Supporting Information

Scalable and Sustainable Mechanochemical Deracemisation by Resonant Acoustic Mixing

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1.1. MCDR-BM: Solvent Screening

1.1.1. Compound 1

Table S1: Parameters of solvent screening for the MCDR-BM of compound **1**. The reactions were carried out at a milling frequency of 30 Hz (Tol: Toluene; Hex: *n*-Hexane).

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LAG	$V_{Solvent}$ [µL]	η [µL/mg]	Jar Material	Final *ee*	Time
0.20	20%	0.66	6.3	Tol	108	0.023	ZrO_2	30%	90 min
0.20	20%	0.66	6.3	MeCN	108	0.023	ZrO_2	49%	90 min
0.20	20%	0.66	6.3	Hex	108	0.023	ZrO_2	44%	90 min
0.20	20%	0.66	6.3	MeOH	108	0.023	ZrO_2	49%	90 min
0.20	20%	0.66	6.3	DCM	108	0.023	ZrO_2	37%	90 min
0.20	20%	0.66	6.3	Tol	1000	0.21	ZrO_2	17%	90 min
0.20	20%	0.66	6.3	MeCN	1,000	0.21	ZrO_2	73%	90 min
0.20	20%	0.66	6.3	Hex	1,000	0.21	ZrO_2	29%	90 min
0.20	20%	0.66	6.3	MeOH	1,000	0.21	ZrO_2	32%	90 min
0.20	20%	0.66	6.3	DCM	1,000	0.21	ZrO_2	61%	90 min
0.28	20%	0.66	6.3	Tol	150	0.023	PTFE	44%	90 min
0.28	20%	0.66	6.3	MeCN	150	0.023	PTFE	66%	90 min
0.28	20%	0.66	6.3	Hex	150	0.023	PTFE	37%	90 min
0.28	20%	0.66	6.3	MeOH	150	0.023	PTFE	38%	90 min
0.28	20%	0.66	6.3	DCM	150	0.023	PTFE	57%	90 min
0.28	20%	0.66	6.3	Tol	1,400	0.21	PTFE	24%	90 min
0.28	20%	0.66	6.3	MeCN	1,400	0.21	PTFE	64%	90 min
0.28	20%	0.66	6.3	Hex	1,400	0.21	PTFE	34%	90 min
0.28	20%	0.66	6.3	MeOH	1,400	0.21	PTFE	23%	90 min
0.28	20%	0.66	6.3	DCM	1,400	0.21	PTFE	66%	90 min
0.28	0%	0.66	6.3	Tol	150	0.023	PTFE	13%	17 h
0.28	0%	0.66	6.3	MeCN	150	0.023	PTFE	84%	17 h
0.28	0%	0.66	6.3	MeCN	1000	0.21	ZrO_2	2%	17 h

1.1.2. Compound 2

Table S2: Parameters of solvent screening for the MCDR-BM of compound **2**. The reactions were carried out at a milling frequency of 30 Hz (Tol: Toluene; Hex: *n*-Hexane).

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LAG	$V_{Solvent}$ [µL]	η [µL/mg]	Jar Material	Final *ee*	Time
0.20	20%	0.3	6.3	Tol	108	0.023	ZrO_2	73%	90 min
0.20	20%	0.3	6.3	MeCN	108	0.023	ZrO_2	83%	90 min
0.20	20%	0.3	6.3	Hex	108	0.023	ZrO_2	60%	90 min
0.20	20%	0.3	6.3	MeOH	108	0.023	ZrO_2	74%	90 min
0.20	20%	0.3	6.3	DCM	108	0.023	ZrO_2	54%	90 min
0.20	20%	0.3	6.3	Tol	1,000	0.21	ZrO_2	32%	90 min
0.20	20%	0.3	6.3	MeCN	1,000	0.21	ZrO_2	74%	90 min
0.20	20%	0.3	6.3	Hex	1,000	0.21	ZrO_2	37%	90 min
0.20	20%	0.3	6.3	MeOH	1,000	0.21	ZrO_2	2%	90 min
0.20	20%	0.3	6.3	DCM	1,000	0.21	ZrO_2	1%	90 min
0.28	20%	0.3	6.3	Tol	150	0.023	PTFE	47%	90 min
0.28	20%	0.3	6.3	MeCN	150	0.023	PTFE	86%	90 min
0.28	20%	0.3	6.3	Hex	150	0.023	PTFE	50%	90 min
0.28	20%	0.3	6.3	MeOH	150	0.023	PTFE	66%	90 min
0.28	20%	0.3	6.3	DCM	150	0.023	PTFE	45%	90 min
0.28	20%	0.3	6.3	Tol	1,400	0.21	PTFE	36%	90 min
0.28	20%	0.3	6.3	MeCN	1,400	0.21	PTFE	56%	90 min
0.28	20%	0.3	6.3	Hex	1,400	0.21	PTFE	55%	90 min
0.28	20%	0.3	6.3	MeOH	1,400	0.21	PTFE	3%	90 min
0.28	20%	0.3	6.3	DCM	1,400	0.21	PTFE	0%	90 min
0.28	0%	0.3	6.3	MeCN	150	0.023	PTFE	85%	24 h
0.28	0%	0.3	6.3	MeCN	150	0.023	PTFE	82%	24 h

1.1.3. Compound 3

Table S3: Parameters of solvent screening for the MCDR-BM of compound **3**. The reactions were carried out at a milling frequency of 30 Hz (Tol: Toluene; Hex: *n*-Hexane).

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LAG	$V_{Solvent}$ [µL]	η [µL/mg]	Jar Material	Final *ee*	Time
0.20	20%	0.3	6.3	Tol	108	0.023	ZrO_2	33%	90 min
0.20	20%	0.3	6.3	MeCN	108	0.023	ZrO_2	33%	90 min
0.20	20%	0.3	6.3	Hex	108	0.023	ZrO_2	33%	90 min
0.20	20%	0.3	6.3	MeOH	108	0.023	ZrO_2	30%	90 min
0.20	20%	0.3	6.3	DCM	108	0.023	ZrO_2	33%	90 min
0.20	20%	0.3	6.3	Tol	1,000	0.21	ZrO_2	27%	90 min
0.20	20%	0.3	6.3	MeCN	1,000	0.21	ZrO_2	36%	90 min
0.20	20%	0.3	6.3	Hex	1,000	0.21	ZrO_2	33%	90 min
0.20	20%	0.3	6.3	MeOH	1,000	0.21	ZrO_2	15%	90 min
0.20	20%	0.3	6.3	DCM	1,000	0.21	ZrO_2	2%	90 min
0.28	20%	0.3	6.3	Tol	150	0.023	PTFE	48%	90 min
0.28	20%	0.3	6.3	MeCN	150	0.023	PTFE	48%	90 min
0.28	20%	0.3	6.3	Hex	150	0.023	PTFE	42%	90 min
0.28	20%	0.3	6.3	MeOH	150	0.023	PTFE	28%	90 min
0.28	20%	0.3	6.3	DCM	150	0.023	PTFE	40%	90 min
0.28	20%	0.3	6.3	Tol	1,400	0.21	PTFE	32%	90 min
0.28	20%	0.3	6.3	MeCN	1,400	0.21	PTFE	35%	90 min
0.28	20%	0.3	6.3	Hex	1,400	0.21	PTFE	31%	90 min
0.28	20%	0.3	6.3	MeOH	1,400	0.21	PTFE	20%	90 min
0.28	20%	0.3	6.3	DCM	1,400	0.21	PTFE	2%	90 min
0.28	0%	0.3	6.3	MeCN	150	0.023	PTFE	74%	48 h

1.1.4. Supplementary Analysis of the Results

Across all three systems, *n*-hexane consistently gave the lowest enantiomeric excess (*ee*). The highest *ee* of 60% was obtained for compound **2** in a ZrO_2 jar at η = 0.023 µL/mg, while at η = 0.21 µL/mg, the *ee* dropped to 50%. Most other experiments, including those with compounds **1** and **3**, did not exceed 45% *ee* under comparable conditions. Methanol produced only moderate results, with compound **1** giving 23–49% *ee* and compound **3** showing slightly lower values (15–30% *ee*). Remarkably, for compound **2** at high η, complete racemization occurred in both ZrO_2 and PTFE jars, whereas at low η, the outcome completely reversed, giving 74% *ee* in ZrO_2 and 66% *ee* in PTFE—the best results obtained with MeOH. DCM gave an overall improvement over MeOH for compound **1** (37–66% *ee*); however, as with MeOH, compounds **2** and **3** underwent complete racemization at high η. At low η, *ee* values ranged from 33% to 54%. Toluene led to the second-highest enantioenrichment. From our previous work, we already knew that toluene performed well for compound **2**—for example, ZrO_2 at low η gave 73% *ee*. However, for compounds **1** and **3**, the results remained moderate (17–48% *ee*). Finally, the highest enantioenrichment was achieved with MeCN as the LAG-additive. Consistent with our earlier findings, MeCN performed efficiently for compound **1**, giving 49–73% *ee*, with the ZrO_2 jar at low η being the only case below 64% *ee*. Although compound **3** remained difficult to deracemize (27–48% *ee*), compound **2** displayed a notable improvement compared to

toluene. Apart from PTFE at high *η*, compound **2** consistently afforded *ee* values above 80% (83–86% *ee*) using MeCN as the LAG-additive, confirming MeCN's superior performance under solvent-minimized mechanochemical conditions.

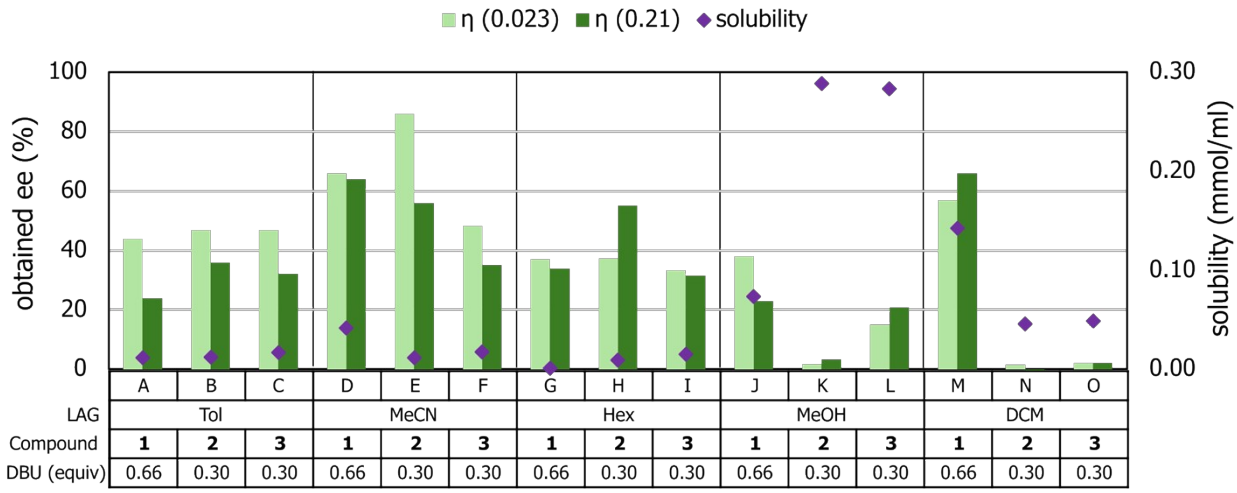


Figure S1 *ee* obtained for compounds **1**, **2**, and **3** from an enantioenriched mixture (20%), combined with their solubility (mmol/mL) in the respective LAG-additive under BM conditions. The table below lists, from top to bottom: LAG-additive, compound, and DBU equivalents. PTFE jars (14 mL) were charged with imine (280 mg, 20% *ee*), NaCl (6.3 g), LAG-additive (*η* = 0.023 µL/mg, 150 µL; *η* = 0.21 µL/mg, 1400 µL) and ZrO_2 balls (3x10 mm) and milled at 30 Hz for 1.5 h.

1.2. MCDR-RAM: Control Experiments

1.2.1. Compound 1

Table S4: Parameters of control experiment for the MCDR-RAM of compound **1**. The reactions were carried out at an acceleration of 100 *g* (Tol: Toluene).

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LARAM	$V_{Solvent}$ [µL]	η [µL/mg]	Jar size (ml)	Final *ee*	Time
0.14	25%	0.66	3.15	-	-	-	5	40%	90 min
0.14	25%	0.66	-	Tol	75	0.54	5	15%	90 min
0.14	25%	0.66	-	MeCN	75	0.54	5	31%	90 min

1.2.2. Compound 2

Table S5: Parameters of control experiment for the MCDR-RAM of compound **2**. The reactions were carried out at an acceleration of 100 *g* (Tol: Toluene).

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LARAM	$V_{Solvent}$ [µL]	η [µL/mg]	Jar size (ml)	Final *ee*	Time
0.14	20%	0.30	3.15	-	-	-	5	32%	90 min
0.14	20%	0.30	-	Tol	75	0.54	5	11%	90 min
0.14	20%	0.30	-	MeCN	75	0.54	5	49%	90 min

1.3. MCDR-RAM: Solvent and Scale-up Effect

1.3.1. Compound 1

Table S6: Parameters used in the solvent- and scale-up study of MCDR-RAM of compound **1**. The reactions were carried out at an acceleration of 100 *g* (Tol: Toluene). Starting from 0% *ee*, the enantiomer enriched is mentioned between brackets.

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LARAM	$V_{Solvent}$ [µL]	η [µL/mg]	Jar size (ml)	Final *ee*	Time
0.14	25%	0.66	3.15	Tol	75	0.02	5	74%	90 min
0.14	25%	0.66	3.15	Tol	75	0.02	5	89%	90 min
0.14	25%	0.66	3.15	Tol	75	0.02	5	82%	90 min
0.14	25%	0.66	3.15	MeCN	75	0.02	5	84%	90 min
0.14	25%	0.66	3.15	MeCN	75	0.02	5	85%	90 min
0.14	25%	0.66	3.15	MeCN	75	0.02	5	78%	90 min
0.14	25%	0.66	3.15	MeCN	75	0.02	5	91%	180 min
0.14	25%	0.66	3.15	MeCN	75	0.02	5	89%	180 min
0.14	25%	0.66	3.15	MeCN	75	0.02	5	50%[1]	180 min
0.14	25%	0.66	3.15	Tol	700	0.21	5	67%	90 min
0.14	25%	0.66	3.15	Tol	700	0.21	5	86%	90 min
0.14	25%	0.66	3.15	Tol	700	0.21	5	77%	90 min
0.14	25%	0.66	3.15	MeCN	700	0.21	5	83%	90 min
0.14	25%	0.66	3.15	MeCN	700	0.21	5	29%	90 min
0.14	25%	0.66	3.15	MeCN	700	0.21	5	0%	90 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	79%	90 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	85%	90 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	89%[2]	90 min
0.70	25%	0.66	15.75	Tol	1700	0.10	25	83%	90 min
0.70	25%	0.66	15.75	Tol	1700	0.10	25	85%	90 min
0.70	25%	0.66	15.75	Tol	1700	0.10	25	88%	90 min
0.70	25%	0.66	15.75	Tol	3500	0.21	25	75%	90 min
0.70	25%	0.66	15.75	Tol	3500	0.21	25	55%	90 min
0.70	25%	0.66	15.75	Tol	3500	0.21	25	91%	90 min
0.70	25%	0.66	15.75	MeCN	375	0.02	25	82%	90 min
0.70	25%	0.66	15.75	MeCN	375	0.02	25	84%	90 min
0.70	25%	0.66	15.75	MeCN	375	0.02	25	85%	90 min
0.70	25%	0.66	15.75	MeCN Tol	292.6 82.4	0.02	25	86%	90 min
0.70	25%	0.66	15.75	MeCN Tol	292.6 82.4	0.02	25	85%	90 min
0.70	25%	0.66	15.75	MeCN Tol	292.6 82.4	0.02	25	87%	90 min

[1] Jar broke during the experiment.
[2] **HPLC** (retention time, min): 12.7, 18.4 (**Figure S11**).

0.70	0%	0.66	15.75	MeCN	375	0.02	25	73% (*S*)	90 min
0.70	0%	0.66	15.75	Tol	375	0.02	25	4%	90 min
0.70	0%	0.66	15.75	Tol	375	0.02	25	78% (*S*)	90 min
0.14	0%	0.66	3.15	Tol	75	0.02	5	1%	17 h
0.14	0%	0.66	3.15	Tol	75	0.02	5	3%	17 h
0.14	0%	0.66	3.15	Tol	75	0.02	5	1%	17 h
0.14	0%	0.66	3.15	MeCN	75	0.02	5	14% (*S*)	17 h
0.14	0%	0.66	3.15	MeCN	75	0.02	5	18% (*S*)	17 h
0.14	0%	0.66	3.15	MeCN	75	0.02	5	50% (*S*)	17 h
0.14	0%	0.66	3.15	Tol	700	0.21	5	0%	17 h
0.14	0%	0.66	3.15	Tol	700	0.21	5	0%	17 h
0.14	0%	0.66	3.15	Tol	700	0.21	5	0%	17 h
0.14	0%	0.66	3.15	MeCN	700	0.21	5	17% (*R*)	17 h
0.14	0%	0.66	3.15	MeCN	700	0.21	5	18% (*S*)	17 h
0.14	0%	0.66	3.15	MeCN	700	0.21	5	86% (*R*)	17 h
0.70	50%	0.66	15.75	Tol	375	0.02	25	88%	90 min
0.70	50%	0.66	15.75	Tol	375	0.02	25	89%	90 min
0.70	50%	0.66	15.75	Tol	375	0.02	25	89%	90 min
0.70	50%	0.66	15.75	MeCN	375	0.02	25	87%	90 min
0.70	50%	0.66	15.75	MeCN	375	0.02	25	88%	90 min
0.70	50%	0.66	15.75	MeCN	375	0.02	25	93%	90 min
0.70	75%	0.66	15.75	Tol	375	0.02	25	90%	90 min
0.70	75%	0.66	15.75	Tol	375	0.02	25	83%	90 min
0.70	75%	0.66	15.75	Tol	375	0.02	25	84%	90 min
0.70	75%	0.66	15.75	MeCN	375	0.02	25	81%	90 min
0.70	75%	0.66	15.75	MeCN	375	0.02	25	92%	90 min
0.70	75%	0.66	15.75	MeCN	375	0.02	25	89%	90 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	76%	15 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	71%	15 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	77%	15 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	66%	30 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	79%	30 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	77%	30 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	81%	60 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	76%	60 min
0.70	25%	0.66	15.75	Tol	375	0.02	25	77%	60 min

1.3.2. Compound 2

Table S7: Parameters used in the solvent- and scale-up study of MCDR-RAM of compound **2**. The reactions were carried out at an acceleration of 100 *g* (Tol: Toluene). Starting from 0% *ee*, the enantiomer enriched is mentioned between brackets.

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LARAM	$V_{Solvent}$ [µL]	η [µL/mg]	Jar size (ml)	Final *ee*	Time
0.14	20%	0.3	3.15	Tol	75	0.02	5	65%	90 min
0.14	20%	0.3	3.15	Tol	75	0.02	5	29%	90 min
0.14	20%	0.3	3.15	Tol	75	0.02	5	18%	90 min
0.14	20%	0.3	3.15	MeCN	75	0.02	5	1%	90 min
0.14	20%	0.3	3.15	MeCN	75	0.02	5	12%	90 min
0.14	20%	0.3	3.15	MeCN	75	0.02	5	12%	90 min
0.14	20%	0.3	3.15	Tol	700	0.21	5	45%	90 min
0.14	20%	0.3	3.15	Tol	700	0.21	5	66%	90 min
0.14	20%	0.3	3.15	Tol	700	0.21	5	0%	90 min
0.14	20%	0.3	3.15	MeCN	700	0.21	5	16%	90 min
0.14	20%	0.3	3.15	MeCN	700	0.21	5	2%	90 min
0.14	20%	0.3	3.15	MeCN	700	0.21	5	5%	90 min
0.70	20%	0.3	15.75	Tol	375	0.02	25	88%[3]	90 min
0.70	20%	0.3	15.75	Tol	375	0.02	25	84%	90 min
0.70	20%	0.3	15.75	Tol	375	0.02	25	84%	90 min
0.70	20%	0.3	15.75	MeCN	375	0.02	25	0%	90 min
0.70	20%	0.3	15.75	MeCN	375	0.02	25	1%	90 min
0.70	20%	0.3	15.75	MeCN	375	0.02	25	1%	90 min
0.14	0%	0.3	3.15	Tol	75	0.02	5	28% (*S*)	17 h
0.14	0%	0.3	3.15	Tol	75	0.02	5	19% (*S*)	17 h
0.14	0%	0.3	3.15	Tol	75	0.02	5	35% (*S*)	17 h
0.14	0%	0.3	3.15	MeCN	75	0.02	5	11% (*S*)	17 h
0.14	0%	0.3	3.15	MeCN	75	0.02	5	4%	17 h
0.14	0%	0.3	3.15	MeCN	75	0.02	5	3%	17 h

[3] **HPLC** (retention time, min): 7.6, 10.5 (**Figure S12**).

1.3.3. Compound 3

Table S8: Parameters used in the solvent- and scale-up study of MCDR-RAM of compound **3**. The reactions were carried out at an acceleration of 100 *g* (Tol: Toluene). Starting from 0% *ee*, the enantiomer enriched is mentioned between brackets.

m_{Imine} [g]	Initial *ee*	DBU (equiv.)	m_{NaCl} [g]	LARAM	$V_{Solvent}$ [µL]	η [µL/mg]	Jar size (ml)	Final *ee*	Time
0.14	20%	0.3	3.15	Tol	75	0.02	5	1%	90 min
0.14	20%	0.3	3.15	Tol	75	0.02	5	10%	90 min
0.14	20%	0.3	3.15	Tol	75	0.02	5	17%	90 min
0.14	20%	0.3	3.15	MeCN	75	0.02	5	3%	90 min
0.14	20%	0.3	3.15	MeCN	75	0.02	5	1%	90 min
0.14	20%	0.3	3.15	MeCN	75	0.02	5	12%	90 min
0.14	20%	0.3	3.15	Tol	700	0.21	5	1%	90 min
0.14	20%	0.3	3.15	Tol	700	0.21	5	1%	90 min
0.14	20%	0.3	3.15	Tol	700	0.21	5	8%	90 min
0.14	20%	0.3	3.15	MeCN	700	0.21	5	1%	90 min
0.14	20%	0.3	3.15	MeCN	700	0.21	5	1%	90 min
0.14	20%	0.3	3.15	MeCN	700	0.21	5	2%	90 min
0.70	20%	0.3	15.75	Tol	375	0.02	25	83%[4]	90 min
0.70	20%	0.3	15.75	Tol	375	0.02	25	82%	90 min
0.70	20%	0.3	15.75	Tol	375	0.02	25	81%	90 min
0.70	20%	0.3	15.75	MeCN	375	0.02	25	2%	90 min
0.70	20%	0.3	15.75	MeCN	375	0.02	25	28%	90 min
0.70	20%	0.3	15.75	MeCN	375	0.02	25	3%	90 min
0.14	0%	0.3	3.15	Tol	75	0.02	5	13% (*R*)	17 h
0.14	0%	0.3	3.15	Tol	75	0.02	5	15% (*R*)	17 h
0.14	0%	0.3	3.15	Tol	75	0.02	5	3%	17 h
0.14	0%	0.3	3.15	MeCN	75	0.02	5	5%	17 h
0.14	0%	0.3	3.15	MeCN	75	0.02	5	5%	17 h
0.14	0%	0.3	3.15	MeCN	75	0.02	5	5%	17 h

[4] **HPLC** (retention time, min): 12.7, 18.6 (**Figure S13**).

2. Experimental Section

2.1. General Information

2.1.1. Materials

All chemicals were obtained from commercial sources and used without further purification

- **Carl Roth**: Sodium chloride (>99.8%)
- **BLDPharm**: (*RS*)-2-Aminobutyramide hydrochloride (95%)[5], (*S*)-2-Aminobutyramide hydrochloride (98%), (*RS*)-Phenylglycine (97%)
- **Fluorochem Ltd**.: (*RS*)-2-Aminobutyramide hydrochloride[6]
- **Sigma-Aldrich**: DBU (98%)[7], N-Methylmorpholine (99%)[5], o-Tolualdehyde (97%)[6]
- **TCI Chemicals**: Benzaldehyde (>98%), DBU (98%)[8], 2-Methylbenzaldehyde (98%), N-Methylmorpholine (>99%)[6], (S)-Phenylglycine (98%), o-Tolualdehyde (98%)[5]
- **Thermo Fisher Scientific**: Ammonia solution (28% NH_3 in H_2O), Thionyl chloride (99.7%),
- **VWR**: Acetonitrile, Dichloromethane, Diethyl ether, *n*-Hexane, Methanol, Toluene

2.1.2. Devices

X-ray powder diffraction (XRPD) measurements were carried out using a Bruker D8 Advance diffractometer equipped with a Cu-Kα radiation source (λ = 1.5406 Å), operating at 40 kV and 30 mA. Data were collected over a 2θ range of 5–40°, with a step size of 0.02° and a total acquisition time of three minutes.

^{1}H-Nuclear Magnetic Resonance (^{1}H-NMR) spectra were recorded on a Jeol JNM-ECZL400 R series spectrometer operating at 400 MHz. Spectra were acquired in DMSO-d_6, using the residual solvent signals as internal references. Chemical shifts and multiplicities are reported as follows: s = singlet, t = triplet, dd = doublet of doublets, td = triplet of doublets and m = multiplet.

Chiral High-Performance Liquid Chromatography (cHPLC) analyses were performed on a Waters ARC HPLC system using various columns, depending on the compound, including Daicel Chiralpak IA and Chiralcel OJ-H (5 µm, 4.6 × 250 mm). The mobile phase consisted of different solvent mixtures, such as isohexane (A), 2-propanol (B), and ethanol (C), with solvent ratios optimized for each analyte. Detection was achieved using a Waters PDA 2998 detector set at 230 nm. The chromatographic conditions for each compound are summarized as follows:

- Compound **1**: Chiralcel OJ-H; mobile phase: isocratic 80% A / 20% C for 30 min at 1 mL·min^{-1}; injection volume: 5 µL.
- Compound **2**: Chiralpak IA; mobile phase: isocratic 90% A / 10% B for 15 min at 1 mL·min^{-1}; injection volume: 5 µL.
- Compound **3**: Chiralpak IA; mobile phase: isocratic 95% A / 5% B for 15 min at 1 mL·min^{-1}; injection volume: 5 µL.

Ball milling experiments were conducted using a Retsch Mixer Mill MM400.

Resonant acoustic mixing (RAM) experiments were performed with a LabRAM I instrument from Resodyn Acoustic Mixers.

[5] For MCDR-BM
[6] For MCDR-RAM
[7] For compounds **2** and **3.**
[8] For compound **1**

2.2. Experimental Protocols

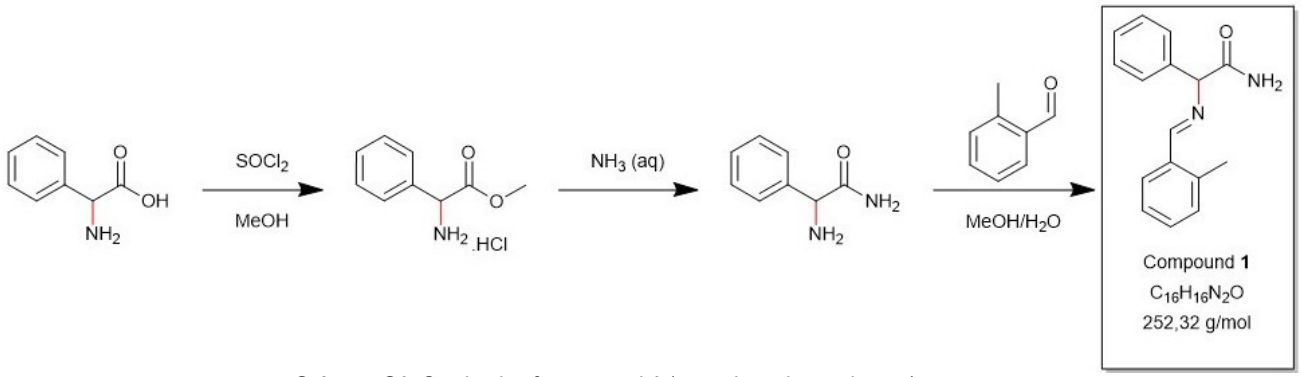
2.2.1. Preparation of Enantioenriched (*ee* = 20%) Starting Materials

For each system, the racemic and enantiopure powders are mixed in such proportions that a mixture with 20% *ee* is obtained. To homogenise the powder, it is dissolved either in DCM (compound **1**) or in methanol (compounds **2** and **3**) and then evaporated under reduced pressure (= 1 batch).

The batches differ slightly in reactivity due to differences in powder properties such as particle size distribution. This latter is crystallization dependent and can be challenging to replicate exactly. Properties such as particle size directly impact the deracemisation kinetics. Therefore, all MCDR-BM experiments were performed with powder from the same batch, while all MCDR-RAM experiments were performed with powder from a second batch (**Figure S8**, **Figure S9**, **Figure S10**, **Figure S16**, **Figure S17**, **Figure S20**, **Figure S23**)

2.2.2. Synthesis of Starting Materials

2.2.2.1. Synthesis of Compound 1



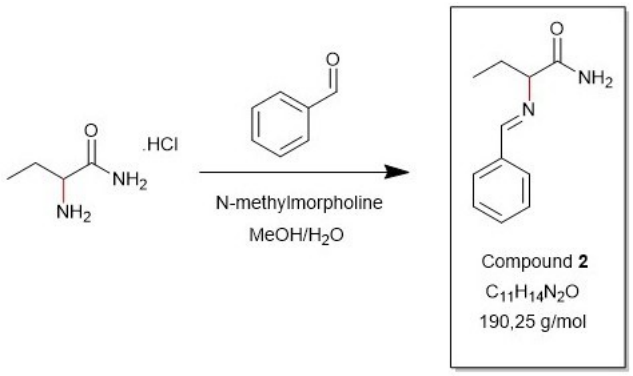
Scheme S1: Synthesis of compound **1** (racemic and enantiopure).

(*R,S*)-*N*-(2-methylbenzylidene)-phenylglycine amide [(*R,S*)-1]: [General procedure for **1**, based on previously reported in literature][1] (*R,S*)-Phenylglycine (10.18 g, 67.34 mmol, 1.0 equiv.) was dissolved in methanol (60 mL), after which the solution was cooled to 0 °C. Thionyl chloride (5.6 mL, 79.09 mmol, 1.2 equiv.) was added dropwise under stirring. The reaction mixture was stirred for 18 h while gradually warming to room temperature (20 °C), then heated to reflux for 1 h, before being allowed to cool again to 20 °C. The volume was reduced by ~1/3 after which diethyl ether (100 mL) was added to induce precipitation of the product. This was collected by filtration, affording 12.18 g of crude intermediate. The crude white solid was redissolved in aqueous ammonia (75 mL, 28% NH_3) and stirred at 20 °C for 22 h. The precipitate obtained was filtered, washed with cold water, and dried to afford the second intermediate product (5.58 g) without further purification. The second intermediate was then dissolved in a methanol/water mixture (30 mL, 2:1, v/v). 2-Methylbenzaldehyde (4.3 mL, 38.86 mmol, 1.0 equiv.) was added dropwise, and the reaction was stirred for 24 h at 20 °C, during which a precipitate gradually formed. The solid was isolated by filtration, washed sequentially with methanol/water (10 mL, 2:1, v/v) and methanol (6 mL), then dried under vacuum to yield a white powder (7.39 g, 29.27 mmol, 43 % overall yield). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.03 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.41 – 7.29 (m, 5H), 7.32 – 7.20 (m, 3H), 4.99 (s, 1H), 2.49 (s, 3H) (**Figure S2**). **XRPD** The experimental diffraction pattern is similar to the simulated one (**Figure S8**). **HPLC** (retention time, min.): 12.7, 18.6 (**Figure S14**).

(*S*)-1: According to the general procedure, starting from enantiopure (*S*)-phenylglycine, instead of the racemic phenylglycine: A white powder was obtained (5.58 g, 22.10 mmol, 33% overall yield). **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.72 (s, 1H), 8.03 (dd, J = 7.8, 1.6 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.41 – 7.31 (m, 5H), 7.31 – 7.21 (m, 3H), 4.99

(s, 1H), 2.50 (s, 3H) (**Figure S3**). **XRPD** The experimental diffraction pattern is similar to the simulated one (**Figure S8**). **HPLC** (retention time, min.): 18.5 (**Figure S15**).

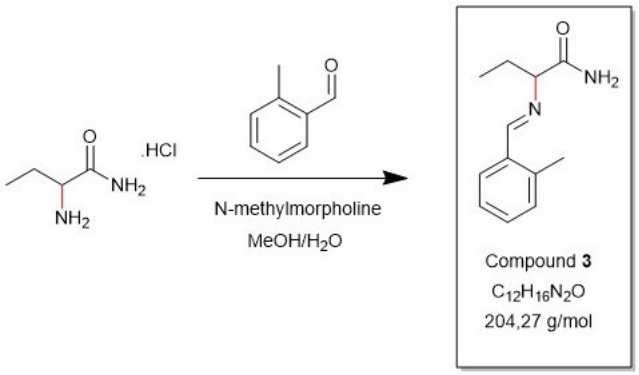
2.2.2.2. Synthesis of Compounds 2 and 3



Scheme S2: Synthesis of compound **2** (racemic and enantiopure).

(*R,S*)-2-((benzylidene)amino)butanamide [(*R,S*)-2]: [General procedure for compounds **2** and **3**, based on previously reported in literature][2] A solution of (*R,S*)-2-aminobutyramide hydrochloride (5.00 g, 36.1 mmol, 1.0 equiv.) was prepared in a 1:1 methanol–water mixture (total volume of 20 mL) at room temperature. N-Methylmorpholine (4.40 mL, 39.7 mmol, 1.1 equiv.) was added to this solution, followed by the dropwise addition of benzaldehyde (3.70 mL, 36.1 mmol, 1.0 equiv.), previously dissolved in methanol (5 mL). The mixture was stirred for 1 h, after which 20 mL of water was slowly added, and stirring was continued for an additional hour. The precipitated solid was collected by filtration, washed with a 1:1 (v/v) methanol–water mixture (10 mL), and dried under reduced pressure to yield a white crystalline powder (3.77 g, 19.8 mmol, 55%). This powder was then recrystallized twice in hot MeCN (4 mL/g of (*R,S*)-**2**) with a real yield of 80%. Note that a hot filtration could be necessary if impurities don't dissolve in hot MeCN. **^{1}H-NMR** (400 MHz, DMSO- d_6) δ 8.32 (s, 1H), 7.89 – 7.79 (m, 2H), 7.53 – 7.42 (m, 3H), 7.16 (s, 1H), 7.11 (s, 1H), 3.64 (dd, 1H), 1.98 – 1.75 (m, 1H), 1.75 – 1.57 (m, 1H), 0.81 (t, 3H) (**Figure S4**). **XRPD** The experimental diffraction pattern is similar to the simulated one (**Figure S9**). **HPLC** (retention time, min.): 7.6, 10.5 (**Figure S20**).

(*S*)-2: According to the general procedure, starting from enantiopure (*S*)-2-aminobutyramide hydrochloride instead, of the racemic 2-aminobutyramide hydrochloride: A white powder was obtained (5.05 g, 26.5 mmol, 74%). The final recrystallization occurred by doubling the amount of MeCN (8 mL/g of (*S*)-**2**). **^{1}H-NMR** (400 MHz, DMSO- d_6) δ 8.33 (s, 1H), 7.90– 7.78 (m, 2H), 7.55 – 7.40 (m, 3H), 7.17 (s, 1H), 7.12 (s, 1H), 3.65 (dd, 1H), 1.93 – 1.79 (m, 1H), 1.72 – 1.59 (m, 1H), 0.81 (t, 3H) (**Figure S5**). **XRPD** The experimental diffraction pattern is similar to the simulated one (**Figure S9**). **HPLC** (retention time, min.): 7.7 (**Figure S21**).

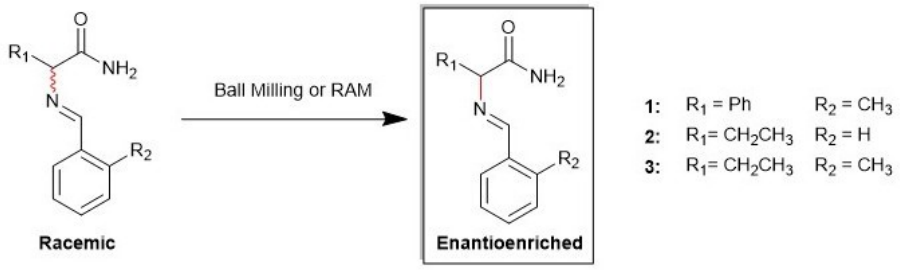


Scheme S3: Synthesis of compound **3** (racemic and enantiopure).

(*R,S*)-2-[(2-methylbenzylidene)amino]butanamide [(*R,S*)-3]: According to the general procedure, starting from *o*-tolualdehyde (4.20 mL, 36.3 mmol, 1.0 equiv.) instead of benzaldehyde: A white powder was obtained (5.30 g, 27.8 mmol, 77%).**^{1}H-NMR** (400 MHz, DMSO- d_6) δ 8.58 (s, 1H), 7.92 (dd, 1H), 7.35 (td, 1H), 7.29 – 7.21 (m, 2H), 7.17 (s, 1H), 7.05 (s, 1H), 3.67 (dd, 1H), 2.49 (s, 3H), 1.93 – 1.75 (m, 1H), 1.78 – 1.60 (m, 1H), 0.82 (t, 3H) (**Figure S6**). **XRPD** The experimental diffraction pattern is similar to the simulated one (**Figure S10**). **HPLC** (retention time, min.): 11.5, 12.6 (**Figure S23**).

(*R,S*)-3: According to the general procedure, starting from enantiopure (*S*)-2-aminobutyramide hydrochloride instead of the racemic one and from *o*-tolualdehyde (4.20 mL, 36.3 mmol, 1.0 equiv.) instead of benzaldehyde: A white powder was obtained (5.80 g, 30.5 mmol, 85%). The final recrystallization occurred by doubling the amount of MeCN (8 mL/g of (*S*)-**3**). **^{1}H-NMR** (400 MHz, DMSO- d_6) δ 8.58 (s, 1H), 7.92 (dd, 1H), 7.35 (td, 1H), 7.29 – 7.23 (m, 2H), 7.16 (s, 1H), 7.05 (s, 1H), 3.67 (dd, 1H), 2.49 (s, 3H), 1.94 – 1.77 (m, 1H), 1.75 – 1.59 (m, 1H), 0.82 (t, 3H) (**Figure S7**). **XRPD** The experimental diffraction pattern is similar to the simulated one (**Figure S10**). **HPLC** (retention time, min.): 11.7 (**Figure S24**).

2.2.3. Mechanochemical Deracemization (MCDR)



Scheme S4: Deracemization of imines.

2.2.3.1. MCDR by Ball-Milling (MCDR-BM)

In ZrO_2 jar

Compound 1: [General procedure based on previously reported in literature][3] A 10 mL ZrO_2 milling jar was charged sequentially with compound **1** (0.200 g, 0.793 mmol, 1.00 equiv.), NaCl (4.5 g) as a bulk material, two ZrO_2 balls (10 mm diameter), DBU (78.0 µL, 0.523 mmol, 0.66 equiv.), and the LAG-additive (for η = 0.023 µL/mg: 108 µL; for η = 0.21 µL/mg: 1.000 µL). The mixture was milled at 30 Hz for 1.5 h[9]. After milling, the solid was suspended in approximately 25 mL of water and filtered to remove NaCl, DBU, and LAG. The final product was obtained as a white powder and was analysed by cHPLC to determine the final *ee*. cHPLC conditions are described in section 2.1.2.

Compound 2: According to the general procedure, starting from compound **2** (0.200 g, 1.05 mmol, 1.00 equiv.) and DBU (47.2 µL, 0.315 mmol, 0.30 equiv.). The crude product was dissolved in MeOH and the solvent was removed under reduced pressure.

Compound 3: According to the general procedure, starting from compound **3** (0.200 g, 0.979 mmol, 1.00 equiv.) and DBU (43.8 µL, 0.294 mmol, 0.30 equiv.). The crude product was dissolved in MeOH and the solvent was removed under reduced pressure.

[9] 90 min when the initial *ee* = 20%. When the starting material is racemic, the time of reaction is specified in the main paper

In PTFE jar

Compound 1: According to the general procedure, in a 14 mL PTFE milling jar charged with compound **1** (0.280 g, 1.11 mmol, 1.00 equiv.), NaCl (6.3 g), three ZrO_2 balls, DBU (109.2 µL, 0.732 mmol, 0.66 equiv.), and the LAG solvent (for η = 0.023 µL/mg: 150 µL; for η = 0.21 µL/mg: 1400 µL).

Compound 2: According to the general procedure, in a 14 mL PTFE milling jar charged with compound **2** (0.280 g, 1.47 mmol, 1.00 equiv.), NaCl (6.3 g), three ZrO_2 balls, DBU (66.0 µL, 0.442 mmol, 0.30 equiv.), and the LAG solvent (for η = 0.023 µL/mg: 150 µL; for η = 0.21 µL/mg: 1400 µL). The crude product was dissolved in MeOH and the solvent was removed under reduced pressure.

Compound 3: According to the general procedure, in a 14 mL PTFE milling jar charged with compound **3** (0.280 g, 1.37 mmol, 1.00 equiv.), NaCl (6.3 g), three ZrO_2 balls, DBU (61.4 µL, 0.411 mmol, 0.30 equiv.), and the LAG solvent (for η = 0.023 µL/mg: 150 µL; for η = 0.21 µL/mg: 1400 µL). The crude product was dissolved in MeOH and the solvent was removed under reduced pressure.

2.2.3.1. MCDR by Resonant Acoustic Mixing (MCDR-RAM)

In 5 mL glass vial

Compound 1: [General procedure] A 5 mL glass vial was charged sequentially with compound **1** (0.140 g, 0.555 mmol, 1.00 equiv.), NaCl (3.15 g) as a bulk material, DBU (54.8 µL, 0.366 mmol, 0.66 equiv.), and the LARAM-additive (for η = 0.023 µL/mg: 75 µL; for η = 0.21 µL/mg: 700 µL). The mixture was accelerated at 100 *g* for 1.5 h.[10] After mixing, the solid was suspended in approximately 25 mL of water and filtered to remove NaCl, DBU, and LARAM-additive. The final product was obtained as a white powder and was analysed by cHPLC to determine the final *ee*. cHPLC conditions is described in section 2.1.2.

Compound 2: According to the general procedure, starting from compound **2** (0.140 g, 0.736 mmol, 1.00 equiv.) and DBU (33.0 µL, 0.221 mmol, 0.30 equiv.).

Compound 3: According to the general procedure, starting from compound **3** (0.140 g, 0.685 mmol, 1.00 equiv.) and DBU (30.8 µL, 0.206 mmol, 0.30 equiv.).

In 25 mL vial

Compound 1: According to the general procedure, in a 25 mL vial charged with compound **1** (0.700 g, 2.77 mmol, 1.00 equiv.), NaCl (15.75 g), DBU (273.8 µL,1.83 mmol, 0.66 equiv.), and the LARAM solvent (375 µL).

Compound 2: According to the general procedure, in a 25mL vial charged with compound **2** (0.700 g, 3.68 mmol, 1.00 equiv.), NaCl (15.75 g), DBU (165.2 µL, 1.10 mmol, 0.30 equiv.), and the LARAM solvent (375 µL).

Compound 3: According to the general procedure in a 25 mL vial charged with compound **3** (0.700 g, 3.43 mmol, 1.00 equiv.), NaCl (15.75 g), DBU (153.8 µL, 1.03 mmol, 0.30 equiv.), and the LARAM solvent (375 µL).

[10] 90 min when the initial *ee* = 20%. When the starting material is racemic, the time of reaction is 17h

3. Characterization

3.1. ^{1}H-NMR-Spectra

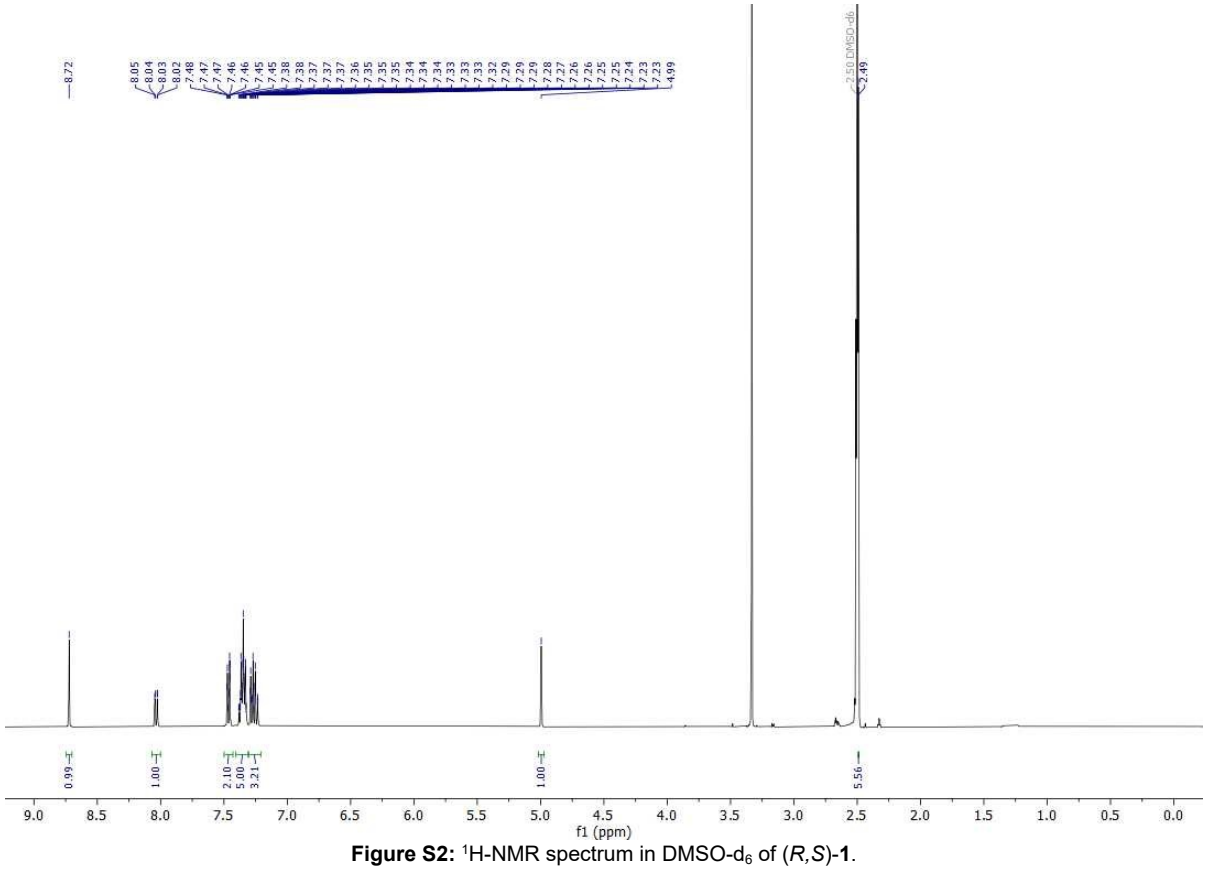


Figure S2: ^{1}H-NMR spectrum in DMSO-d_6 of (*R,S*)-**1**.

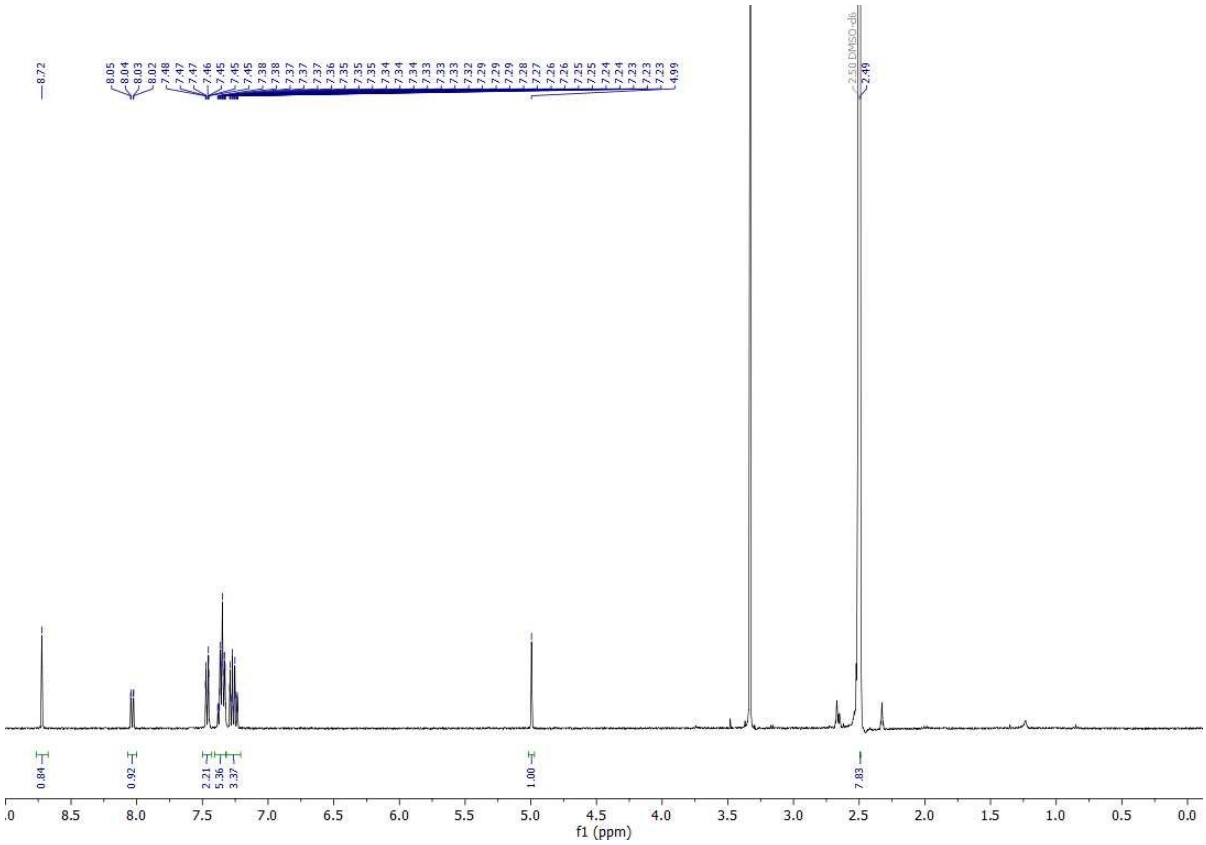


Figure S3: ^{1}H-NMR spectrum in DMSO-d_6 of (*S*)-1.

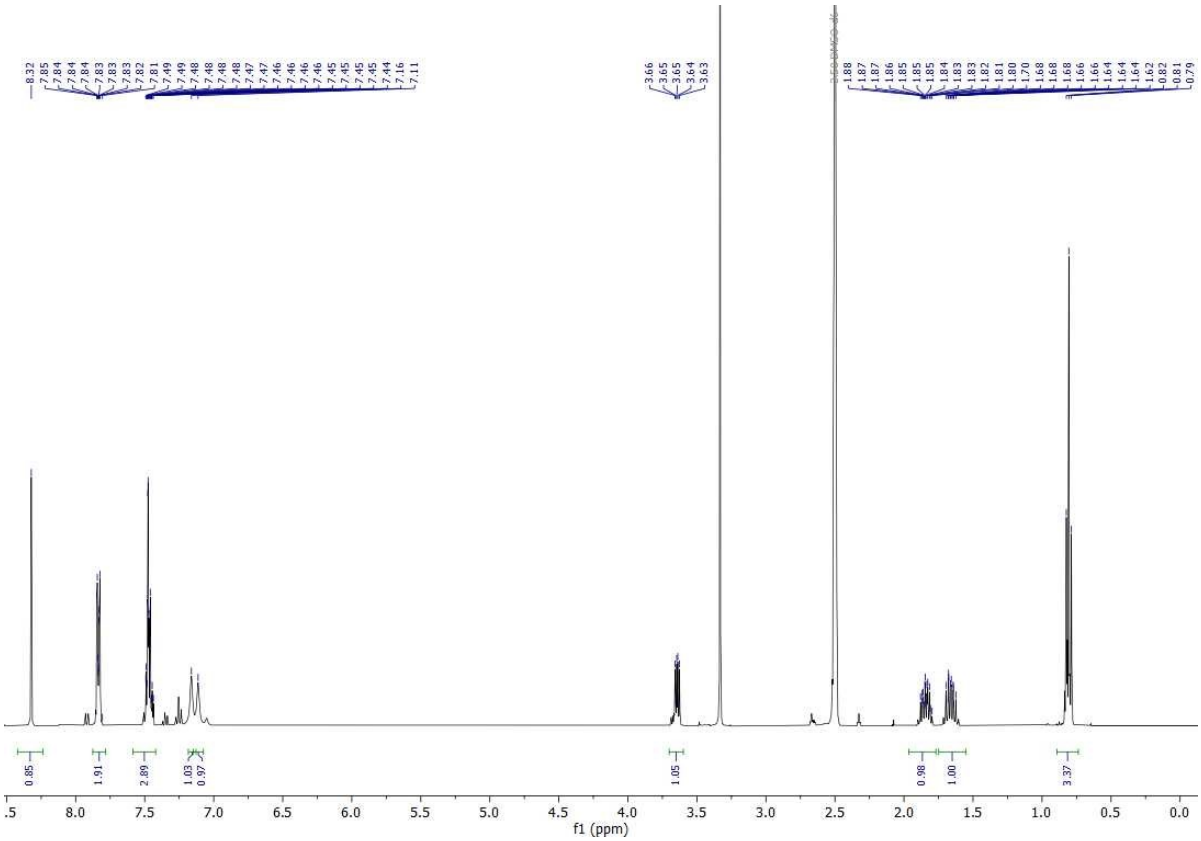


Figure S4: ^{1}H-NMR spectrum in DMSO-d_6 of (*R*,*S*)-**2**.

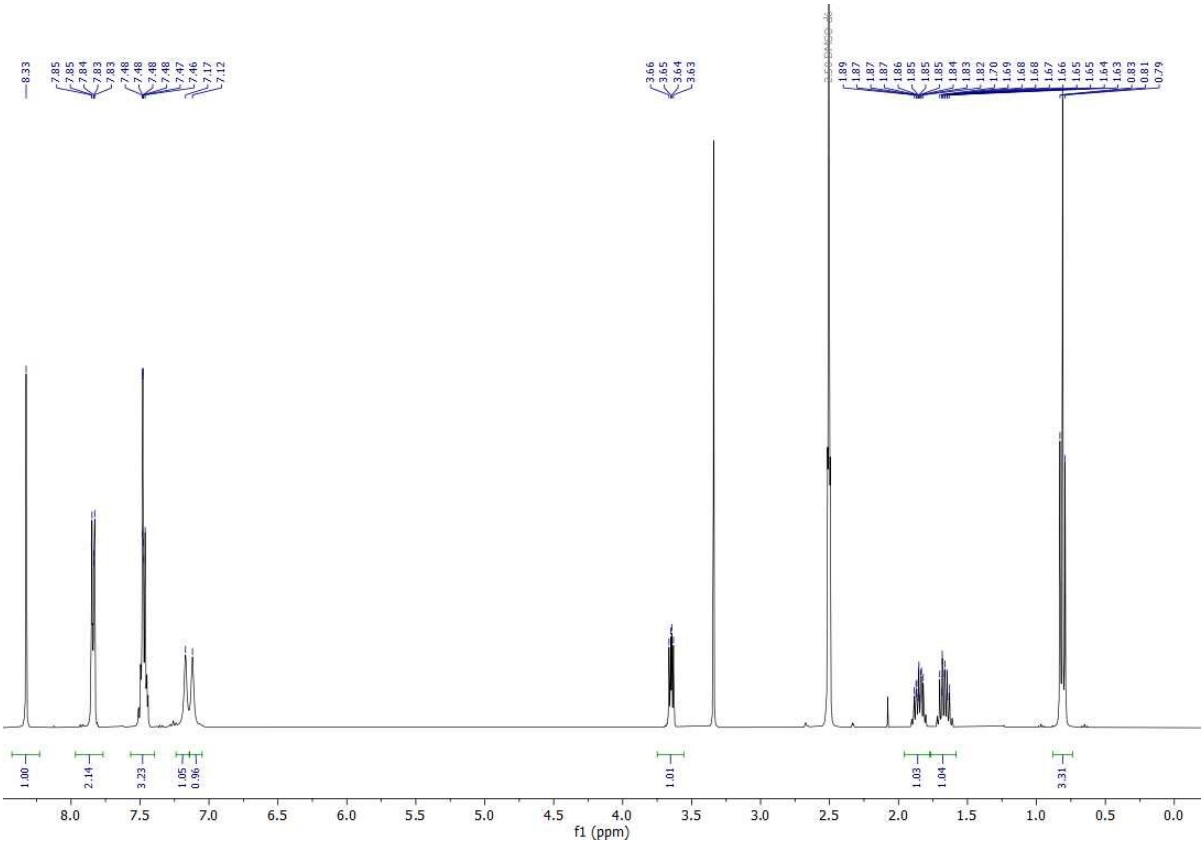


Figure S5: ^{1}H-NMR spectrum in DMSO-d_6 of (*S*)-**2.**

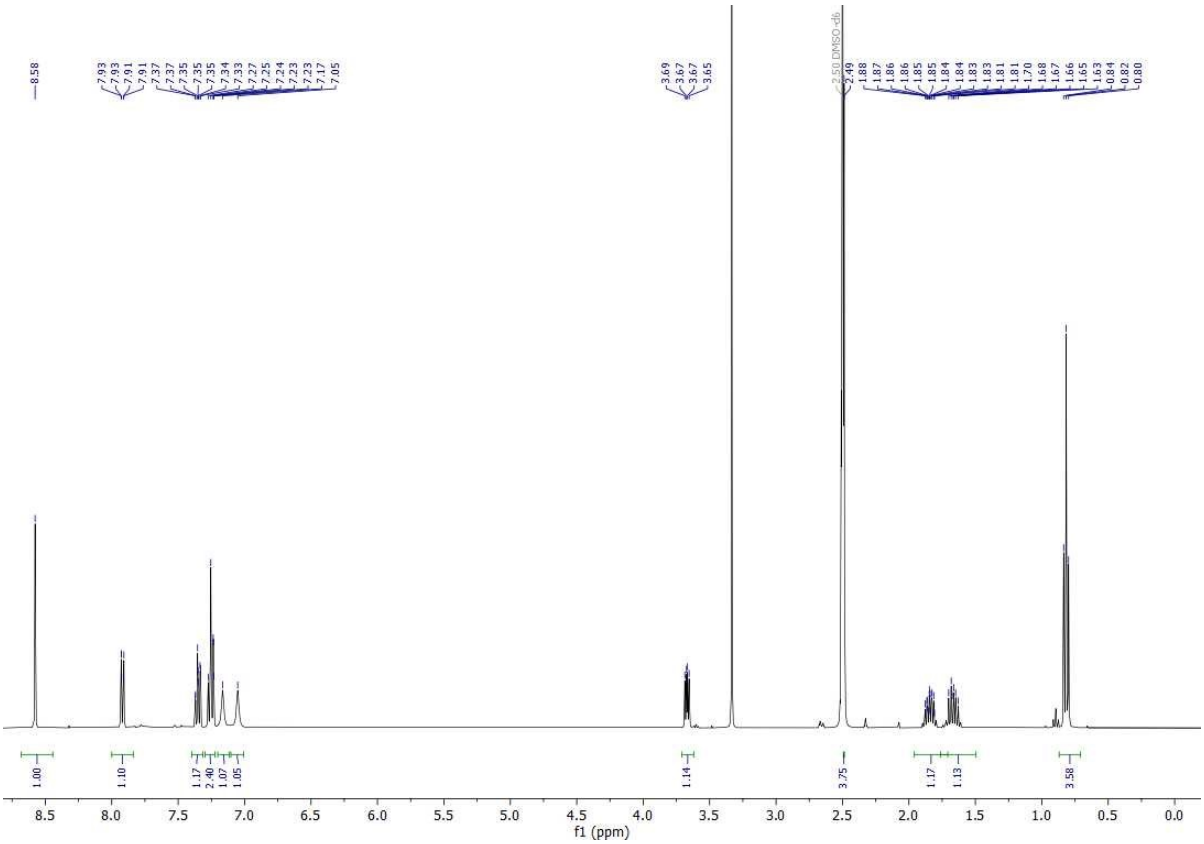


Figure S6: ^{1}H-NMR spectrum in DMSO-d_6 of (*R*,*S*)-**3**.

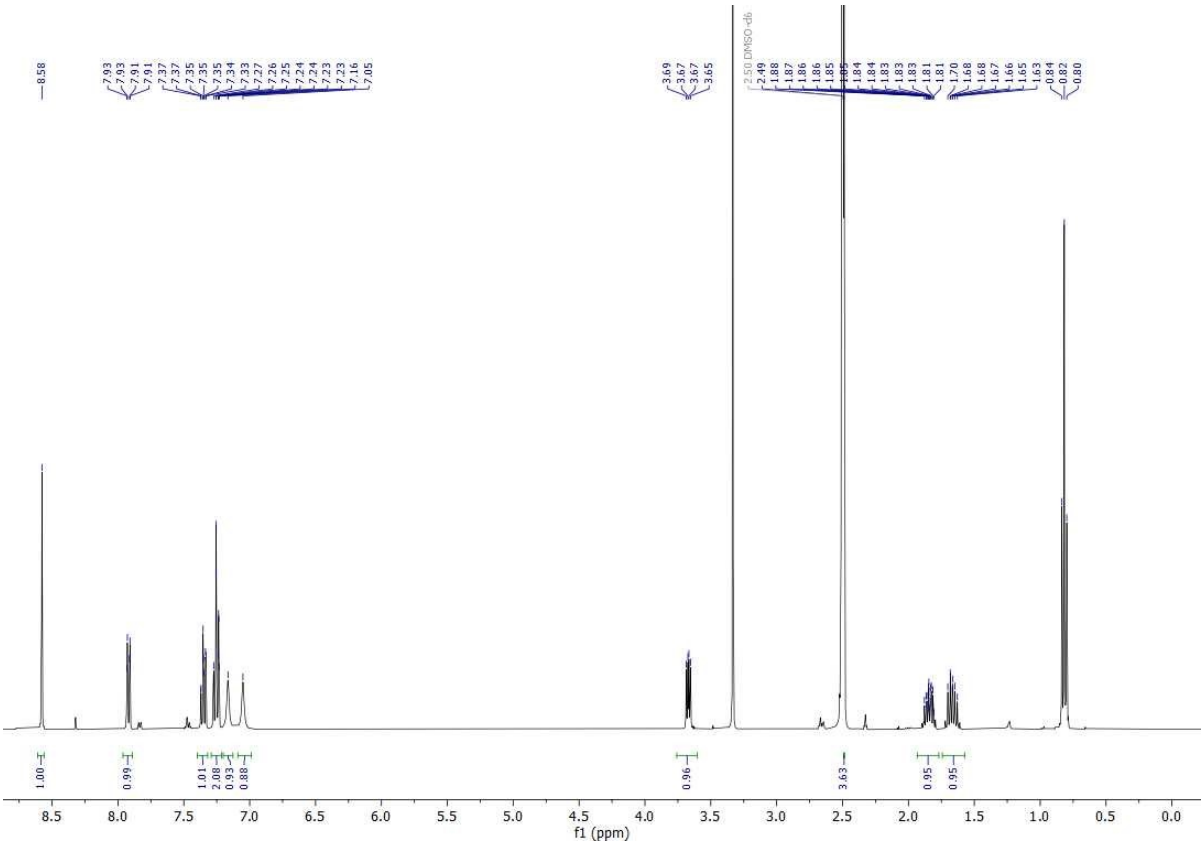


Figure S7: ^{1}H-NMR spectrum in DMSO-d_6 of (*S*)-**3**.

3.2. XRPD Analysis

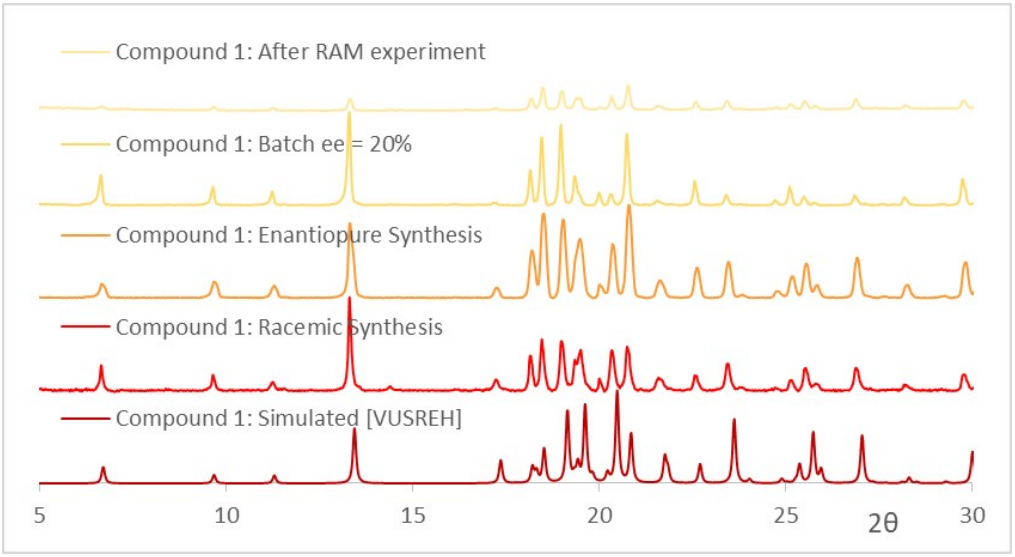


Figure S8: Experimental and simulated diffraction patterns of compound **1**. CCDC code in parentheses.

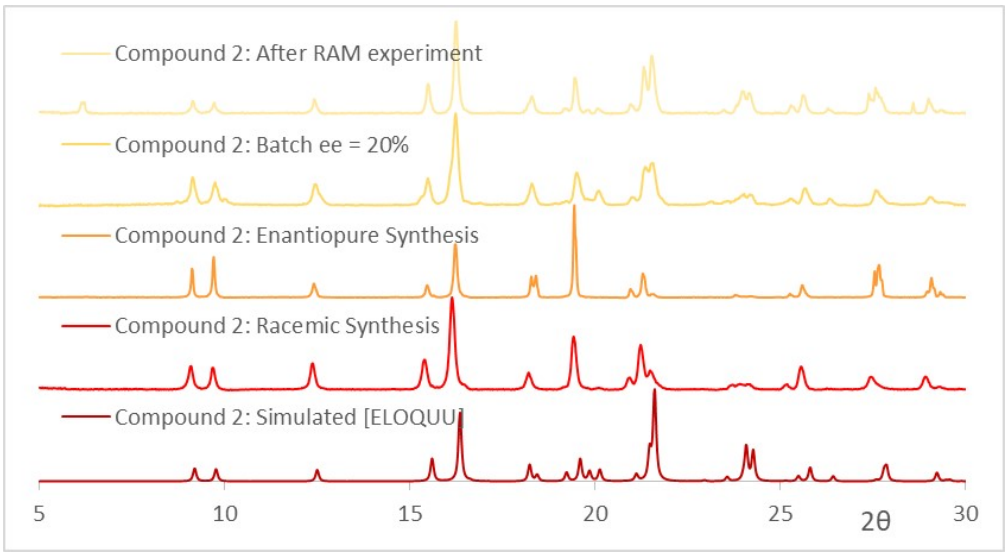


Figure S9: Experimental and simulated diffraction patterns of compound **2**. CCDC code in parentheses.

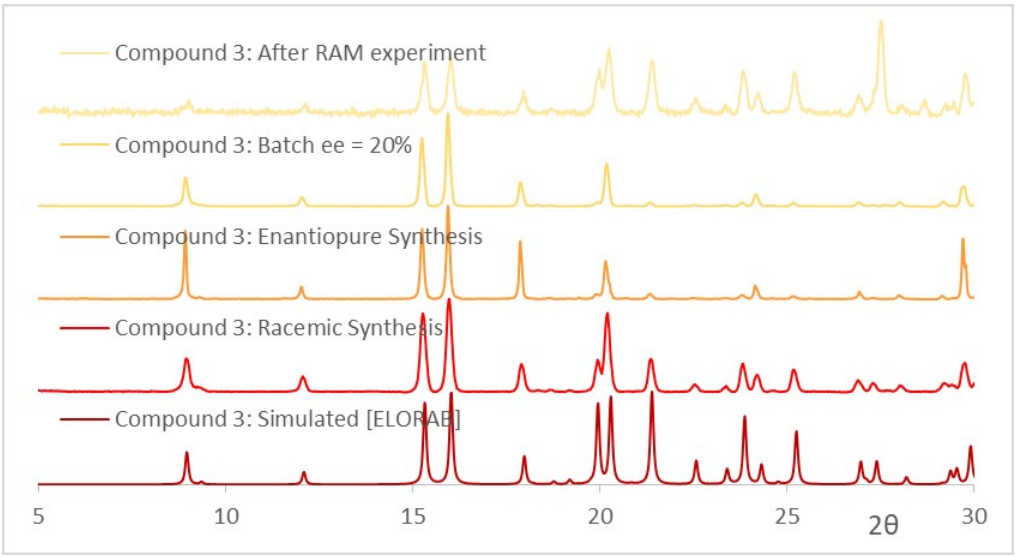
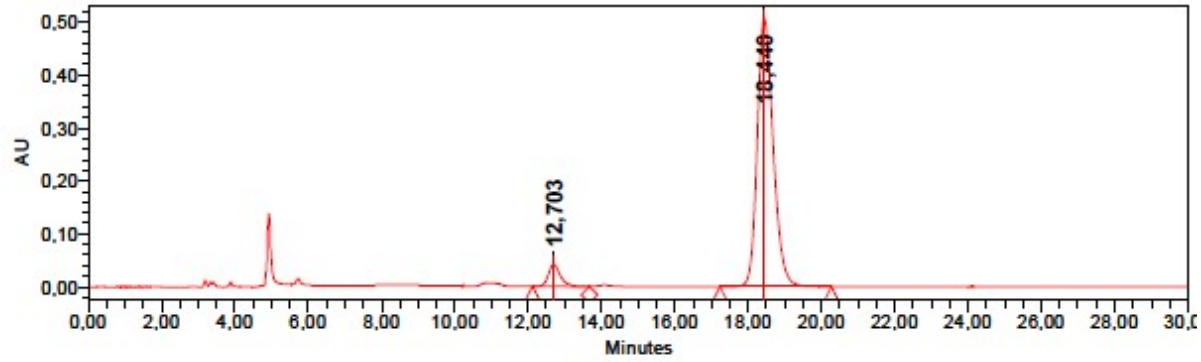


Figure S10: Experimental and simulated diffraction patterns of compound **3**. CCDC code in parentheses.

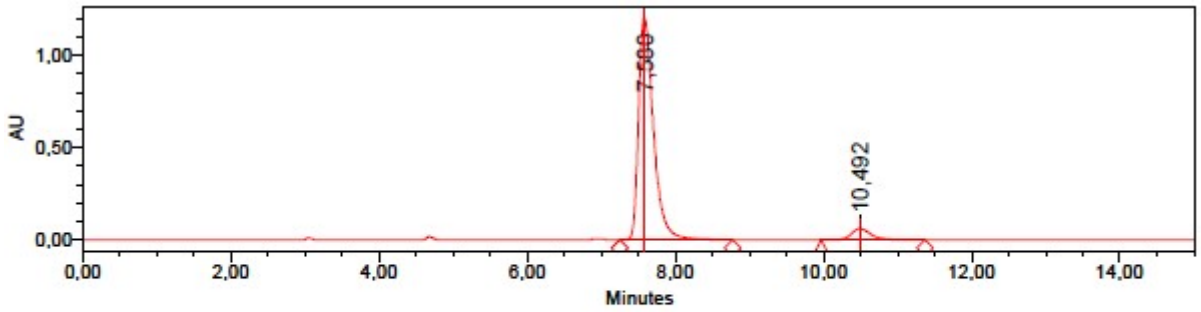
3.3. HPLC Analysis



Peak Results

	Name	RT	Area	% Area
1		12,703	932591	5,73
2		18,440	15331623	94,27

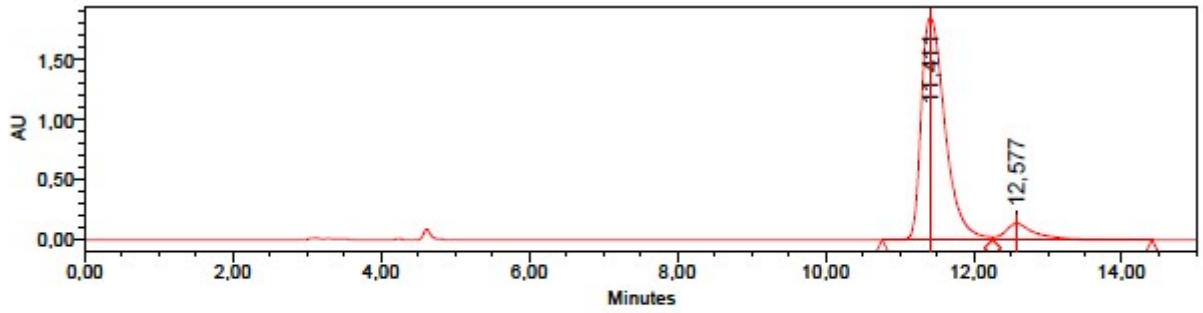
Figure S11: HPLC analysis of compound **1** after RAM, in 25 mL vials, with toluene.



Peak Results

	Name	RT	Area	% Area
1		7,580	16831300	93,80
2		10,492	1111942	6,20

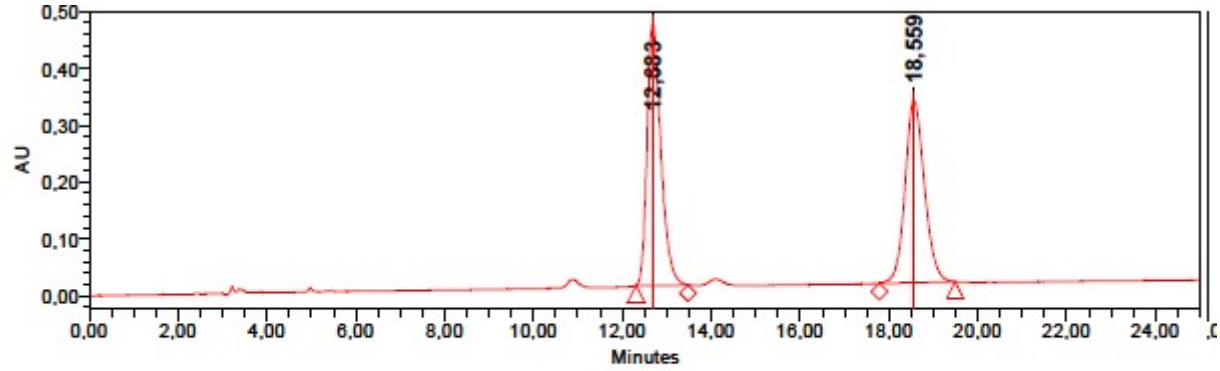
Figure S12: HPLC analysis of compound **2** after RAM, in 25 mL vials, with toluene.



Peak Results

	Name	RT	Area	% Area
1		11,411	41482196	91,68
2		12,577	3764874	8,32

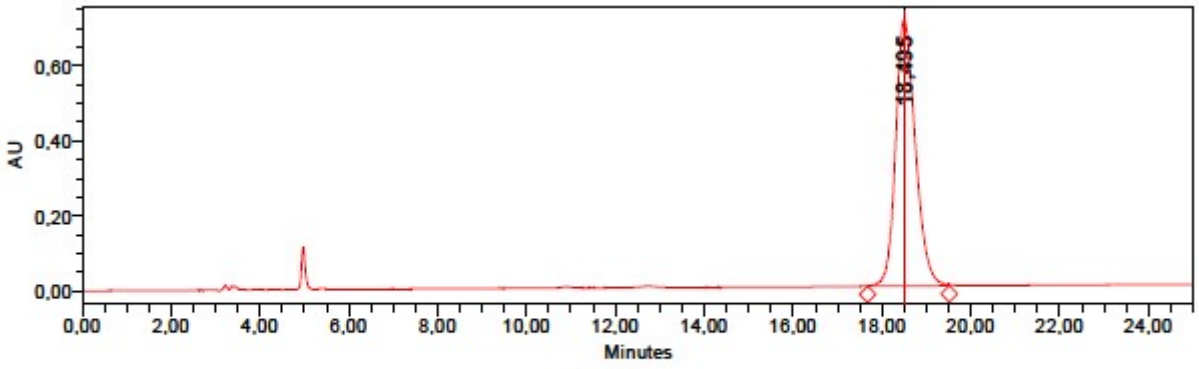
Figure S13: HPLC analysis of compound **3** after RAM, in 25 mL vials, with toluene.



Peak Results

	Name	RT	Area	% Area
1		12,683	9788662	50,07
2		18,559	9761434	49,93

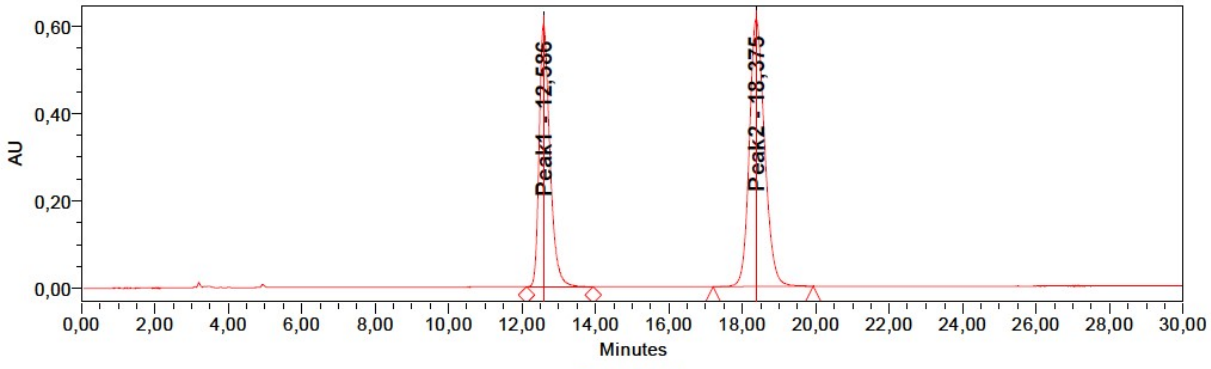
Figure S14: HPLC analysis of synthetized (*R,S*)-**1**.



Peak Results

	Name	RT	Area	% Area
1		18,495	21985779	100,00

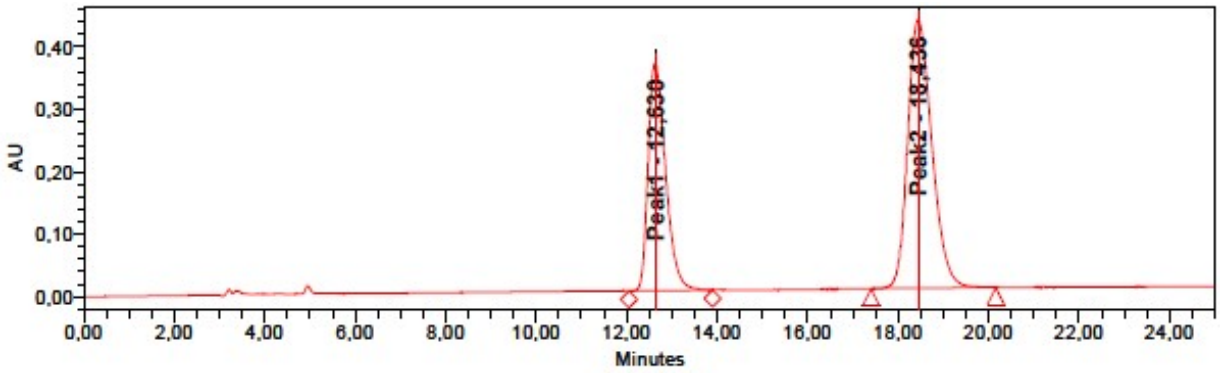
Figure S15: HPLC analysis of synthetized (*S*)-**1**.



Peak Results

	Name	RT	Area	% Area
1	Peak1	12,586	12285880	40,86
2	Peak2	18,375	17783904	59,14

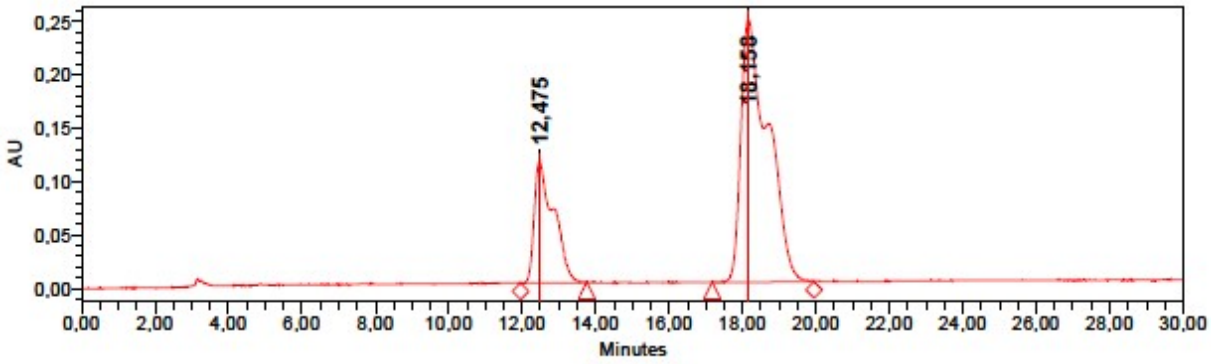
Figure S16: HPLC analysis of the 20% *ee* -batch of compound **1**.



Peak Results

	Name	RT	Area	% Area
1	Peak1	12,630	9623062	37,58
2	Peak2	18,436	15986338	62,42

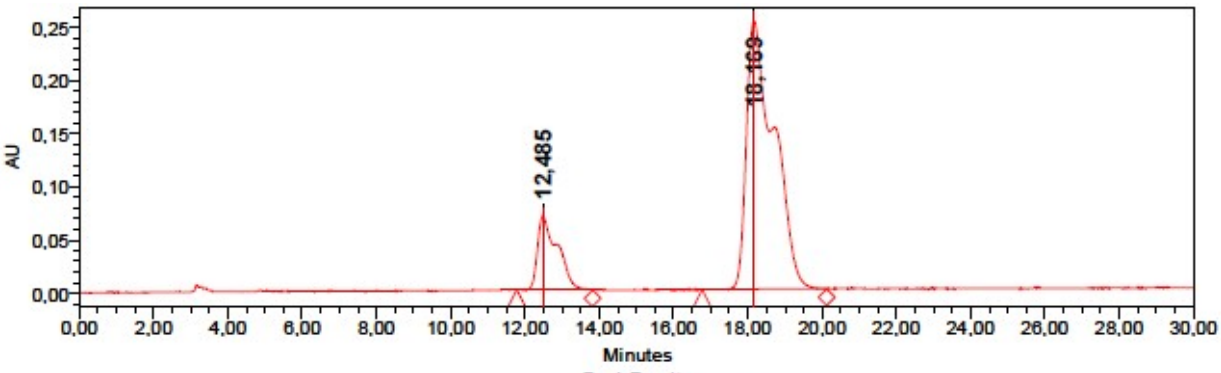
Figure S17: HPLC analysis of the 25% *ee* -batch of compound **1**.



Peak Results

	Name	RT	Area	% Area
1		12,475	4171495	24,75
2		18,158	12682877	75,25

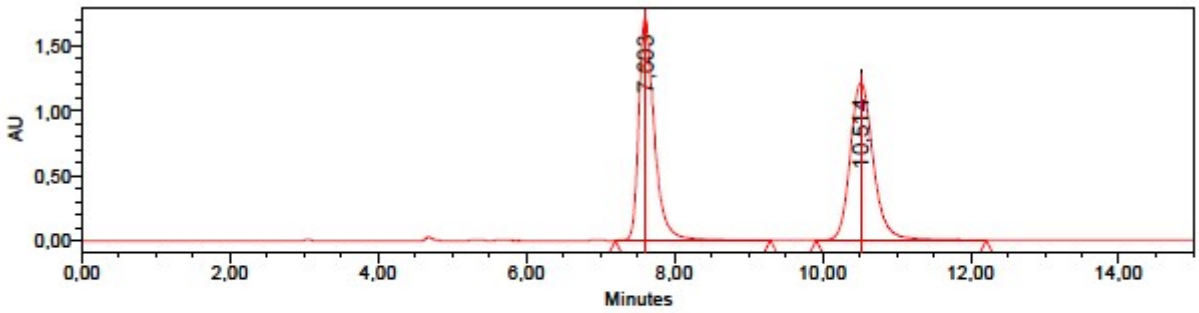
Figure S18: HPLC analysis of the 50% *ee* -batch of compound **1**.



Peak Results

	Name	RT	Area	% Area
1		12,485	2551937	16,33
2		18,169	13072580	83,67

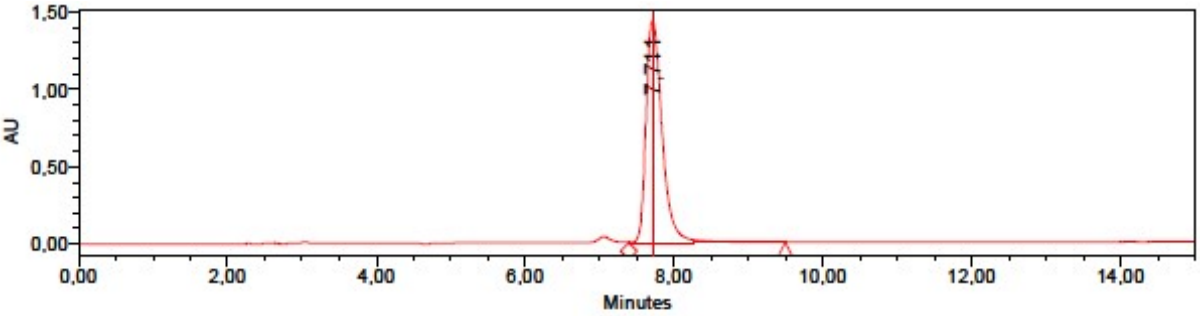
Figure S19: HPLC analysis of the 75% *ee* -batch of compound **1**.



Peak Results

	Name	RT	Area	% Area
1		7,603	24725666	48,51
2		10,514	26239612	51,49

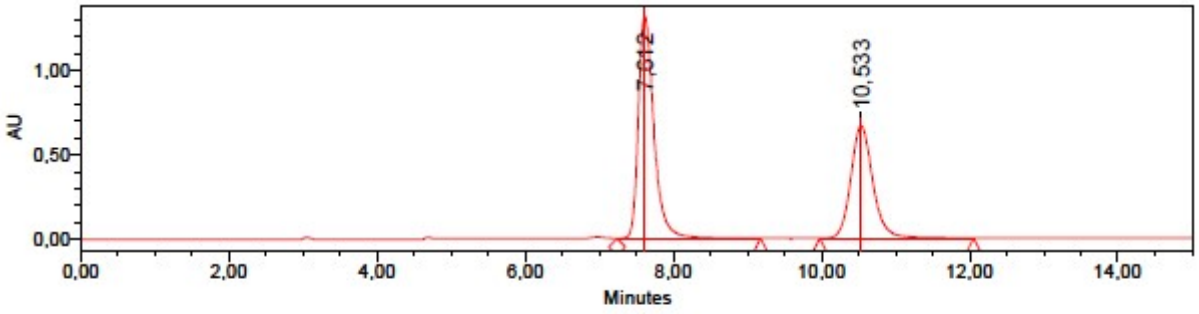
Figure S20: HPLC analysis of synthetized (*R,S*)-**2**.



Peak Results

	Name	RT	Area	% Area
1		7,711	21581527	100,00

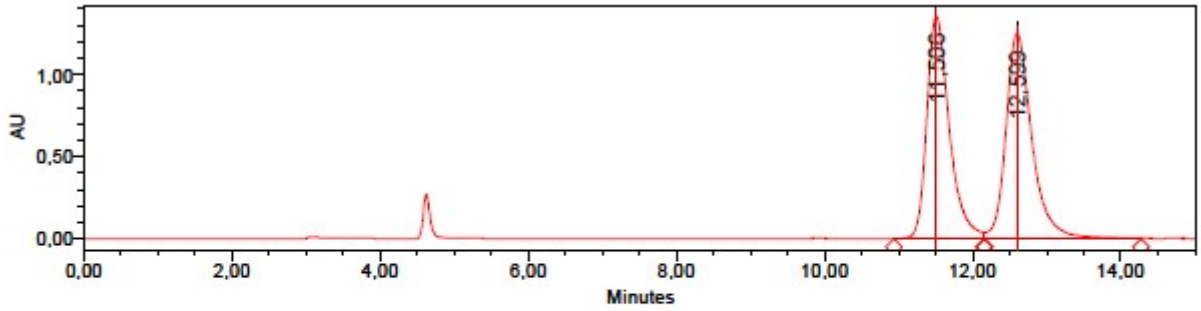
Figure S21: HPLC analysis of synthetized (*S*)-**2**.



Peak Results

	Name	RT	Area	% Area
1		7,612	19152973	58,10
2		10,533	13811648	41,90

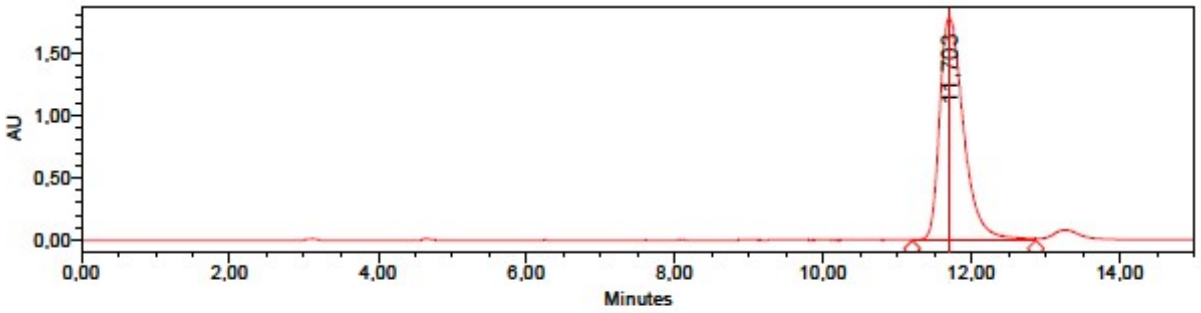
Figure S22: HPLC analysis of the 20% *ee*-batch of compound **2**.



Peak Results

	Name	RT	Area	% Area
1		11,506	28670932	48,41
2		12,599	30555095	51,59

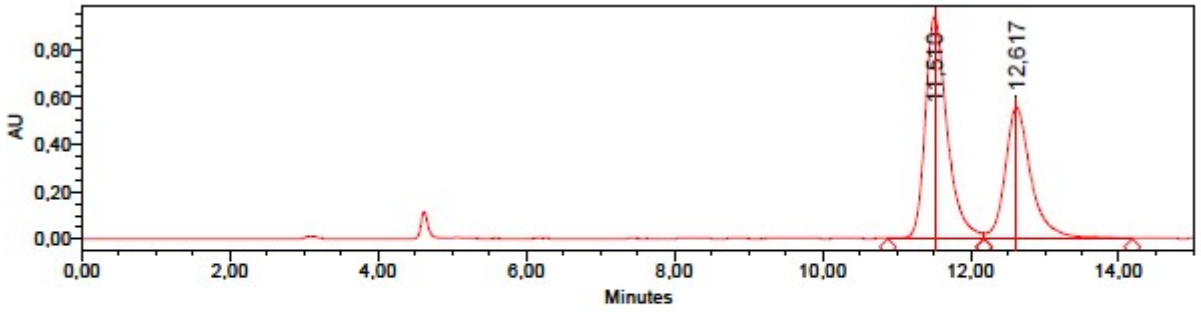
Figure S23: HPLC analysis of synthetized (*R,S*)-**3**.



Peak Results

	Name	RT	Area	% Area
1		11,703	39754137	100,00

Figure S24: HPLC analysis of synthetized (S)-**3**.



Peak Results

	Name	RT	Area	% Area
1		11,510	19321207	58,82
2		12,617	13528706	41,18

Figure S25: HPLC analysis of the 20% *ee* -batch of compound **3**.

4. References

1 W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg and D. G. Blackmond, *J. Am. Chem. Soc.*, 2008, **130**, 1158–1159.
2 I. Baglai, M. Leeman, R. M. Kellogg and W. L. Noorduin, *Org. Biomol. Chem.*, 2018, **17**, 35–38.
3 J. Gieling, G. Wéry, C. Lopes, J. de Meester, C. Brandel, Y. Cartigny, T. Leyssens and D. M. Baier, *Chem. – Eur. J.*, 2025, **31**, e202404120.