

# Intensification of Free-Radical Racemization for a Non-activated Amine in a Continuous Flow Reactor

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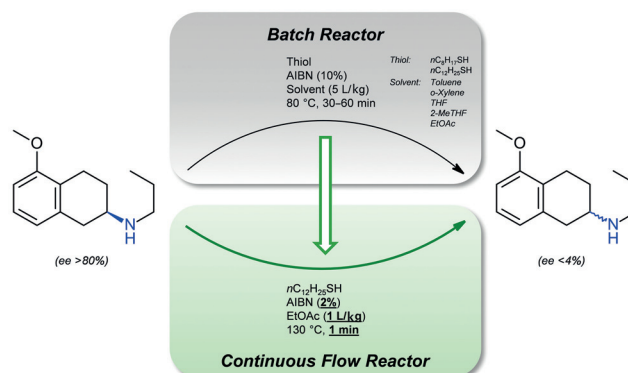
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**Abstract** The free-radical racemization of non-activated amines is a powerful tool for process design in the pharmaceutical industry, allowing the recycling of undesired enantiomers after chiral separation. This paper describes the development of the free-radical racemization of a key API intermediate in a continuous flow reactor. Upon development, a significant reduction of the solvent usage and radical initiator was made possible thanks to the conversion into a continuous flow mode. This intensification positively impacted both the environmental footprint and the safety of the reaction as well as maintaining satisfactory productivity.

**Key words** racemization, radical reaction, hydrogen atom transfer, flow chemistry, intensification, drugs

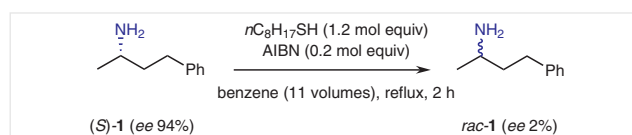
The control of chirality during the molecular construction of active pharmaceutical ingredients (APIs) is a major field of research and development in the pharmaceutical sector.<sup>1</sup> Chirality can be controlled by using compounds derived from ‘the natural pool’ of chiral molecules (e.g., amino acids,<sup>2</sup> sugars,<sup>3</sup> enzymes<sup>4</sup>), by inversion of chiral centers, or by chiral separation (e.g., preferential diastereoisomer crystallization, chiral chromatography).

If applied in later stages of the synthesis of a complex API, the chiral separation of enantiomers may dramatically impact the cost of the overall process, since half of the total product is the separated undesired enantiomer. Therefore, a recycling of this undesired enantiomer should be envisaged to ensure both a minimal financial cost of the final API and a minimal environmental impact of the industrial production process.

The recycling of an undesired enantiomer consists of its racemization: the so-produced racemic mixture can be entered in a new cycle of chiral separation and racemization.

Although numerous APIs and pharmaceutical intermediates have chiral centers based at carbon atoms which can easily be deprotonated, numerous non-activated chiral species cannot undergo racemization by acid/base-mediated exchange.

For instance, APIs containing non-activated amines at the  $\alpha$ -position of chiral centers cannot be easily racemized by deprotonation. A strategy for the racemization of such compounds, firstly proposed by Escoubet et al.<sup>5</sup> (Scheme 1), consists of a free-radical hydrogen atom transfer (HAT) catalyzed by thiyl radical (polarity reversal catalysis).<sup>6</sup>



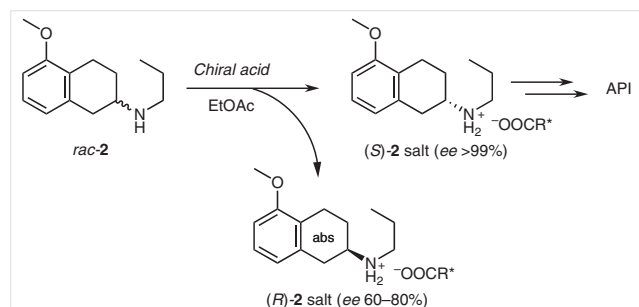
**Scheme 1** Thiyl radical mediated racemization of amine (Escoubet et al.<sup>5</sup>)

In this reaction, the reduction of enantiomeric excess (ee) is achieved by forward and backward transfers of the hydrogen atom between the chiral carbon bearing the amine group at the  $\alpha$ -position and a thiyl radical acting as electrophilic polarity reversal catalyst.

Discovered in 1952 by Barrett and Waters<sup>7</sup> on decarboxylation reactions, this property of thiyl radicals in polarity reversal catalysis has been thoroughly exemplified in numerous other applications,<sup>8</sup> such as deoxygenations,<sup>9</sup> epimerizations of alcohols,<sup>10</sup> acetal rearrangements,<sup>11</sup> dehalogenations,<sup>12</sup> cyclizations,<sup>13</sup> and deuterium incorporations on amines<sup>14</sup> and aldehydes,<sup>15</sup> and by halogen–deuterium exchanges.<sup>16</sup>

Several examples of racemization have already confirmed the efficiency of this methodology<sup>17</sup> and could even be coupled with a resolution of an enantiomer mixture.<sup>18</sup>

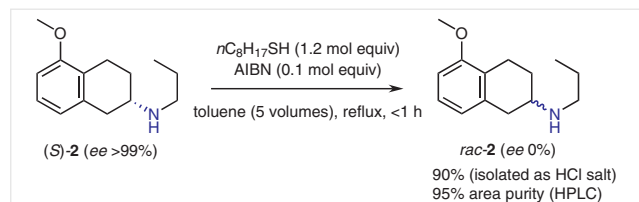
At UCB Pharma, it has long been our goal to design efficient chemical processes for our pharmaceutical products. In the production of a key API intermediate, (*S*)-*N*-propyl-5-methoxy-2-aminotetralin [(*S*)-**2**], isolation of the desired enantiomer was performed by preferential diastereoisomer crystallization (Scheme 2). The main drawback of this unit operation was the sacrifice of the undesired enantiomer (*R*)-**2**: the process yield of the chiral purification was therefore limited to a maximum of 50%.



**Scheme 2** Preferential crystallization of (*S*)-**2** salt with chiral acid and rejection of (*R*)-**2** salt in the mother liquors

Based on the work of Escoubet et al.,<sup>5</sup> the recycling of the undesired enantiomer (*R*)-**2** was evaluated. The design of an industrial process for the racemization of (*R*)-**2** would have to satisfy three key conditions: (1) an enantiomer excess of the isolated product  $\leq 4\%$ , (2) an isolated yield of the product  $\geq 95\%$  (mol), and (3) a purity of the isolated product  $\geq 99\%$  area.

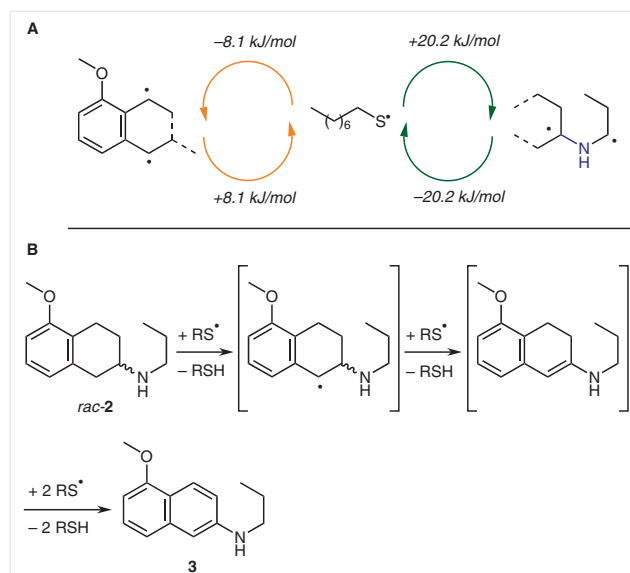
As a proof of concept, an experiment was performed on the readily available, optically pure (*S*)-**2** enantiomer (Scheme 3), before testing the recycled enriched (*R*)-**2** mother liquors. The reaction was performed with octanethiol as thiol catalyst and 2,2'-azobis(isobutyronitrile) (AIBN) as radical initiator, in toluene (5 mL/g, 5 volumes) at reflux, and successfully delivered the racemic product in good yield and purity.



**Scheme 3** Proof-of-concept racemization of optically pure (*S*)-**2**

This first proof of concept revealed the viability of our approach, but also revealed some challenges that would be encountered during the development work. Substrate **2** appeared prone to several hydrogen atom exchanges competing with each other, which might lead to the production of impurities.

The aromatization product **3** was detected up to 1.0% area in the reaction mixture after the racemization reaction (Scheme 4). Based on the proposed mechanism for the formation of benzylic radicals and impurity **3**, the amount of thiol radicals available in the reaction mixture, and thus the amount of AIBN loaded in the reaction, is expected to directly impact the level of that impurity.



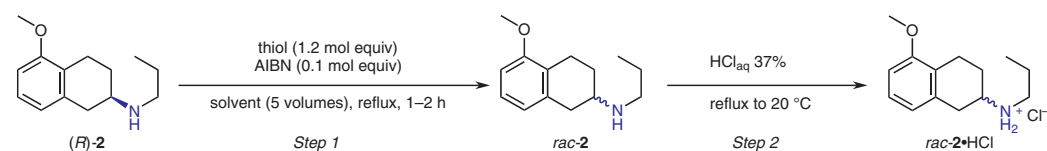
**Scheme 4** (A) Competitive hydrogen atom transfers<sup>19</sup> on **2**; (B) proposed mechanism<sup>20</sup> for the formation of impurity **3**

As a first wave of optimization, six solvents and two thiol catalysts [octanethiol (OctSH) and dodecanethiol (DodSH)] were tested on the material from recycled enriched (*R*)-**2** mother liquors (Table 1). All solvents except isobutyl acetate (Table 1, entries 9–12) and the two thiol catalysts gave comparable results in terms of enantiomeric excess reduction and purity of the isolated product. In the case of isobutyl acetate, the reaction produced a significant amount of impurity **3**.

Based on the competitive hydrogen atom transfers previously presented (Scheme 4), it could be hypothesized that isobutyl acetate could also participate in such exchanges with its tertiary carbon (Scheme 5). Although a mechanism for a preferential production of impurity **3** was not yet proposed, the high molar equivalence excess of isobutyl acetate (8.3 mol equiv vs the amine) and the nucleophilic nature of the isobutyl acetate radical might explain this significant production of impurity **3**.

From this first set of experiments, ethyl acetate was chosen as solvent for practical reasons as it was already used in the previous step of chiral separation. The recycled enriched (*R*)-**2** mother liquors could be directly used in the racemization process without an additional step of solvent

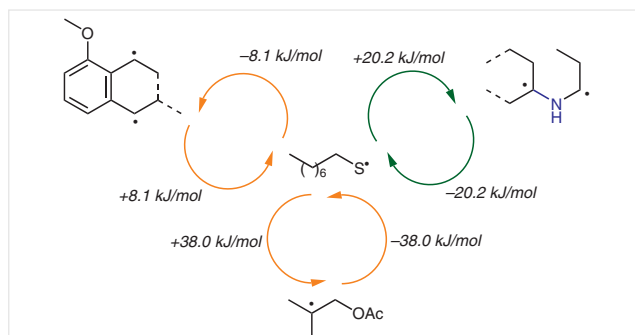
**Table 1** Screening of Solvents and Thiol Catalysts in the Racemization Reaction of Enriched (*R*)-**2** Material and Isolation Reaction in the Batch Reactor



| Entry           | Solvent  | Thiol catalyst | Step(s) | ee (HPLC) (%) | Purity (HPLC) (% area) | Impurity <b>3</b> (HPLC) (% area) | Residual thiol (HPLC) (% area) |
|-----------------|----------|----------------|---------|---------------|------------------------|-----------------------------------|--------------------------------|
| 1 <sup>a</sup>  | toluene  | OctSH          | 1       | 0.6           | 94.07                  | 0.77                              | 3.38                           |
| 2 <sup>a</sup>  |          |                | 1 + 2   | –             | 96.85                  | 1.85                              | 0.00                           |
| 3 <sup>b</sup>  |          | DodSH          | 1       | 0.4           | 91.47                  | 0.72                              | 3.19                           |
| 4 <sup>b</sup>  |          |                | 1 + 2   | –             | 96.85                  | 1.65                              | 0.00                           |
| 5 <sup>a</sup>  | o-xylene | OctSH          | 1       | 0.7           | 93.39                  | 1.17                              | 2.60                           |
| 6 <sup>a</sup>  |          |                | 1 + 2   | –             | 97.71                  | 0.93                              | 0.00                           |
| 7 <sup>b</sup>  |          | DodSH          | 1       | 0.1           | 92.32                  | 0.75                              | 2.8                            |
| 8 <sup>b</sup>  |          |                | 1 + 2   | –             | 98.26                  | 0.62                              | 0.00                           |
| 9 <sup>a</sup>  | iBuOAc   | OctSH          | 1       | 0.8           | 86.65                  | 7.76                              | 3.01                           |
| 10 <sup>a</sup> |          |                | 1 + 2   | –             | 97.84                  | 1.34                              | 0.00                           |
| 11 <sup>b</sup> |          | DodSH          | 1       | 0.0           | 87.66                  | 7.35                              | 2.94                           |
| 12 <sup>b</sup> |          |                | 1 + 2   | –             | 98.03                  | 1.17                              | 0.00                           |
| 13 <sup>a</sup> | THF      | OctSH          | 1       | 0.1           | 93.80                  | 0.39                              | 3.44                           |
| 14 <sup>a</sup> |          |                | 1 + 2   | –             | 99.00                  | 0.37                              | 0.00                           |
| 15 <sup>b</sup> |          | DodSH          | 1       | 0.0           | 92.55                  | 0.57                              | 2.80                           |
| 16 <sup>b</sup> |          |                | 1 + 2   | –             | 99.09                  | 0.30                              | 0.00                           |
| 17 <sup>a</sup> | 2-MeTHF  | OctSH          | 1       | 0.2           | 92.10                  | 0.81                              | 3.13                           |
| 18 <sup>a</sup> |          |                | 1 + 2   | –             | 98.40                  | 0.73                              | 0.00                           |
| 19 <sup>b</sup> |          | DodSH          | 1       | 0.0           | 93.25                  | 0.40                              | 2.95                           |
| 20 <sup>b</sup> |          |                | 1 + 2   | –             | 98.53                  | 0.25                              | 0.00                           |
| 21 <sup>a</sup> | EtOAc    | OctSH          | 1       | 0.5           | 94.65                  | 0.37                              | 2.69                           |
| 22 <sup>a</sup> |          |                | 1 + 2   | –             | 98.46                  | 0.76                              | 0.00                           |
| 23 <sup>b</sup> |          | DodSH          | 1       | 0.0           | 95.66                  | 0.32                              | 2.64                           |
| 24 <sup>b</sup> |          |                | 1 + 2   | –             | 98.77                  | 0.59                              | 0.00                           |

<sup>a</sup> Starting material: enriched (*R*)-**2** (ee 65%, purity 94.72% area).

<sup>b</sup> Starting material: enriched (*R*)-**2** (ee 83%, purity 94.99% area).

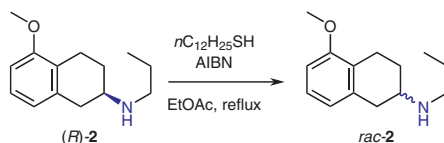


**Scheme 5** Competitive hydrogen atom transfers<sup>19</sup> between amines, benzylic carbons, and isobutyl acetate

swap. Finally, dodecanethiol was preferred as catalyst as its limited stretch made it more convenient to handle at industrial scale (Table 1, entries 23 and 24).

Once the categorical parameters were determined, optimization of the continuous parameters of the racemization were investigated. The optimal molar equivalences of AIBN and dodecanethiol were determined, as well as the dilution in ethyl acetate (Table 2). It appeared that the loading of AIBN cannot be lowered without dramatically decreasing the racemization rate: none of the experiments performed with less than 0.10 molar equivalents of AIBN gave a satisfactory reduction of the enantiomeric excess. Among three experiments (Table 2, entries 6–8) resulting in good conversions, only the conditions with an excess of dodecanethiol

**Table 2** Optimization of Racemization Parameters in the Batch Reactor



| Entry <sup>a</sup> | AIBN (mol equiv) | DodSH (mol equiv) | EtOAc (volumes) | Reaction time (min) | ee (HPLC) (%) | Purity (HPLC) (% area) | Impurity <b>3</b> (HPLC) (% area) |
|--------------------|------------------|-------------------|-----------------|---------------------|---------------|------------------------|-----------------------------------|
| 1                  | 0.02             | 0.5               | 5               | 360                 | 35            | 95.63                  | 0.38                              |
| 2                  |                  | 0.5               | 15              | 360                 | 49            | 95.36                  | 0.46                              |
| 3                  |                  | 1.5               | 5               | 360                 | 13            | 93.12                  | 0.57                              |
| 4                  |                  | 1.5               | 15              | 360                 | 30            | 95.15                  | 0.41                              |
| 5                  | 0.06             | 1.0               | 10              | 360                 | 24            | 92.41                  | 0.44                              |
| 6                  | 0.10             | 0.5               | 5               | 60                  | 1             | 94.69                  | 1.11                              |
| 7                  |                  | 0.5               | 15              | 180                 | 1             | 90.00                  | 1.97                              |
| 8                  |                  | 1.5               | 5               | 30                  | 0             | 95.92                  | 0.53                              |
| 9                  |                  | 1.5               | 15              | 360                 | 11            | 90.83                  | 0.76                              |

<sup>a</sup> Starting material: enriched (*R*)-**2** (ee 65%, purity 94.72% area).

(Table 2, entry 8) gave a low level of impurity **3** and a higher purity of the product. These conditions (Table 2, entry 8) were selected for the rest of the study.

The control of the radical initiation had to be thoroughly understood in order to design a safe and reliable addition of AIBN to the reaction mixture while allowing an efficient initiation of the racemization. Continuous flow reactor (CFR) technology would address these challenges by ensuring a safe and fast heating of the reaction mixture containing the AIBN initiator and a better control of both temperature and pressure within the reactor. Based on our experience in continuous flow reactor technology, stainless steel flow reactors from Ehrfeld Mikrotechnik GmbH were selected for the study. A flow reactor setup was quickly designed with Ehrfeld MMRS modules, including a 11.3 mL 'Meander'-type flow reactor and two coaxial heat exchangers: an even larger 30.0 mL 'Sandwich' continuous flow reactor was considered in the study (Figure 1).

This optimization study (Table 3) in the continuous flow reactor setup confirmed that the level of impurity **3** in the isolated product significantly increases with a higher molar equivalence of AIBN and with a higher reaction temperature. Unsurprisingly, the enantiomeric excess significantly decreases with a higher molar equivalence of AIBN, with a higher reaction temperature, and with a more concentrated reaction mixture.

The first tests in the continuous flow reactor were a replicate of the optimization previously performed in the batch reactor (Table 3). So, the molar equivalences of AIBN and dodecanethiol as well as the dilution in ethyl acetate were studied. Since each reaction mixture composition meant the preparation of a stock solution, the reaction tempera-

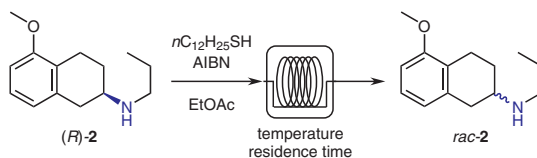
ture and the residence time were easily investigated for each composition.

The best result of the optimization (Table 3, entry 14) was selected to refine the determination of an adequate residence time in the continuous flow reactor (Table 4). In order to achieve a satisfactory decrease of enantiomeric excess, a residence time of 3 minutes appeared to be sufficient.

A demonstration of the final racemization process in the continuous flow reactor and the isolation reaction was performed (final procedure given in the experimental section). The enantiomeric excess, the purity, and the level of impurity **3** were measured for each step of the process (Table 5).

A mass balance analysis of the product *rac*-**2** (Table 6) was also conducted. The molar yield of the overall racemization and isolation is 96.0% and the mass balance of the process is 97.5%.

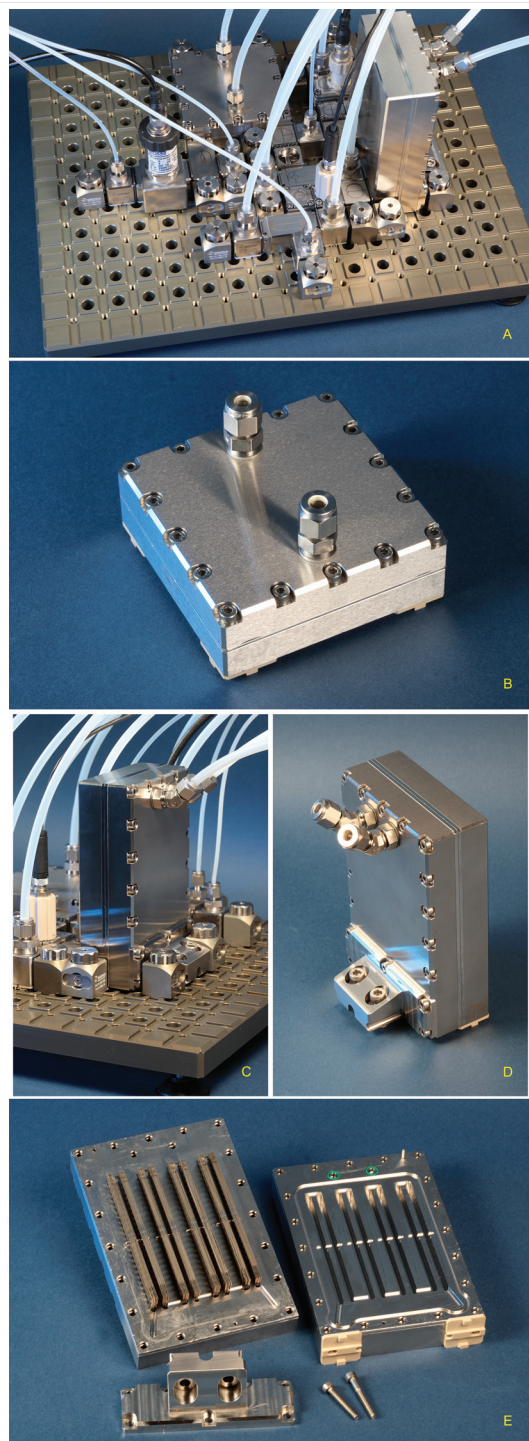
Racemization in the continuous flow reactor proved to deliver a reliable recycling process of the undesired enantiomer (*R*)-**2** with a reduction of enantiomeric excess to 3%, an isolated yield of 96.0%, and a product purity of 99.5% area. Productivity in the continuous flow reactor, defined as the quantity of product *rac*-**2** exiting a continuous flow reactor of 1 L·h<sup>-1</sup>, is 2.88 kg·L<sup>-1</sup>·h<sup>-1</sup>. The racemization was also tested in a larger version of the flow reactor 'Sandwich' (30 mL) (Figure 1) and did not show any significant difference in terms of yield or purity of isolated product: it demonstrated the easy scale-up of such a process. With these excellent results, the intensification of the process was attempted to maximize the productivity of the racemization reaction. Our efforts were directed towards a decrease of the residence time via both an increase of the temperature

**Table 3** Optimization of Racemization Parameters in the CFR

| Entry <sup>a</sup> | AIBN<br>(mol equiv) | DodSH<br>(mol equiv) | EtOAc<br>(volumes) | Temp<br>(°C) | Residence time<br>(min) | ee (HPLC)<br>(%) | Purity (HPLC)<br>(% area) | Impurity <b>3</b> (HPLC)<br>(% area) |
|--------------------|---------------------|----------------------|--------------------|--------------|-------------------------|------------------|---------------------------|--------------------------------------|
| 1                  | 0.02                | 0.5                  | 5                  | 80           | 5                       | 64               | 99.13                     | 0.00                                 |
| 2                  |                     |                      |                    | 80           | 25                      | 48               | 98.91                     | 0.05                                 |
| 3                  |                     |                      |                    | 100          | 15                      | 7                | 98.27                     | 0.45                                 |
| 4                  |                     |                      |                    | 120          | 5                       | 10               | 97.98                     | 0.51                                 |
| 5                  |                     |                      |                    | 120          | 25                      | 8                | 98.05                     | 0.61                                 |
| 6                  |                     |                      | 15                 | 80           | 5                       | 65               | 99.24                     | 0.00                                 |
| 7                  |                     |                      |                    | 80           | 25                      | 59               | 98.97                     | 0.06                                 |
| 8                  |                     |                      |                    | 100          | 15                      | 27               | 98.23                     | 0.49                                 |
| 9                  |                     |                      |                    | 120          | 5                       | 28               | 97.89                     | 0.57                                 |
| 10                 |                     |                      |                    | 120          | 25                      | 23               | 98.01                     | 0.58                                 |
| 11                 |                     | 1.5                  | 5                  | 80           | 5                       | 60               | 99.18                     | 0.02                                 |
| 12                 |                     |                      |                    | 80           | 25                      | 44               | 99.21                     | 0.03                                 |
| 13                 |                     |                      |                    | 100          | 15                      | 1                | 98.64                     | 0.42                                 |
| 14                 |                     |                      |                    | 120          | 5                       | 0                | 97.91                     | 0.74                                 |
| 15                 |                     |                      |                    | 120          | 25                      | 0                | 97.98                     | 0.79                                 |
| 16                 |                     |                      | 15                 | 80           | 5                       | 64               | 98.84                     | 0.00                                 |
| 17                 |                     |                      |                    | 80           | 25                      | 55               | 98.96                     | 0.05                                 |
| 18                 |                     |                      |                    | 100          | 15                      | 8                | 98.32                     | 0.55                                 |
| 19                 |                     |                      |                    | 120          | 5                       | 7                | 97.54                     | 0.83                                 |
| 20                 |                     |                      |                    | 120          | 25                      | 6                | 97.63                     | 0.87                                 |
| 21                 | 0.06                | 1.0                  | 10                 | 80           | 5                       | 55               | 98.97                     | 0.04                                 |
| 22                 |                     |                      |                    | 80           | 25                      | 14               | 98.84                     | 0.29                                 |
| 23                 |                     |                      |                    | 100          | 15                      | 0                | 96.46                     | 1.43                                 |
| 24                 |                     |                      |                    | 120          | 5                       | 1                | 95.86                     | 1.40                                 |
| 25                 |                     |                      |                    | 120          | 25                      | 0                | 95.61                     | 1.66                                 |
| 26                 | 0.10                | 0.5                  | 5                  | 80           | 5                       | 44               | 99.23                     | 0.08                                 |
| 27                 |                     |                      |                    | 80           | 25                      | 10               | 98.35                     | 0.48                                 |
| 28                 |                     |                      |                    | 100          | 15                      | 2                | 95.81                     | 1.74                                 |
| 29                 |                     |                      |                    | 120          | 5                       | 1                | 94.70                     | 1.74                                 |
| 30                 |                     |                      |                    | 120          | 25                      | 1                | 94.03                     | 2.07                                 |
| 31                 |                     | 1.5                  | 15                 | 80           | 5                       | 49               | 98.95                     | 0.15                                 |
| 32                 |                     |                      |                    | 80           | 25                      | 5                | 98.26                     | 0.61                                 |
| 33                 |                     |                      |                    | 100          | 15                      | 0                | 95.12                     | 2.36                                 |
| 34                 |                     |                      |                    | 120          | 5                       | 0                | 94.10                     | 2.26                                 |
| 35                 |                     |                      |                    | 120          | 25                      | 0                | 93.86                     | 2.58                                 |

<sup>a</sup> Starting material: enriched (*R*)-**2** (ee 65%, purity 94.72% area).





**Figure 1** (A) Assembled continuous flow reactor setup with Ehrfeld MMRS modules; (B) stainless steel 'Meander' flow reactor module (11.3 mL); (C/D/E) stainless steel 'Sandwich' flow reactor module (30.0 mL) equipped with mixer grid in the reactor channels. Photo: Courtesy of Ehrfeld Mikrotechnik GmbH.

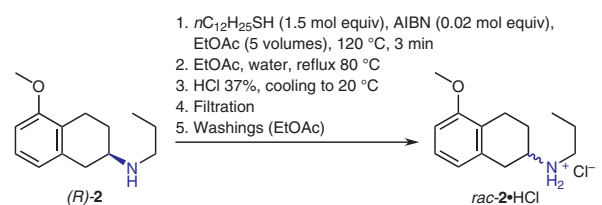
**Table 4** Study of Residence Time on the Racemization Reaction in the CFR<sup>a</sup>

| Entry | Residence time (min) | ee (HPLC) (%) | Purity (HPLC) (% area) | Impurity <b>3</b> (HPLC) (% area) |
|-------|----------------------|---------------|------------------------|-----------------------------------|
| 1     | 0.0                  | 66            | 99.32 <sup>b</sup>     | 0.00                              |
| 2     | 1.0                  | 21            | 99.02                  | 0.18                              |
| 3     | 2.0                  | 8             | 98.61                  | 0.45                              |
| 4     | 3.0                  | 4             | 98.31                  | 0.56                              |
| 5     | 4.0                  | 3             | 98.22                  | 0.61                              |
| 6     | 5.0                  | 2             | 97.91                  | 0.72                              |

<sup>a</sup> Reaction conditions: AIBN (0.02 mol equiv), DodSH (1.5 mol equiv), EtOAc (5 volumes), 120 °C.

<sup>b</sup> Mother liquors purified on charcoal before racemization.

**Table 5** Demonstration of Racemization and Isolation Process in the CFR



| Entry | Step             | ee (HPLC) (%) | Purity (HPLC) (% area) | Impurity <b>3</b> (HPLC) (% area) |
|-------|------------------|---------------|------------------------|-----------------------------------|
| 1     | feed             | 65            | 99.36 <sup>a</sup>     | 0.00                              |
| 2     | racemization     | 3             | 98.17                  | 0.69                              |
| 3     | holding 80 °C    | –             | 98.42                  | 0.60                              |
| 4     | mother liquors   | –             | 43.08                  | 18.60                             |
| 5     | washing 1        | –             | 42.25                  | 16.38                             |
| 6     | washing 2        | –             | 42.48                  | 0.00                              |
| 7     | isolated product | 3             | 99.57                  | 0.13                              |

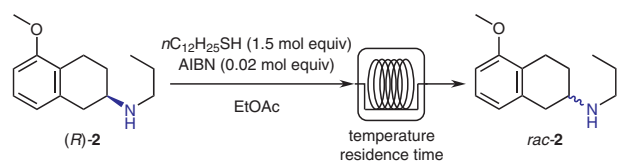
<sup>a</sup> Mother liquors purified on charcoal before racemization.

**Table 6** Mass Balance Analysis of Equivalent *rac*-**2**·HCl Product in Input/Outputs of the Continuous Flow Racemization and Isolation Processes

| Entry | Input/output     | Mass (g) | <i>rac</i> - <b>2</b> ·HCl (% w/w) | <i>rac</i> - <b>2</b> ·HCl (g) | mol%  |
|-------|------------------|----------|------------------------------------|--------------------------------|-------|
| 1     | feed             | –        | –                                  | 23.32                          | 100.0 |
| 2     | mother liquors   | 201.77   | 0.17                               | 0.34                           | 1.4   |
| 3     | washing 1        | 16.45    | 0.09                               | 0.01                           | 0.1   |
| 4     | washing 2        | 11.39    | 0.00                               | 0.00                           | 0.0   |
| 5     | isolated product | 22.39    | >99.9                              | 22.39                          | 96.0  |
| 6     | total            | –        | –                                  | –                              | 97.5  |

and concentration (Table 7). The racemization was successfully performed in only 1 volume of ethyl acetate and 1 minute of residence time and at a temperature of 130 °C (Table 7, entry 2). The intensification allowed the productivity to be increased to 20.4 kg·L<sup>-1</sup>·h<sup>-1</sup>.

**Table 7** Intensification of the Racemization Process in the CFR



| Entry <sup>a</sup> | EtOAc (volumes) | Temp (°C) | Residence time (min) | ee (HPLC) (%) | Impurity 3 (HPLC) (% area) |
|--------------------|-----------------|-----------|----------------------|---------------|----------------------------|
| 1                  | 1               | 130       | 0.5                  | 18            | 0.28                       |
| 2                  |                 |           | 1.0                  | 4             | 0.64                       |
| 3                  |                 | 140       | 0.5                  | 6             | 0.61                       |
| 4                  |                 |           | 1.0                  | 2             | 0.89                       |
| 5                  | 3               | 130       | 0.5                  | 20            | 0.30                       |
| 6                  |                 |           | 1.0                  | 6             | 0.64                       |
| 7                  |                 | 140       | 0.5                  | 7             | 0.59                       |
| 8                  |                 |           | 1.0                  | 4             | 0.84                       |
| 9                  | 5               | 120       | 1.0                  | 22            | 0.35                       |
| 10                 |                 |           | 3.0                  | 3             | 0.97                       |
| 11                 |                 |           | 5.0                  | 3             | 0.95                       |
| 12                 |                 |           | 1.0                  | 8             | 0.67                       |
| 13                 |                 | 130       | 3.0                  | 3             | 1.20                       |
| 14                 |                 |           | 5.0                  | 3             | 1.20                       |
| 15                 |                 | 140       | 1.0                  | 6             | 0.93                       |
| 16                 |                 |           | 3.0                  | 5             | 0.92                       |
| 17                 |                 |           | 5.0                  | 4             | 0.94                       |
| 18                 |                 |           | 1.0                  | 8             | 0.83                       |
| 19                 |                 | 150       | 3.0                  | 8             | 0.95                       |
| 20                 |                 |           | 5.0                  | 7             | 0.98                       |
| 21                 | 160             | 160       | 1.0                  | 10            | 0.79                       |
| 22                 |                 |           | 3.0                  | 10            | 0.82                       |
| 23                 |                 |           | 5.0                  | 6             | 0.93                       |

<sup>a</sup> Starting material: enriched (R)-2 (ee 65%, purity 94.72% area).

In an industrial perspective, this value of productivity was used to calculate the requirements for the treatment of 500 kg of (R)-2 (Table 8) with the best racemization process in the batch reactor (Table 2, entry 8) and with the intensified process in the continuous flow reactor (Table 7, entry 2).

These preliminary calculations gave some insights into the potential benefits at industrial scale. A continuous flow reactor with a volume of 5 L would be sufficient to ensure

**Table 8** Calculations for Estimated Productivity and Production Time in the Batch Reactor and in the CFR

| Reactor | Productivity (L)  | DodSH (kg·L <sup>-1</sup> ·h <sup>-1</sup> ) | AIBN (L) | EtOAc (kg) | Production time (h) |
|---------|-------------------|--|----------|------------|---------------------|
| batch   | 5000 <sup>a</sup> | 0.029  | 819      | 37.5       | 2500                |
| CFR     | 5                 | 20.4   | 819      | 7.5        | 500                 |

<sup>a</sup> A 5000 L batch reactor was selected as a medium range batch reactor for a pharma production; 5000 L is the maximal volume of the reactor and the maximal volume of the reaction mixture at 20 °C is estimated at 3480 L.

<sup>b</sup> Production time in the batch reactor was estimated on the basis of typical times for addition of all reagents (3 h), heating (1 h), and reaction (1 h).

<sup>c</sup> Production time in the CFR only takes into account the production time in flow, as preparation of the mixture can be performed during the production time in flow.

the racemization of 500 kg with a cycle time comparable to the expected productivity of a 5000 L industrial batch reactor. A reduction of ethyl acetate would also lower the waste amount generated. Finally, a reduction of AIBN loading would also make the storage, the handling, and the addition of this hazardous reagent safer in an industrial environment.

In conclusion, a free-radical racemization process for a chiral amine has been successfully demonstrated, allowing the recycling of an undesired enantiomer after chiral separation. With a decrease of enantiomeric excess to 4%, an isolated yield of 96%, and a purity of isolated product above 99% w/w, this racemization process satisfied our three key conditions for an implementation at industrial scale. It was possible to drastically upscale the process by using a continuous flow reactor which significantly contributed to a reduction of the amounts of solvent and radical initiator required. These improvements rendered the overall process more efficient, environmentally friendly, and cost-competitive to meet an industrial demand.

This example of process intensification showcases the benefits of continuous flow reactor technology in the development of safer, greener, and cost-effective large-scale processes of free-radical hydrogen atom transfers whose applications can be expanded beyond the racemization of non-activated amines.

All chemicals were purchased from Sigma-Aldrich, VWR, or Acros Organics. <sup>1</sup>H NMR spectra (400 MHz) and <sup>13</sup>C NMR spectra (100 MHz) were measured in deuterated solvents with TMS as an internal standard on a Varian 400 MHz spectrometer at room temperature. HPLC spectra were recorded on an Alliance Waters 2695 system equipped with an Atlantis T3 3 μm column (4.6 × 100 mm), with detection at 200 nm; starting solvent composition = water: 90 vol %/water + 1% H<sub>3</sub>PO<sub>4</sub>: 10 vol %; final solvent composition = water + 1% H<sub>3</sub>PO<sub>4</sub>: 10 vol %/acetonitrile: 90 vol % in 6 min, followed by a re-equilibration period of 1 min to the initial solvent composition. Chiral HPLC was recorded on an Alliance Waters 2695 system equipped with a Chiralpak AD-H 5 μm (250 × 4.6 mm) column, with detection at 229 nm. Mass

spectra were recorded on a Waters 3100 triple quadrupole spectrometer.

### Free-Radical Racemization of (*R*)-*N*-Propyl-5-methoxy-2-amino-tetralin [(*R*)-2]

To a degassed solution of enriched (*R*)-2 (23.32 g, ee 66%, purity 99.32%) in EtOAc (69.96 mL, 3 mL/g) previously treated on charcoal were added, in a nitrogen-flushed and dried Schott glass bottle, EtOAc (46.67 mL, 2 mL/g), 2,2'-azobis(isobutyronitrile) (AIBN; 0.35 g, 0.02 mol equiv), and 1-dodecanethiol (32.27 g, 1.50 mol equiv). The mixture was allowed to stir at room temperature to ensure the full solubilization of AIBN. The mixture was then injected at a flow rate of 3.9 mL/min by a Knauer pump (ceramic pump head 50 mL, model K-501) in an MMRS continuous flow reactor setup (Ehrfeld Mikrotechnik GmbH) (Figure 1) equipped with a Meander reactor (11.3 mL, model Ehrfeld 0211-2-0311-F) heated at 120 °C by heating fluid and pressurized at 15 barg by a back-pressure controller (model Ehrfeld 0515-1-8011-F). Cooling of the mixture after reaction was ensured by a co-axial heat exchanger (model Ehrfeld 0309-3-0001-F), cooled at 15 °C by heating fluid. Monitoring of the temperature of the reaction at the outlet of the reactor and after the cooling was ensured by two temperature probes (model Ehrfeld 0501-2-1001-F). The reaction mixture was collected in a Schott glass bottle at the outlet of the continuous flow reactor setup (ee 3%, purity HPLC 98.2% area).

### Isolation of *rac*-2-HCl Salt

To the solution collected from the continuous flow reactor were added EtOAc (116.6 mL, 5 mL/g) and water (11.66 mL, 0.5 mL/g). The mixture was transferred to a batch reactor and was heated to reflux (inner temperature ~76 °C). An aqueous solution of HCl 37% w/w (11.53 g, 1.1 mol equiv) was added to the mixture at reflux over 20 min. Precipitation of *rac*-2-HCl salt was observed during the addition of the HCl solution and the suspension was stirred at reflux for 1 h. The suspension was cooled to 20 °C (cooling ramp: -10 K/h) and stirred at 20 °C for 1 h. The solid was collected by filtration and washed with EtOAc (2 × 23 mL, 2 × 1 mL/g). The isolated solid was dried under vacuum at 40 °C; yield: 26.11 g (96%); ee 3%; purity HPLC 99.5% area; assay HPLC >99.9% w/w.

<sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ = 9.10 (broad s, 2 H), 7.13 (t, *J* = 6.0 Hz, 1 H), 6.79 (d, *J* = 6.0 Hz, 1 H), 6.72 (d, *J* = 6.0 Hz, 1 H), 3.77 (s, 1 H), 3.17 (dd, *J* = 3.4, 3.0 Hz, 1 H), 2.90 (m, 4 H), 2.49 (m, 4 H), 2.29 (m, 1 H), 1.72 (m, 3 H), 0.95 (t, *J* = 5.6 Hz, 3 H).

<sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ = 156.68, 133.89, 126.78, 123.35, 121.04, 107.87, 55.24, 52.89, 45.57, 31.34, 24.77, 21.51, 19.25, 11.12.

MS (ES<sup>+</sup>): *m/z* (%) = 161.2 (100), 220.2 (47) [M + H]<sup>+</sup>.

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