

Co-Crystallization-Induced Spontaneous Deracemization: An Optimization Study

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ABSTRACT: We recently introduced a thermodynamically based deracemization process, co-crystallization-induced spontaneous deracemization (CoISD). Following the successful development of the CoISD process, we aimed at improving both yield and deracemization and, consequently, the productivity of the process. As the process is based on co-crystallization of the target enantiomer combined with a racemization reaction of the undesired enantiomer, both reaction and crystallization kinetics and thermodynamics need to be considered for optimization. Taking previously published kinetic parameters into account, here we investigate the nature of the solvent, concentration of the racemizing agent, equivalent of the acid co-former, and temperature of the crystallization cell. The evaluation of each parameter allowed for improvement of the yield and/or deracemization, ultimately providing an optimized process with a yield of 73% of pure co-crystals for an overall deracemization of 80%, in parallel, highlighting the viability of recycling the remaining mother liquors.

KEYWORDS: Deracemization, CoISD, Optimization, Co-crystallization

1. INTRODUCTION

Single process deracemization processes offer considerable advantages over resolution as they allow access to a theoretical 100% yield in the desired enantiomer through conversion of the distomer in the eutomer.¹⁻³ Deracemization processes respond to the ever-increasing demand for enantiopure material, in particular for the pharmaceutical industry.^{4,5} Crystallization-induced diastereomer transformation (CIDT) is likely the oldest single-step deracemization process available. In this process, one enantiomer of a racemic acid (base) is crystallized through addition of an enantiopure base (acid) while the solution excess of the distomer is continuously racemized.⁶ The last decade also saw the development of dynamic preferential crystallization⁷⁻¹⁰ and the introduction of abrasive grinding-based Viedma Ripening^{11,12} as techniques for the deracemization of conglomerates.¹³⁻¹⁵ We recently introduced a novel thermodynamic deracemization process¹⁰ based on co-crystallization of the target enantiomer from solution and simultaneous racemization of the remaining distomer.^{17–19}

We demonstrated the feasibility of this co-crystallizationinduced spontaneous deracemization (CoISD) process, deracemizing 4,4-dimethyl-1-(4-fluorophenyl)-2-(1*H*-1,2,4-triazol-1-yl)-pentan-3-one (BnFTP) using 3-phenylbutyric acid (PBA) as the co-former and 1,8-diazabicyclo[5.4.0]undec-7ene (DBU) as the racemizing agent. The racemization reaction kinetics of this reaction were shown to respond to first-order reactivity in agreement with a keto-enol racemization scheme.²⁰⁻²² Addition of the co-former, nevertheless, had a significant impact on the overall process kinetics, with racemization no longer occurring at room temperature, imposing a racemization temperature of 90 °C and leading to an overall yield of 51% and deracemization of 64%. The goal of this work is to further optimize this system, aiming at reaching yields similar to CIDT in the range from 70 to 90% with high enantiopurity.^{6,23} Reaching these numbers requires optimal combination of crystallization²⁴ and racemization²⁵ conditions. To do so, we studied the impact of operational parameters such as catalyst concentration, solvent nature, and crystallization temperature on the overall process outcome,^{26–28} ultimately yielding an optimal process with an overall 80% deracemization and 73% enantiopure co-crystal yield. CoISD is therefore shown to display yields comparable to other deracemization methods, paving the way toward further development of this methodology for other systems.

2. EXPERIMENTAL SECTION

2.1. Deracemization Processes. (R,S)-BnFTP was synthetized according to the protocol previously described,¹⁶ while (R)- or (S)-PBA was resolved from commercial (R,S)-PBA with the same protocol as described previously too.¹⁶ All solvents and DBU were purchased from commercial sources and used as is. Demineralized water was used.

The system is composed of two double-jacket vessels, the temperature of which is regulated; two pumps continuously transferring the solution from one cell to the other; tubes that are made of PTFE to resist toluene; and a filtration unit in the "cool" cell to avoid transferring solids. A bottom stirrer in each cell stirs the mixture magnetically. The process was carried out

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Article



Table 1. var	ying Para	meters	from the	General Proc	edure	for all Kuns				
experiment [co-former]	$C_{ m BnFTP} \ (m mol/L)$	eq PBA	solvent	V _{DBU} (μL) eq (mol %)	$V_{ m water} \ (\mu { m L})$	$T_{ m cryst}$	end T_{cryst} (°C)	work time (days)	$E_{(cake)}$	ratio <i>R/S</i> in filtrate
run 1 [(S)-3-PBA]	0.30	1	toluene	305, 7.5	?	10 °C		2		28/72
run 2 $[(S)-3-PBA]$	0.30	1	toluene	305, 7.5		10 °C	0	5	100%	57/43
run 3 $[(S)-3-PBA]$	0.30	1	toluene	305, 7.5	150	10 °C	0	5	100%	43.5/56.5
run 4 [(S)-3-PBA]	0.30	1	propanol	305, 7.5		10 °C	0	5	95%	43/57
run 5 [(S)-3-PBA]	0.30	1	butanol	305, 7.5		10 °C	0	5	100%	51.5/48.5
run 6 [(S)-3-PBA]	0.20	1	toluene	203, 7.5	150	10 °C	0	5	98%	61/39
run 7 [(S)-3-PBA]	0.30	1.2	toluene	305, 7.5	150	10 °C	0	5	100%	60/40
run 8 [(R)-3-PBA]	0.30	1.25	toluene	610, 15	150	10 °C	0	5s	100%	54/46
run 9	0.20	1.25	toluono	1017 25	150	day 1: 10 °C	10	4	100%	61 5 / 28 5 40 / 60
[(R)-3-PBA]	0.30	1.25	toluene	1017, 25	150	day 2: 5 °C day 3: 0 °C day 4: -5 °C	-10	4	100%, 97%	01.5/38.5, 40/00
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Co-crystal	→ H → o F in susper	hsion					ſ			
		— (Crystallia	zation, 10°C		Ra	acemizat	tion, 90°	C Y	

Figure 1. On top, from left to right, BnFTP, PBA, DBU, and toluene. Below, 3D representation of the two-vessel setup with the co-crystal in suspension in the crystallization vessel on the left and the racemization vessel on the right.^{16,20}

semi-continuously: the pumps were turned on only during the day for 8 h and turned off at night. This was done for practical reasons since the system needed supervision, which was not possible overnight.

The resulting compounds were analyzed by chiral HPLC. The method was as follows: the pump was a Waters 600, the auto-sampler was a Waters 717, and the UV detector was a Waters 996. The column was a Chiral Pak 1B chiral column of 250 mm length and 4.6 mm diameter with a particle diameter of 5 μ m. The mobile phase was composed of a mixture of 95:5 isohexane/ethanol at a flow rate of 1 mL/min. The wavelength used for analysis of the chromatograms was 264 nm. Each sample was diluted using a 20:80 mixture of ethanol and

isohexane and sonicated when necessary to speed up dissolution.

2.1.1. General Procedure for all Runs. A specified equivalent of PBA (to BnFTP) was added to a stirring solution of a specified concentration of (R,S)-BnFTP in 90 mL of solvent in the crystallization cell at 10 °C. The pumps were turned on. The system was stirred for 1 h to reach equilibrium. After that, the pumps were turned off, the racemization cell was heated to 90 °C, and DBU was added to the racemization cell with or without 150 μ L of water. When water was added, at day 1, the same volume was added again at day 3. Racemization alone was performed for 2 h. Then, the pumps were turned on for the rest of the day. Each evening, the



Figure 2. (Left) Time evolution of the enantiomeric excess E in BnFTP of an (*R*)-BnFTP–(*R*)-PBA toluene solution with 0.16% vol of water and 6.8 g/L of DBU. (Right) Time evolution of the natural logarithm of the enantiomeric excess E in BnFTP of an (*R*)-BnFTP–(*R*)-PBA toluene solution with 0.16% vol of water and 6.8 g/L of DBU (29 mol %).

pumps and the heater were turned off. The cooler was left as is except when specified otherwise. On every following morning, the pumps were turned on and the heater put back at 90 $^{\circ}$ C, after which the system was left to work for 8 h. This was repeated each day until the end of the last day when the pumps were turned off, the cooler put at a specific temperature, the heater turned off, and all the liquid phase transferred to the crystallization cell and allowed to equilibrate over the weekend (2 days). One-night minimum of equilibrium was necessary to ensure reaching the thermodynamic equilibrium. Then, the mixture was filtered and washed with toluene at the end temperature of the crystallization cell.

The specific conditions for each run are given in Table 1. Runs 9 and 10 give the optimized procedure. We can specify that no clogging was observed over time at the filtration unit (probably due to gravity).

2.2. Kinetic Measurements. 2.2.1. Racemization Curves with Toluene, Toluene–Water, Propanol, and Butanol. 0.200 g of the (R,R)-BnFTP and PBA co-crystal was added to 3 mL of solvent heated at 90 °C in a POLAR Bear Plus Crystal device. Then, 20 μ L of DBU was added to the solution. Samples were taken over time and directly quenched with HCl (1 M). Ethyl acetate was added and the biphasic mixture was shaken two times. Then, the organic layer was taken out and put in a vial to evaporate. The dried samples were then analyzed by chiral HPLC with the same setup as specified above.

2.2.2. Study of Racemization Kinetics of BnFTP and PBA Co-Crystal in Toluene–Water Mixtures. The (S)-enantioenriched mixture was obtained with the following protocol: 1.99 g of (S)-3-PBA (0.0115 mol) and 3.14 g of (R,S)-BnFTP (0.0114 mol) were added to 20 mL of toluene. The resulting mixture was stirred overnight at RT and then filtered. The cake and filtrate were recovered and dried. The filtrate was then analyzed by chiral HPLC. The filtrate was used as the (S)enantio-enriched mixture.

The protocol for the kinetic measurements was the following: 0.3924 g of this (S)-enantio-enriched mixture was added to a mixture of 3 mL of toluene and 0-1.21-2.43-4.82-7.23-9.65-16.88-24.12-48.24-96.48 and 192.96 μ L of water. Water was added using the corresponding micropipette. The solution was heated to 90 °C and 20 μ L of DBU (15 mol %) was added. Samples were taken over time, directly quenched with HCl (1 M), and treated in the same way as for the full-curve measurements.

2.3. Solubility Curves. Solubility curves were measured using a Crystal16 device from Technobis. Using turbidity, the device measures the opacity of the solution over time. Each point was obtained from a certain concentration in the solvent to which a ramp of temperature was applied ($0.05 \, ^\circ C/min$). A point results from the couple (concentration, temperature) when the solution reaches a transmittance of 100%.

3. RESULTS AND DISCUSSION

3.1. System. Figure 1 summarizes the principles of the deracemization process. Starting from a racemic BnFTP solution in toluene, addition of (R)-PBA will lead to the selective crystallization of the less soluble (R-R)-co-crystal diastereomer, leaving the solution enriched in (S)-BnFTP. In principle, addition a racemizing agent (DBU) would pull the solution enantiomeric imbalance back to equilibrium, decreasing the concentration of (S)-BnFTP in favor of (R)-BnFTP. This latter continues to co-crystallize, reinstalling the solution enantiomeric imbalance, and hence racemization continues also. Even though this process could in principle be performed in a one-pot setup, we encountered difficulties in combining crystallization and racemization conditions due to incompatibility between heating, necessary for racemization, and crystallization. For this reason, a two-vessel setup was devised, with the crystallization working in a vessel kept at 10 °C and the racemization occurring in a vessel placed at 90 °C. The continuous transfer of solution between both vessels assures the continuity of the process.

Using this setup, we previously observed a negative impact of a decrease in racemization temperature, which will therefore remain fixed at 90 °C in this contribution. The goal here is to evaluate how other parameters impact the process performance, evaluated by the overall deracemization ratio (overall enantiomeric excess—cake and filtrate combined, E_{tot}) as well as the yield Y (amount of the co-crystal recovered from the process vs the total amount that can be recovered should there be a full deracemization and complete crystallization). Solvent nature, equivalents of base and acid, and temperature of the crystallization cell were evaluated for their impact on the overall process.

A first reference experiment (run 1) was performed using a BnFTP (and PBA) concentration of 0.30 M and a 7.5 mol % concentration in DBU using toluene as a solvent based on conditions used in our initial work.¹⁶ After having carried out the process for 2 days, a phase separation was observed, with a

water phase appearing in the bottom of the racemization reactor.^{*a*} The process was stopped but to our surprise gave a very good overall deracemization (44%). This finding incited us to study the impact of small amounts of water on the overall process performance prior to studying all other parameters.

3.2. Water Impact on the Process. To study the water impact, the reactants were dried and the process was conducted avoiding all traces of water (run 2). This reference experiment unambiguously confirmed a lower overall deracemization level (20%) even upon a prolonged working time (5 days instead of 2). As a small amount of water seemingly has a positive impact on the overall process, we looked for its optimal value. To do so, the racemization rate constant was evaluated for various quantities of water. As observed previously, the racemization reaction responds to first-order kinetics even in the presence of water (Figure 2).

Figure 3 shows the impact of the amount of water on the obtained rate constants (the original curves and linearization



Figure 3. Value of the observed rate constant according to the % vol of water in toluene for the racemization of a (*S*)-BnFTP-enriched solution in the presence of 1 equiv of (*S*)-PBA and 6.8 g/L of DBU (15 mol %). The red line shows when the phase separation occurs at 90 °C. The error bar represents the experimental error (10%) previously determined.²⁰

are given in the Supporting Information). Results show that for a water/toluene volume ratio of less than 0.16%, water has no significant impact on the racemization kinetics. However, a positive impact is seen as soon as phase separation occurs. This positive effect remains present up to about 0.32% of water present. The positive effect of water is therefore inherently linked to the phase separation and can potentially be due to the presence of hydroxide ions in the aqueous phase, with a phase transfer phenomenon enhancing the reaction. However, this enhancement is no longer present when the amount of water becomes too important, which could be due to the DBU–PBA pair moving to the water phase or dilution effects on the hydroxide ion concentration.

Run 3 (Table 2) was performed under similar conditions as run 2 but with a controlled amount of water added to the system in order to confirm its positive impact. The volume of water was chosen according to the results of Figure 3. 150 μ L of water corresponds to a volume percentage of 0.16% between water and toluene, which is the necessary value to get demixion at 90 °C and giving the best result. After 2 days, de-mixing was no longer visible in the system, likely due to crystallization of the co-crystal, and another 0.16% of water was added. Upon filtration, a similar yield of around 30% of the enantiopure cocrystal was obtained with an overall deracemization of 41%, double the value obtained with respect to the run without water. For further process development, we decided to set the added water to 0.16% of the toluene volume with an additional 0.16% added 2 days later, going up to an overall 0.32% of ratio of added water.

3.3. Alternative Solvents. Our kinetic study²⁰ showed protic polar solvents to increase the racemization rate. Furthermore, with water having an impact on the process, toluene was likely not the most optimal solvent for the racemization reaction. However, for our CoISD process, one should also take the impact of the solvent on the crystallization process (co-crystal solubility) into account. Too high solubilities lead to a reduced yield and associated overall deracemization. We therefore determined the solubility curves (Figure 4) for the same seven solvents used in our kinetic study. Van't Hoff plots (Supporting Information) allowed extracting enthalpy (ΔH°) and entropy of crystallization (ΔS°), shown in Table 3.

The entropy of dissolution is comparable for all solvents, with the difference in solubility being mainly due to the enthalpic part (representative of intermolecular interactions). As expected, dissolution of the co-crystal is endothermic, with acetone and THF showing the lowest enthalpy of dissolution, which is possibly explained by a stabilizing interaction of these solvents both for BnFTP as well as for PBA, resulting in a higher solubility at 10 °C. Alcohols mainly act on the acid through hydrogen bonding interaction, all showing a similar dissolution enthalpy. Finally, toluene shows the highest

Гabl	e 2.	Resul	ts O	btaine	l Du	ring	the	Process	Op	otimization	Showi	ıg the	• Overal	l Yie	eld	l Y and	th	e Overal	l Dera	acemization	E_{tot}	u t
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experiment	$C_{\text{BnFTP}} (\text{mol/L})$	Eq PBA	solvent	$C_{\rm DBU} (g/L) / \% mol$	Y (%)	$E_{\rm tot}$ (%)
run 1	0.30	1	toluene + water	3.5/7.5		44 ^b
run 2	0.30	1	toluene	3.5/7.5	33	20
run 3	0.30	1	toluene + water	3.5/7.5	33	41
run 4	0.30	1	propanol	3.5/7.5	15	26
run 5	0.30	1	butanol	3.5/7.5	30	28
run 6	0.20	1	toluene + water	2.3/7.5	30	14
run 7	0.30	1.2	toluene + water	6.9/15	56	47
run 8	0.30	1.25	toluene + water	11.5/25	55.5	59
run 9	0.30	1.25	toluene + water	11.5/25	73	80
run 10					80	74

^{*a*}The overall deracemization stands for the percentage of the unwanted enantiomer that was deracemized. It is calculated as the enantiomeric excess of the overall composition of (R) and (S)-BnFTP obtained at the end combining both the cake and the filtrate. ^{*b*}With no filtration done, the filtrate ratio represents the overall enantiomeric ratio.



Figure 4. Evolution of the (S-S) co-crystal solubility with temperature in seven different solvents.

Table 3. Experimental Values of ΔH°_{diss} and ΔS°_{diss} of the (S-S)-Co-crystal of BnFTP and PBA for Each Studied Solvent Alongside Its Solubility at 10 °C

$\Delta H_{ m diss}^{ m o} [{ m KJ/mol}]$	$\Delta S^{\circ}_{ m diss}$ [J/mol K]	s (10 °C) [g/L]
90.8	259	10.9
44.8	145	200.4
80.2	233	21.3
59.8	194	97.3
82.5	250	36.6
71.4	211	37.3
78.9	232	26.6
	ΔH ^o _{diss} [KJ/mol] 90.8 44.8 80.2 59.8 82.5 71.4 78.9	$\begin{array}{c c} \Delta H^{\circ}_{\rm diss} \ [\rm KJ/mol] & \Delta S^{\circ}_{\rm diss} \ [\rm J/mol \ \rm K] \\ \hline 90.8 & 259 \\ 44.8 & 145 \\ 80.2 & 233 \\ 59.8 & 194 \\ 82.5 & 250 \\ 71.4 & 211 \\ 78.9 & 232 \end{array}$

enthalpy of dissolution and lowest associated solubility. Using high-solubility solvents will be detrimental for the overall yield, and hence, toluene and alternatively an alcohol solvent are advisable for the process.

Propanol (run 4, Table 2) and butanol (run 5, Table 2) were therefore tested on the system as alternative solvents to toluene using similar conditions of overall concentration. 1-Butanol and, to a lesser extent, 1-propanol led to more viscous solutions than toluene (solvents more viscous + higher solubilities), which resulted experimentally in increased difficulties in transferring the solution between both vessels and the appearance of air bubbles over time. The use of both solvents did not impact the enantiopurity of the resulting outcome, showing enantiopure co-crystal material. However, the yield (15 and 30%, respectively) compared to the toluene/ water mixture (33%) as well as the overall deracemization (26 and 28%, respectively, compared to 41%) were reduced. We therefore decided to continue with this latter solvent system even though butanol remains an interesting alternative, likely requiring a longer working time.

3.4. DBU Concentration. We then turned to optimizing the concentration of DBU as our earlier work showed an exponential impact of DBU on the apparent rate constant^b when working with substoichiometric amounts of DBU.²⁰ This impact reflects in run 6 (Table 2), where a lower concentration of DBU was used.^c The overall deracemization strongly decreased from 41 to 14%. The reduced overall deracemization can be a reflection of the reduced racemization kinetics or alternatively a shift in the racemization thermodynamics as will be discussed later on. One can, however, not increase the DBU equivalents (and hence concentration) freely as this would imply a deprotonation of the acid available for cocrystallization and hence a strong impact on the process yield. For this reason, runs 7 and 8 (Table 2) were conducted,

increasing both DBU and PBA concentrations in such a manner that at least 1 equiv. of unreacted acid was present to co-crystallize with BnFTP. The results showed a significant increase in the overall deracemization with respectively 47% and 59% compared to run 3 ($E_{tot} = 41\%$). Regarding yield, both runs produced roughly the same quantity of the enantiopure co-crystal, overcoming the 50% maximum yield of resolution (Y = 56%). The yield was strongly increased compared to run 3 (Y = 33%).

These results highlight that not only the kinetics but likely also the thermodynamics of the system are impacted by the overall BnFTP/PBA/DBU proportion. However, it is clear that working with at least "1 equiv. of unprotonated PBA" is beneficial to the yield and overall deracemization ratio, while increasing the DBU concentration increases the overall deracemization for a given working time.

3.4.1. Process Follow-Up. Additionally, for run 8, the enantiomeric excess of the overall liquid phase was followed from the addition of DBU to the last day (Table 4). The

Table 4. Follow-Up of the Deracemization Run 8, (R)-PBA was Used as the Co-Former and (R,R)-Co-Crystal Precipitated

	before addition of DBU	n start of day 2	end of day 2	start of day 3	end of day 3
$E_{ m liquid\ phase}$	56% [S]	29% [S]	13% [S]	013% [S]	1% [S]
	start of day 4	end of day 4	start of day 5	end of day 5	filtrate
$E_{ m liquid\ phase}$	6% [R]	7% [R]	4% [R]	11% [R]	8% [R]

evaluation was done sampling the overall liquid phase (combining both racemization and crystallization vessel liquids). Chromatograms are given in the Supporting Information.

From Table 4, we can observe that the enantiomeric excess of the unwanted enantiomer in the liquid phase was decreasing over time, which was coherent with deracemization occurring. Indeed, the more deracemization occurs the less there are unwanted enantiomers in the solution. Then, at some point (from day 4 on) the enantiomeric ratio was inversed, meaning the major enantiomer in solution was the wanted one. After this, the enantiomeric ratio of R slightly increased, indicating that deracemization was not finished but close to finishing since the increase remained slight and seemed to oscillate at around 0.08. Thus, from this table, it is clear that



Figure 5. Solubility curves of the (S)-BnFTP + (S)-PBA co-crystal and the (R)-BnFTP + (S)-PBA co-crystal in toluene.

deracemization occurs throughout the first 3 days. Past the third day, the process was close to completion and appeared to have finished around the fourth or fifth day. Furthermore, the strongest evolution in the enantiomeric excess was observed during the first few days in correlation with the kinetic study results.

3.4.2. Thermodynamics. In order to confirm the presence of full racemization in the liquid phase, the mixture was left at 90 °C for several days in order to investigate the thermodynamics. After 3 days, an enantiomeric excess close to 0 was obtained (0.08 [R]), which did not alter anymore in the following days, showing that deracemization/racemization had reached equilibrium. Even though close to 0, the enantiomeric excess at equilibrium was slightly in favor of the (*R*)-enantiomer (the starting was in favor of the (*S*)-enantiomer (0.51 [*S*])). Solution interactions between the (*R*)-PBA co-former and the (*R*)-enantiomer of the target compound likely explain this slight solution imbalance. This slight imbalance will furthermore contribute to the overall deracemization process, even if only very lightly.

3.5. Temperature of the Crystallization Cell. Intuitively, decreasing the temperature of the crystallization cell is expected to lead to an increased yield as the reduced solubility will lead to an increased amount of solid crystallizing out. As shown in Figure 5, both diastereomers have a strong difference in solubility. Furthermore, the less stable co-crystal displays a sharper evolution of its solubility with temperature, leading to an increased solubility difference between both diastereomers at high temperatures. To avoid crystallization of the undesired diastereomer at the onset of our process, we decided to start the overall process keeping the crystallization cell at 10 °C (run 9, Table 2). We then gradually decreased the temperature by 5 °C increments each day, reaching -10 °C after 4 days. Compared to run 8, which, with exception of the crystallization temperature, was performed under similar conditions, an impressive increase in both yield (+17%) and overall deracemization (+21%) was observed. This led to an ultimate process showing a 73% yield and an 80% overall deracemization ratio. Table 5 sums up the optimized values for all the studied parameters.

Next, productivity was even further improved by recycling the compound present in the filtrate. Indeed, the filtrate of run

Table 5. Table Summing up the Results of the Optimization

	solvent		$C_{ m BnFTP}$	$C_{\rm PBA}$
toluene with	a 2 × 0.16 %	of water	0.30 mol/L	0.375 mol/L
[DBU]	$T_{\rm rac}$		T_{cryst}	
11.5 g/L	90 °C	decrease	d over time from 1	0 °C to -10 °C

9 was recovered and evaporated to dryness. Then, a racemic amount of BnFTP and an equivalent of (S)-PBA were added, corresponding to the amount of the enantiopure co-crystal crystallized from run 9. Run 10 (Table 2) was then carried out under the same conditions as run 9 without adding an additional amount of racemizing agent (as DBU is not supposed to have been removed). The results of this run followed those of run 9 with a similar deracemization and an even higher yield, reaching 80%. On top, considering only the amount of racemic BnFTP and (R)-PBA added, 9.59 g of the (S-S)-co-crystal was recovered, which would correspond to a 100% yield. This shows that starting with an initial solution at equilibrium (or alternatively recovered from a first process) can yield a 100% transformation of the undesired enantiomer into the desired one.

3.6. Productivity of the Process. Decreasing the process time while not decreasing yield allows for an efficient increase in productivity (the mass of the co-crystal obtained per unit time). For runs 9 and 10, productivities^{*d*} could be calculated to be respectively 0.12 kg kg_{RSCC}⁻¹ day⁻¹ and 0.18 kg kg_{RSCC}⁻¹ day⁻¹ when considering the working time and the crystal-lization time. When only considering the working time (not taking the overnight crystallization into account), productivity increased respectively to 0.55 kg kg_{RSCC}⁻¹ day⁻¹ and 0.82 kg kg_{RSCC}⁻¹ day⁻¹. As a point of comparison, the best result of productivity we had prior to optimization was 0.38 kg kg_{RSCC}⁻¹ day⁻¹. Productivity was more than doubled when looking at run 10, highlighting the success of the optimization.

3.7. Chart Diagram for the Development and Optimization of a New CoISD Process. Going further, Figure 6 is a chart diagram detailing the steps and recommendations when developing a CoISD process for a chiral API. This diagram was constructed upon our observations and results in developing and optimizing the CoISD process on our system. This is meant to guide any new adventurers in the CoSID process development.

4. CONCLUSIONS

In this paper, we studied the impact of process parameters on the recently introduced spontaneous deracemization induced by co-crystallization (CoISD). Deracemizing BnFTP using PBA as the co-former and DBU as the racemizing agent, an overall 80% deracemization and 73% enantiopure co-crystal yield are achieved. This was mainly achieved by addition of small amounts of water to the process, by adapting the amount of base, and by reducing the crystallization temperature. Best process parameters are obtained by keeping the racemization vessel at 90 °C and adding a sufficient amount of water, allowing for phase separation. Furthermore, a gradual decrease of the crystallization temperature is also beneficial for the

Article



Figure 6. Chart diagram of the CoISD process development on a chiral API.

overall yield. Ultimately, we highlighted the possibility of using the recovered mother liquor as the starting solution. This then allows for a full deracemization of any added racemic material, showing the feasibility of a 100% deracemization in the context of this process.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00538.

Racemization curves and linearizations for kinetics measurements and chiral HPLC chromatograms and Van't Hoff calculation and linearization for solubility curves (PDF)

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Notes

The authors declare no competing financial interest.

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ADDITIONAL NOTES

"Water was present in the PBA reactant and originated from the phase separation of PBA and phenylethylamine during the resolution of PBA by diastereomeric salt formation.

^{*b*} The apparent rate constant k' includes the effect of the concentration in DBU.

^cKeeping a similar compound/DBU ratio, the overall concentration was reduced.

^dPr = $\frac{m_1 \times (E+1)}{2m_0 t}$ with m_1 the mass of the output (kg), E the

enantiomeric excess of the output, m_0 the mass of the input (kg_{RSCC}, RSCC meaning the RS-co-crystal), and t the duration of the process (day).^{29,30}

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Organic Process Research & Development

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