following figure. (**Figure S5**)

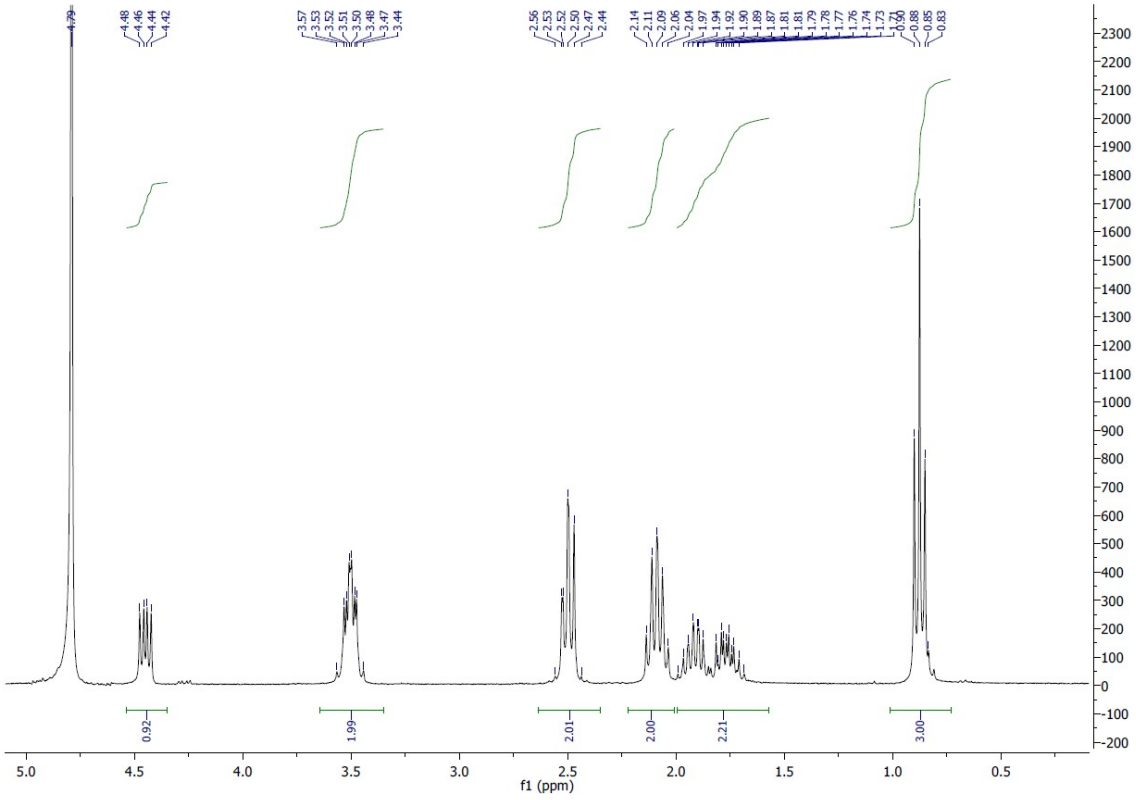


Figure S5 :1H NMR of the ground product (NaOH, 30Hz, 60min).

iii. Infra-red spectrometry (IR)

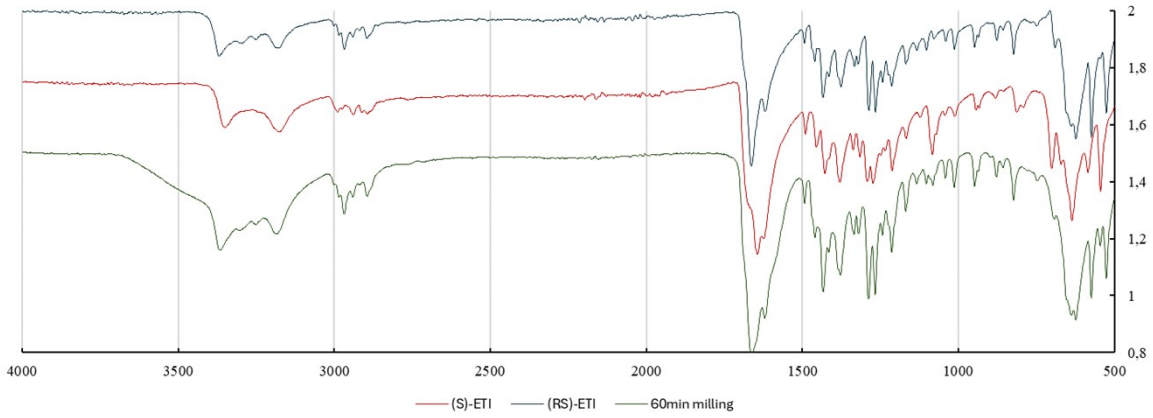


Figure S6 : IR spectra of the ground product (NaOH, 60min, 30Hz, in blue) compared to the enantiopure reference (red) and the racemic one (green)

3. Increasing NaOH equivalent

Table S6 : Mechanochemical racemization performed using NaOH as racemizing agent (0.5eq.,30Hz).

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (g)	Eq.	*e.e.* (%)	*Mean*	*Standard deviation*
0.201	0.020	0.43	83.16	68.7	12.2
0.202	0.021	0.44	76.98		
0.199	0.020	0.43	67.6		
0.200	0.022	0.47	48.76		
0.198	0.021	0.46	78.04		
0.203	0.022	0.46	65.96		
0.202	0.022	0.47	69.86		
0.202	0.022	0.46	52.24		

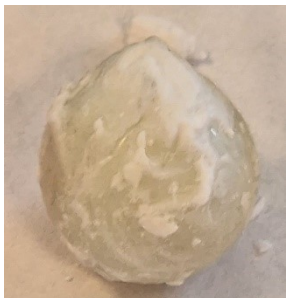


Figure S7 : Picture of the bead and milling jar after 60minutes of milling by using 0.5 eq. of NaOH as racemizing agent

4. Water LAG experiments

i. Without glove bag

Table S7 : Mechanochemical racemization performed using NaOH as racemizing agent and 10µL of water (30Hz, η=0.05µL.mg^{-1})

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (g)	Eq.	*e.e.* (%)	V_{H_2O} (µl)	*Mean*	*Standard deviation*
0.200	0.006	0.13	82.4	10	87.4	11.5
0.202	0.005	0.11	94.6			
0,202	0,006	0,13	82,4			
0,202	0,005	0,11	94,6			
0,201	0,006	0,13	91,8			

0,199	0,006	0,13	81,0
0,200	0,007	0,15	63,3
0,196	0,008	0,17	98,1

ii. With glove bag

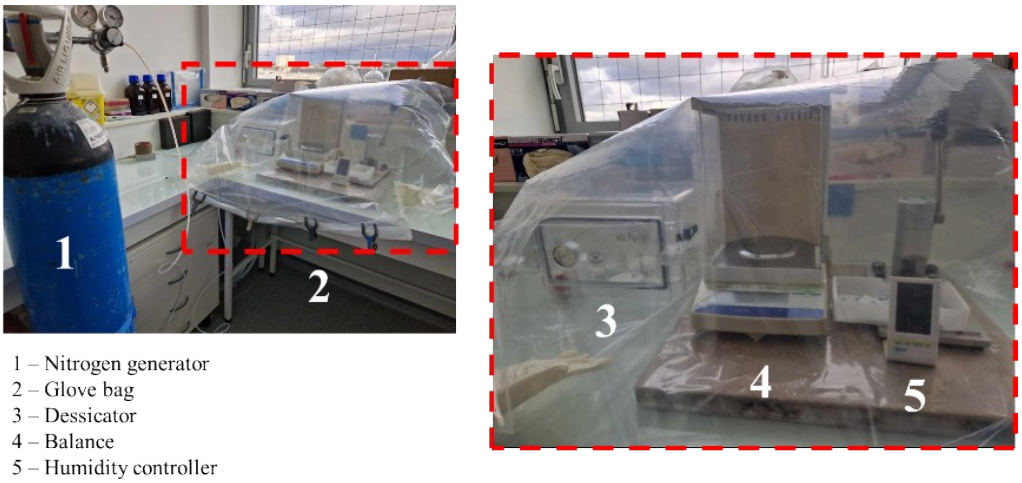
Table S8 : Mechanochemical racemization performed using NaOH as racemizing agent and 10µL of water. Glove bag has been used for the filling step (30Hz, η=0.05µL.mg^{-1})

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (g)	Eq.	*e.e.* (%)	V_{H_2O} (µl)	*Mean*	*Standard deviation*
0,200	0,0061	0,13	99,1	10	98	1.5
0,201	0,0077	0,16	98,5			
0,200	0,0065	0,14	99,5			
0,202	0,0075	0,16	98,6			
0,199	0,0065	0,14	95,9			
0,199	0,006	0,13	96,4			

5. Implementation of the glove bag

i. Experimental procedure

Samples are stored in a desiccator where relative humidity is controlled by pentoxide phosphorous (P_2O_5). This desiccator is putted in a glove bag where the jar will be filled (following picture, **Figure S8**). The relative humidity is decreased by flushing as much as necessary nitrogen in the glove bag. A humidity controller permits to keep RH under 20%. Once the filling is performed, the jar is closed and a piece of tap is putted on the junction. The milling starts directly after this step.



1 – Nitrogen generator
2 – Glove bag
3 – Dessicator
4 – Balance
5 – Humidity controller

Figure S8 : Picture of the experimental set-up of the glove bag used for the mechanochemical experiments.

ii. Reproducibility study

The results found in **Table S9** are a series of milling done during 60min without adding solvent (30Hz).

Table S9 : Mechanochemical racemization performed using NaOH as racemizing agent. Glove bag has been used for the filling step (30Hz, $t_{milling}$ = 60min)

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (g)	Eq.	*e.e.* (%)	*Mean*	*Standard deviation*
0.202	0.0082	0.17	9.2	56.7	26.1
0.201	0.0074	0.16	23.0		
0.200	0.0078	0.17	36.7		
0.202	0.0076	0.16	37.2		
0.205	0.0074	0.15	38.5		

0.203	0.0078	0.16	46.5
0.202	0.0072	0.15	46.5
0.200	0.007	0.15	49.5
0.202	0.0063	0.13	60.5
0.202	0.0074	0.16	64.5
0.199	0.007	0.15	67.3
0.202	0.0074	0.16	69.2
0.201	0.0065	0.14	70.6
0.205	0.0076	0.16	71.0
0.201	0.007	0.15	72.1
0.202	0.0073	0.15	73.7
0.203	0.0061	0.13	74.9
0.203	0.0062	0.13	77.9
0.201	0.0075	0.16	88.8
0.202	0.0058	0.12	96.1

6. Adding NaCl as a solid auxiliary

i. Without using glove bag

Table S10 : Mechanochemical racemization performed using NaOH as racemizing agent and NaCl as solid lubricant. (30Hz, $t_{milling}$ = 60min)

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (g)	Eq.	m_{NaCl} (g)	Ratio *(S)*-ETI:NaCl	*e.e.* (%)	*Mean*	*Standard deviation*
0,1996	0,0074	0,16	0,1014	1:0.5	9.2	56.6	29.2
0,2014	0,007	0,15	0,0996		23.0		
0,2043	0,0063	0,13	0,0995		36.7		
0,2039	0,0092	0,19	0,0971		37.2		
0,2016	0,0091	0,19	0,1009		38.5		
0,2014	0,0079	0,17	0,104		46.5		

Figure S9 : Picture of the bead and milling jar after 60minutes of milling by using NaOH as racemizing agent and NaCl as solid lubricant

ii. Using glove bag – influence of the loading

Table S11 : Mechanochemical racemization performed using NaOH as racemizing agent and NaCl as solid lubricant. Glove bag has been used for the filling step (30Hz, $t_{milling}$ = 60min)

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (mg)	Eq.	$m_{(NaCl)}$ (g)	$m_{(NaCl)}$/ $m_{((S)\text{-ETI})}$	*e.e.* (%)	*Mean*	*Standard deviation*
203.9	7.1	0.15	50.0	0.25	85.4	54.2	18.0
198.1	7.4	0.16	50.5	0.25	58.4		
201.1	8.0	0.17	52.8	0.26	45.0		

202.9	7.2	0.15	53.3	0.26	59.3		
201.4	7.2	0.15	54.4	0.27	42.0		
198.8	7.1	0.15	55.7	0.28	35.1		
203.8	7.8	0.16	98.4	0.48	76.3		
202.7	7.1	0.15	100.2	0.49	60.1		
205.4	7.3	0.15	102.9	0.50	86.2		
201.8	7.0	0.15	101.3	0.50	83.1		
200.5	7.3	0.16	101.6	0.51	71.5		
202.7	8.9	0.19	103.2	0.51	53.5	75.5	12.5
199.9	7.9	0.17	101.9	0.51	76.3		
201.6	8.9	0.19	103.1	0.51	56.0		
204.4	7.1	0.15	104.8	0.51	87.1		
198.3	7.1	0.15	104.0	0.52	84.9		
201.2	7.1	0.15	105.6	0.52	86.2		
199.5	7.1	0.15	105.2	0.53	85.3		
201.9	6.8	0.14	200.2	0.99	86.1		
200.2	7.3	0.15	199.2	0.99	95.5		
203.8	7.2	0.15	203.4	1.00	77.0	88.3	8.6
204.4	6.9	0.14	204.5	1.00	94.5		
200.7	7.8	0.17	201.9	1.01	89.7		

iii. Kinetics study

Table S12 : Mechanochemical kinetics of racemization performed using NaOH as racemizing agent and NaCl as solid lubricant. Glove bag has been used for the filling step (30Hz, $t_{milling}$ = 60min)

$m_{((S)\text{-ETI})}$ (g)	$m_{(NaOH)}$ (g)	Eq.	$m_{(NaCl)}$ (g)	$m_{(NaCl)}/ m_{((S)\text{-ETI})}$	*e.e.* (%)	Time (min)	*Mean*	*Standard deviation*
203.8	7.8	0.16	98.4	0.48	76.3			
202.7	7.1	0.15	100.2	0.49	60.1			
205.4	7.3	0.15	102.9	0.50	86.2			
201.8	7.0	0.15	101.3	0.50	83.1			
200.5	7.3	0.16	101.6	0.51	71.5			
202.7	8.9	0.19	103.2	0.51	53.5			
199.9	7.9	0.17	101.9	0.51	76.3			
201.6	8.9	0.19	103.1	0.51	56.0	60	75.5	79.7
204.4	7.1	0.15	104.8	0.51	87.1			
198.3	7.1	0.15	104.0	0.52	84.9			
201.2	7.1	0.15	105.6	0.52	86.2			
199.5	7.1	0.15	105.2	0.53	85.3			
201.9	6.8	0.14	200.2	0.99	86.1			
200.2	7.3	0.15	199.2	0.99	95.5			
206.0	7.9	0.16	98.3	0.48	49.5			
206.9	8.0	0.16	100.0	0.48	26.8			
202.5	7.3	0.15	98.1	0.48	45.0			
204.9	7.8	0.16	100.1	0.49	12.2	120	36.4	14.1
201.2	7.9	0.17	100.1	0.50	41.5			
203.5	7.5	0.16	107.1	0.53	43.2			

203.2	7.1	0.15	97.9	0.48	15.0	180	21.3	16.8
203.7	7.4	0.15	98.3	0.48	31.5			
201.4	8.5	0.18	103.1	0.51	1.6			
204.0	8.2	0.17	106.0	0.52	25.3			
200.5	8.2	0.17	105.0	0.52	7.4			
199.8	7.2	0.15	106.9	0.53	47.2			
202.6	7.6	0.16	96.0	0.47	3.0	240	2.8	3.7
203.2	7.0	0.15	102.3	0.50	0.6			
201.7	7.8	0.16	101.9	0.50	0.3			
198.8	7.7	0.16	100.5	0.51	2.1			
201.9	7.9	0.17	102.7	0.51	10.0			
199.6	7.5	0.16	104.7	0.52	0.9			

Figure S10 : Picture of the bead and milling jar after 60minutes of milling by using NaOH as racemizing agent and NaCl as solid lubricant. Glove bag has been used for the filling step.

7. In-situ monitoring via PXRD.

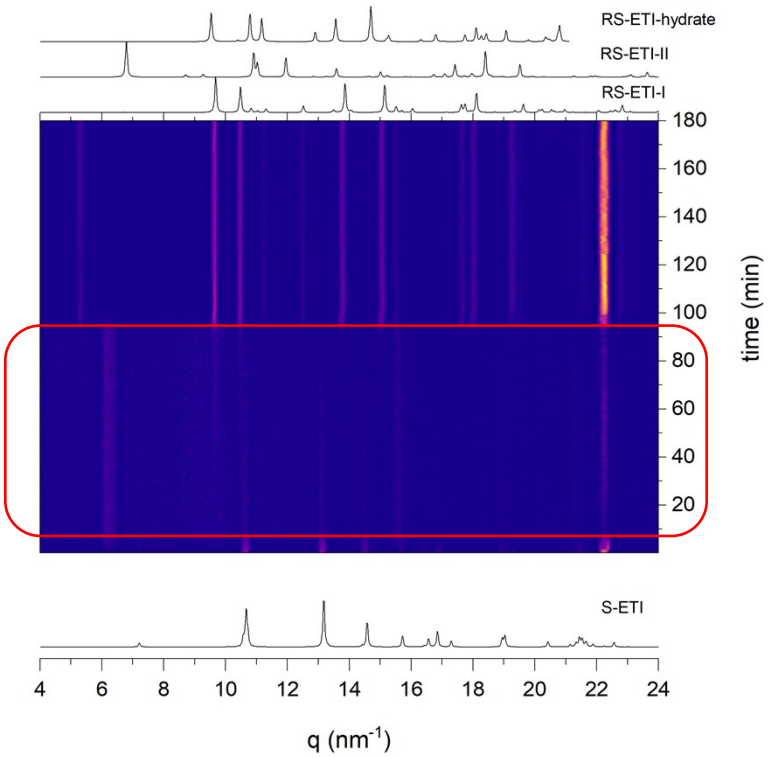


Figure S11a : Plotting of the data collected via in situ monitoring of the mechanochemical reaction. We can see the 'same' path as in **Figure 4** in the main text, but with the appearance of Form I after more than 1 hour of 'sticky' phase (red rectangle).

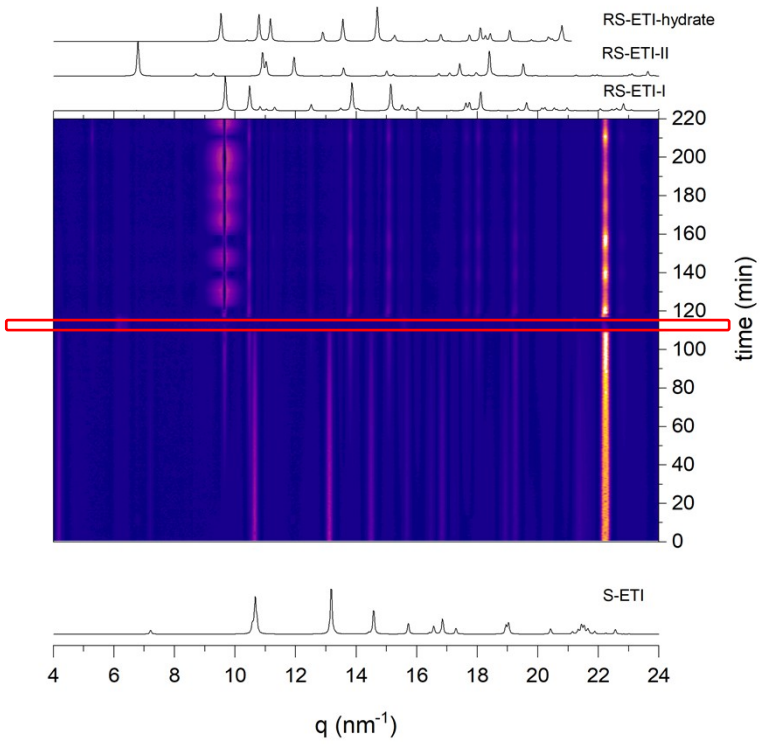


Figure S11b: Plotting of the data collected via in situ monitoring of the mechanochemical reaction. We can see the 'same' path as in **Figure 4** in the main text, but with the full conversion of Form I after more than 1 hour, **but** just ten minutes of 'sticky' phase (red rectangle). N.B. is there an artefact in the data treatment for the peak in position ca 10 nm^{-1}.