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A Flash Thermal Racemization Protocol for the Chemoenzymatic Dynamic Kinetic Resolution and Stereoinversion of Chiral Amines

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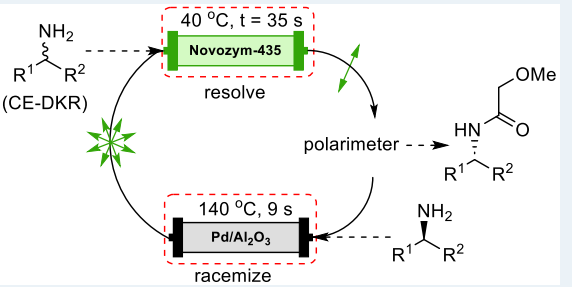
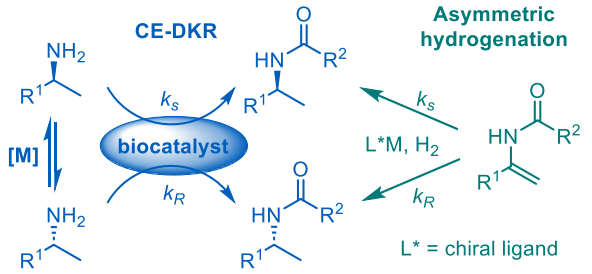
ABSTRACT: A highly practical and effective 'Flash Thermal Racemization' (FTR) protocol was developed in continuous flow, without needing a base or a H donor. This can be integrated with an enzyme to enable the chemoenzymatic kinetic resolution of primary amines to be achieved in a more atom-efficient manner without additives. An unprecedented space-time yield of up to 1362 μmol mL^{-1} h^{-1} can be achieved for the dynamic kinetic resolution of 1-aminoindane, which is at least 10 times more productive than previously reported, and up to 1700-fold more productive when the Pd catalyst loading is taken into account. With a slight modification, the flow reactor system can also be used to convert an optically active amine to its opposite enantiomer.



KEYWORDS: *dynamic kinetic resolution, chiral amines, design-of-experiment optimization, flash thermal racemization, continuous flow synthesis, stereochemical inversion*

Chemoenzymatic dynamic kinetic resolution (CE-DKR) is a powerful synthetic strategy that combines both chemo- and biocatalysts to convert a racemic mixture into enantioenriched products. The process usually involves the use of a transition-metal catalyst, [M], to interconvert the enantiomers, working in tandem with a biocatalyst to convert one of the isomers selectively into an optically active derivative (Scheme 1, in blue).[1] Compared to transition-metal-catalyzed asymmetric hydrogenation reactions (Scheme 1, in green),[2] CE-DKR does not require expensive or proprietary chiral phosphine ligands nor specialized equipment for safe handling of high H_2 pressures.

Scheme 1. Chemoenzymatic Dynamic Kinetic Resolution (CE-DKR) Vs Asymmetric Hydrogenation, for the Synthesis of Chiral Amine Derivatives



In recent years, interests in CE-DKR processes are rekindled by advances in protein engineering and biotechnology that expand the number of modified enzymes available for the kinetic resolution of chiral compounds.[3−5] To date, there are far fewer reports of CE-DKR of amines compared to alcohols. The former is generally more challenging to racemize than the latter,[6] due to the propensity of primary amines to produce imine intermediates and secondary amine side products during the H-transfer processes (Scheme 2). The addition of an H-donor, typically H_2 or ammonium formate, is necessary to suppress side product formation. Very often, an inorganic base, e.g., sodium carbonate, is also added, although the role of this additive is ill-defined. The need to employ these extraneous reagents is one of the biggest drawbacks of applying CE-DKR to produce chiral amine derivatives at scale.

In 1996, the first CE-DKR of a chiral amine was reported in a short communication by Reetz and Shimossek,[7] where Pd/C was combined with Novozym-435 in a Schlenk tube under H_2, to achieve CE-DKR of a racemic 1-phenylethylamine (**1**) to its optically active N-acetyl derivative in 99% ee and 64% yield in 8 days. This was followed by a corpus of work in the ensuing decades, most notably by Bäckvall and co-workers, on the CE-DKR of alcohols and amines.[6]

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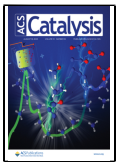
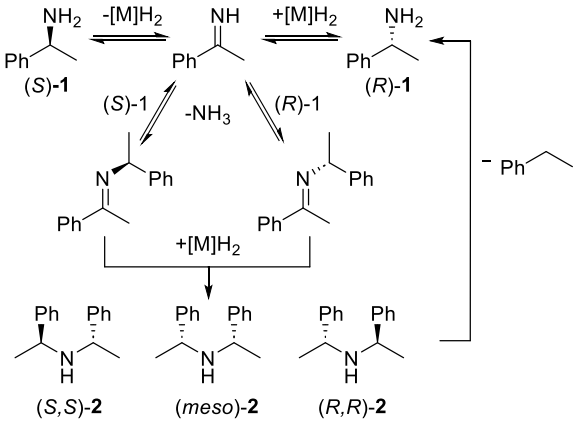
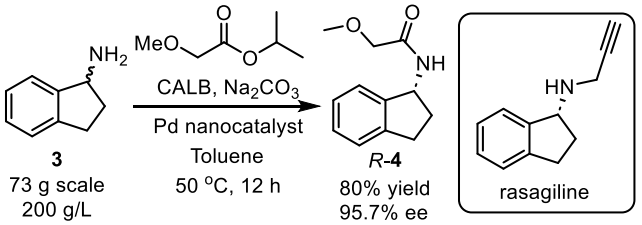


Scheme 2. Metal-Catalyzed Racemization of Chiral Primary Amine 1 and Competitive Formation of Imine Intermediates and Diastereomeric Secondary Amines 2



While *Candida antarctica* lipase (CALB, or its immobilized form, Novozym-435) was always deployed as the biocatalyst, a plethora of catalysts had been reported for the racemization step, including homogeneous[8,9] and heterogeneous[10] Ru catalysts, Pd nanoparticles on different supports,[11−16] as well as Raney Ni and Co.[17] Other interesting approaches include the preparation of hybrid catalysts containing both CALB and Pd on a support[18,19] or by combining the two heterogeneous catalysts in a packed bed.[20] In all of these cases, both catalysts are deployed in a single reaction vessel ("one-pot").[21] While this may be operationally simple, it invariably entails compromises between the catalysts' performance and stability. These issues were illustrated by Jia et al. in the multigram-scale CE-DKR of 1-aminoindane **3**, a chiral precursor of rasagiline (Scheme 3), an active pharmaceutical ingredient for the

Scheme 3. Multigram Synthesis of Rasagiline by CE-DKR in One Pot[22]



treatment of Parkinson's disease.[22] Using a combination of a Pd nanocatalyst, CALB, and sodium carbonate in one pot, 73 g of (*rac*)-**3** could be converted to the optically active amide (*R*)-**4** with 96% ee in 12 h (80% yield). While the catalysts can be recovered and reused up to five times, the formation of impurities resulting from the decomposition of the enzyme was found to be an intractable issue, which required additional product purification steps.

The compatibility issue between the catalysts can be overcome by compartmentalizing the racemization and kinetic resolution processes into separate units of operation. This can be achieved by immobilizing the catalysts in separate reactors connected by a closed loop to recycle the unwanted enantiomer. A hybrid batch-flow system was reported by de Miranda et al. in 2014 (Figure 1),[19,23] where the kinetic resolution was performed in a packed bed of the enzyme at room temperature, and the racemization was conducted in the

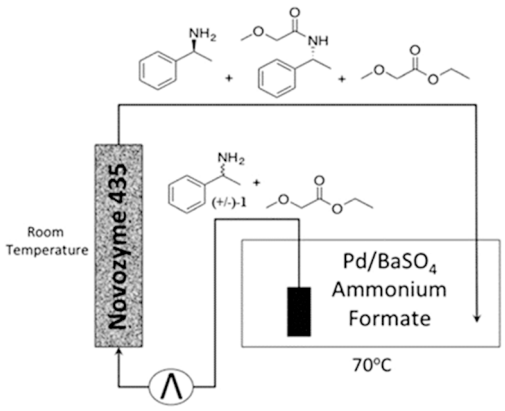


Figure 1. CE-DKR of (*rac*)-**1** using the hybrid semibatch flow system (Reproduced with permission from reference 23. Copyright 2014 The Royal Society of Chemistry).

presence of a heterogeneous Pd catalyst ($Pd/BaSO_4$), sodium carbonate, and ammonium formate in a batch reactor at 70 °C. Using this system, 388 mg (3.2 mmol) of the racemic 1-phenylethylamine (**1**) can be converted to the *N*-amide (*R*)-**6** with 95% ee, but only a moderate conversion of 77% can be attained in 10 h (Scheme 3). The low productivity is attributed to the presence of ammonium formate in the system, which could poison enzyme catalysis by the liberation of NH_3 or CO_2.

In this paper, we describe the development of a new approach to achieve the fast metal-catalyzed racemization of a chiral amine, without the need for an extraneous base or H donor. The 'Flash Thermal Racemization' (FTR) method capitalizes upon the wider reaction space and residence time control afforded by a continuous flow reactor to achieve the desired racemization without compromising selectivity, resulting to a step-change in productivity of CE-DKR processes that paves the way for their eventual industrial deployment.

The idea was inspired by "Flash Chemistry" pioneered by Yoshida and co-workers.[24] The metal-catalyzed racemization may be considered as a facile reaction involving an unstable imine intermediate (Scheme 2), which is likely to benefit from the short residence times afforded by a flow reactor. To test this hypothesis, the racemization of 1-phenylethylamine (*S*)-**1** was chosen to test the effectiveness of the approach, as this can be compared directly with previous literature examples. In this preliminary work, commercially available 5% Pd/Al_2O_3 and Novozym-425 were selected as the racemization and enzyme catalysts, respectively. A similar combination of catalysts was previously reported for the CE-DKR of (*rac*)-**1** in one pot, at 70 °C, in a batch reactor, where the commercially available Pd/Al_2O_3 was reported to be much less effective than custom-made Pd/AlO(OH) with very small Pd nanoparticles (*ca.* 1.73 nm).[25,26] However, we postulated that the catalytic activity can be restored at elevated temperatures.

The investigation was initiated with the construction of a flow reactor system to evaluate the FTR of (*S*)-**1** (Figure 2). A piston pump was used to deliver either a solution of the chiral amine or toluene solvent to a catalyst cartridge containing a packed bed of Pd/Al_2O_3 dispersed in silicon carbide (SiC), an inert, thermally conductive material that can be electrically heated. A back-pressure regulator (BPR) maintained the pressure of the system at 8 bar, so as to retain the liquid phase when it is heated above the boiling point of toluene. As

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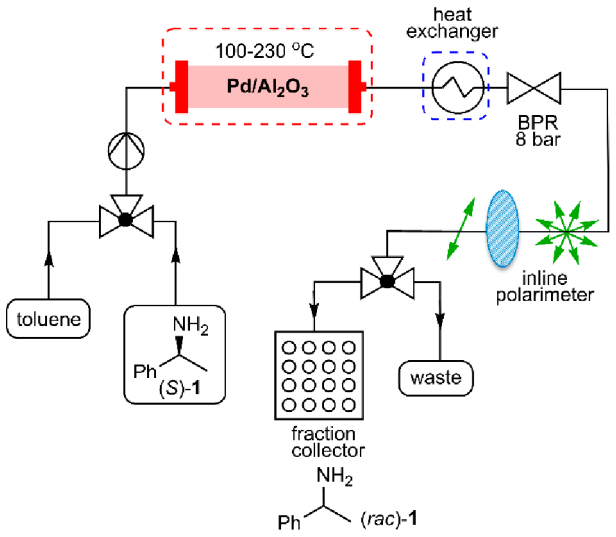
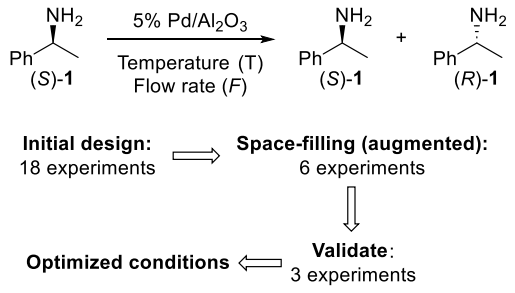


Figure 2. Schematic of the custom-built flow reactor for FTR.

the reaction mixture eluted from the packed bed, it was actively cooled by a thermoelectric (Peltier) heat exchanger, before it was passed through an inline polarimeter, to provide real-time information on the catalyst performance *via* optical rotation readings. Once a steady state was established, the reaction mixture was collected automatically by a fraction collector. The resultant samples were analyzed by chiral high-performance liquid chromatography (HPLC) and gas chromatography (GC), to determine the amine's ee and selectivity, respectively.

The conditions for FTR of (*S*)-**1** were optimized using Design-of-Experiments (DoE),[27] including flow rates between 1 and 7 mL min^{-1}, temperatures from 100 to 230 °C, and initial concentrations of (*S*)-**1** between 20.5 and 82.5 mM (Scheme 4). This was composed of an initial I-optimal split-

Scheme 4. DoE-Optimization of the FTR of (*S*)-1



plot response surface design of 18 experiments (Supporting Information, Table S1, entries 1−18), which identified temperature and flow rate as being the statistically significant reaction parameters with respect to the extent of racemization (ee), while all three variables were significant in suppressing the formation of unwanted byproducts (selectivity). The model was augmented by six further experiments (Table S1, entries 19−24), before it was used to predict the reaction outcomes from three different conditions, which were validated experimentally (Table 1, Entries 1−3). Finally, the model was used to predict the optimal reaction parameters (Table 1, entry 4): At a flow rate of 7 mL min^{-1} (corresponding to a residence time, τ, of 9 s), the racemization of (*S*)-**1** can be obtained with 91% selectivity and 42% ee.

Table 1. Validation Experiments for the DoE Model and Optimized Conditions for the FTR[a]

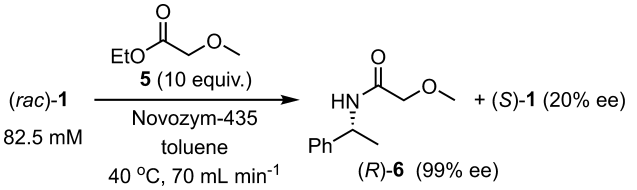
Entry	*T* (°C)	*F* (mL min^{-1})	[*S*-**1**] (mM)	ee[b,d] (%)	Sel.[c,d] (%)
1	165	4	51.6	5 (8)	65 (63)
2	125	5.5	51.6	90 (70)	100 (88)
3	200	2	51.6	<5 (0)	26 (36)
4	140	7	82.5	42	91

[a]All experiments started with a solution of optically pure (*S*)-**1** in anhydrous toluene. [b]Determined by chiral HPLC. [c]Determined by GC. [d]Values in parentheses predicted by the DoE model.

To ensure that catalyst does not deactivate during the DoE study, the initial conditions of an earlier experiment were duplicated periodically between experiments (8 times in total). By doing so, we were able to establish that no noticeable catalyst deactivation was observed across 36 experiments. Given that this includes temperature excursions of up to 230 °C, the activity of the Pd/Al_2O_3 catalyst remained remarkably robust during the FTR process.

Next, the kinetic resolution of (*rac*)-**1** was investigated, using a combination of Novozym-425 and ethyl 2-methoxyacetate (**5**) as an acylating agent.[28] For this part of the work, the Pd catalyst in Figure 2 was replaced by a larger packed bed of the biocatalyst. With the flow rate set to 7 mL/min under 8 bar of pressure (optimized for the FTR), a small screen of the concentration of (*rac*)-**1**, equivalents of the acyl donor **5**, and reaction temperatures (Table S2). It was found that at 40 °C, 82.5 mM of the racemic amine can be converted to the amide (*R*)-**2** with 25% conversion and 99% ee (t = 35 s, Scheme 5).

Scheme 5. Optimized Conditions for the Kinetic Resolution of (*rac*)-1 at 7 mL/min



This corresponds to a selectivity factor (*s*-factor) of 242, which is commensurate with reported values.[20,23,29] In principle, the single-pass conversion can be further improved by increasing the size of the packed bed and the amount of enzyme. However, as the conversion is compatible with the output of the *R*-isomer afforded by the FTR (71:29 er), this was deemed to be unnecessary at this stage.

Finally, the two catalytic packed bed reactors were combined in tandem, to form a closed-loop semibatch reactor system for the FTR-DKR of (*rac*)-**1** and **3** (Figure 3). The efficiency of the system was improved by incorporating molecular sieves in the reservoir to remove the ethanol byproduct, which can affect the stability of the Pd catalyst (Supporting Information, Figure S11).

Using the flow system, 1 g of (*rac*)-**1** was converted to (*R*)-**6** in 1 h, in 90% conversion, 96% selectivity for the primary amine, and 95% ee (Scheme 6, eq 1). Under the same conditions, 92% of (*rac*)-**3** can be converted into (*R*)-**4** with 99% ee and 99% selectivity (eq 2). To improve the process mass intensity (PMI), the amount of acylating agent was reduced from 10 to 2 equiv, with only a slight decrease in productivity: (*R*)-**4** can be obtained with 98% ee in 85%

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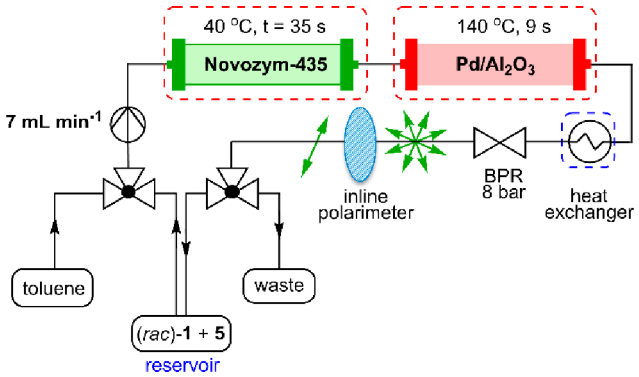
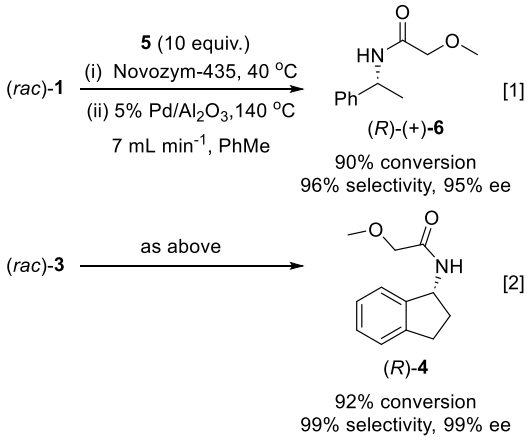


Figure 3. Schematic of a custom-built CE-FTR-DKR reactor system.

Scheme 6. Gram-Scale CE-FTR-DKR of (*rac*)-1 and 3



conversion in 1.5 h, while maintaining a very high level of selectivity (99%). This encouraging result bodes well for future improvements of sustainability metrics, which we envisage to be attainable by reoptimizing the process parameters for **3**, as well as improving catalyst and reactor designs.

As the system does not require a base or a H donor, no special workup procedure is required. The optically active acylated product can be isolated simply by subjecting the reaction mixture to an acid wash, if necessary, followed by the evaporation of the reaction mixture. The resultant crude products were found to be of high purity by NMR spectroscopy (Supporting Information, Figures S4−S7).

The success of the approach is contingent on the stereochemistry of the kinetically resolved amide to be preserved under FTR conditions. This was shown by monitoring the selectivity and enantioselectivity of (*R*)-**6**, which was maintained at a consistently high level throughout the process (Supporting Information, Figures S8 & S9).

The productivity of the new FTR-DKR method compared very favorably against the space-time yields (STYs) reported previously using the one-pot hybrid catch-flow systems (Table 2). In both cases, at least > 10-fold increase in productivity can be demonstrated. When the Pd loading is taken into account, >500-fold increase in efficiency can be achieved for the production of (*R*)-**6** and a remarkable >1700-fold increase for the API intermediate (*R*)-**4**. The extraordinary improvement can be attributed to the efficiency of the FTR process as well as the exceptional stability of the catalysts afforded by the reactor design.

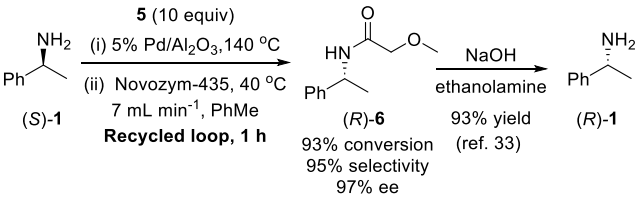
Table 2. Comparison of ee and Productivities[a]

Product	*R*-4	*R*-6
Conversion (%)	92 (87.6[22])	90 (77[23])
Enantioselectivity (%)	99 (96[22])	95 (95[23])
STY (μmol mL^{-1} h^{-1})	1362 (109.6[22])	1465 (14.5[23])
STY [μmol μmol(Pd)$^{-1}$ mL^{-1} h^{-1}]	14.5 (0.008[22])	15.5 (0.030[23])

[a]STY values based on molar conversion of amine precursor. Values in parathesis correspond to literature values (see Supporting Information for calculations).

In a stereoinversion process, an optically pure compound is converted to its opposite enantiomer. This is exemplified by the Mitsunobu reaction, where the stereochemistry of chiral secondary alcohols can be inverted.[30,31] To date, DKR reactions are always used to convert racemate compounds into particular stereoisomer. In principle, the method can also be used in the stereoinversion of an optically active amine, which has never been demonstrated. By switching the positions of the packed beds in Figure 3, (*S*)-**1** can be converted to (*R*)−**6** with 93% conversion, 95% selectivity, and 97% ee in 1 h. The amide group in (*R*)-**6** can be removed under basic conditions to provide the opposite enantiomer of (*S*)-**1** (Scheme 7).[33]

Scheme 7. Inverting the Stereochemistry of (*S*)-1 to Its Opposite Enantiomer



The ability to invert the stereochemistry of a C−N bond may be considered as a form of "molecular editing",[32] where the stereochemistry of a particular functional group in a complex molecule, e.g., natural product, can be inverted, offering greater diversity and new chemical spaces that are otherwise difficult to access.

In this preliminary work, we have successfully demonstrated a flash thermal racemization (FTR) protocol that enables the facile racemization of a primary amine without the need for extraneous reagents. This enables CE-DKR to be achieved with very high selectivity and productivity. In parallel work, we also showed that the system can be used to invert the stereochemistry of a chiral amine very efficiently. Work is currently underway to explore the scope of this methodology in the synthesis of biologically interesting molecules, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c02859.

Experimental details, additional data, copies of ^{1}H, ^{13}C NMR spectra, HPLC and GC chromatographs (PDF)

Calculations of STY (XLSX)

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Author Contributions

The experiments were performed by MJT. The manuscript was prepared by MJT and KKH and revised by all the authors, who have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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