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**BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS**

**FACULTY OF CHEMICAL TECHNOLOGY AND BIOTECHNOLOGY**

**GEORGE OLAH DOCTORAL SCHOOL**

**Application of novel synthesis methods for the preparation of drug intermediates and candidates containing heterocyclic moieties**

Thesis book

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Chemical Works of Gedeon Richter Plc.; Pharmaceutical Research Laboratory-I



RICHTER GEDEON

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## 1. INTRODUCTION

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Over the past 20 years, synthetic chemistry has been undergoing a renaissance thanks to the introduction of innovative technologies that allow chemists to select from a broader range of tools that best suits their task.<sup>1</sup>

New technologies have a vital role in increasing the efficiency of academic research and expanding the boundaries of science so far. At the same time, the chemical industry invests significant resources to stimulate innovation in synthetic methods, in order to meet increasingly stringent safety and quality standards. In addition, these new methods offer great potential from an economic point of view as they often reduce production time and cost while increasing productivity.

In this changing environment, flow-based chemical technologies significantly support these efforts. By taking advantage of these innovative technology, it is possible to make existing chemical transformations safer and more environmentally friendly, accelerate the construction of molecular libraries, support the early stages of drug research, and enable robust and reliable scaling in the optimization of manufacturing technologies.

The subject of my doctoral thesis is the elaboration of alternate flow chemical syntheses to eliminate the disadvantages of known batch synthesis of building blocks which are widely used as a central unit of pharmaceutical chemistry.

Benzimidazole and tricyclic benzimidazole derivatives, due to their diverse biological activity, are found in several drug substances. In designing the preparation of these compounds, efforts have been made to develop a method that can be integrated with other generally applicable continuous-flow synthetic steps, free of toxic reagents. Although the synthesis of these molecular frameworks by batch technology is widely discussed in the literature, due to their low efficiency and narrow applicability, their use is not advantageous, and it is difficult to combine the consecutive chemical steps.

Our aim was to carry out the *N*-acylation step in a flow system starting from commercially available 2-nitroaniline derivatives and to accomplish the intramolecular ring closure under the conditions of reduction of the nitro group.

Another area of my doctoral research is the development of diastereoselective flow

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(1) Ingham, R. J.; Battilocchio, C.; Fitzpatrick, D. E.; Sliwinski, E.; Hawkins, J. M.; Ley, S. V. *Angew. Chem. Int. Ed.* **2014**, *53*, 1–6.

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chemical synthesis of the *cis*-4-aminocyclohexanol backbone. The chemical importance of *cis*-4-aminocyclohexanol is due to the fact that the hydroxyl function offers many possibilities for chemical conversions, so that it can be used as a building block for many active substances and intermediates. Our aim was to provide the desired derivative from *N*-protected 2-oxa-3-azabicyclo[2.2.2]oct-5-ene by *cis* selective reductive ring opening. Another challenging synthetic problem is the implementation of the nitroso Diels-Alder reaction and the oxidation of hydroxamic acid forming the nitroso reagent and its coupling to the reductive ring opening step in a flow system.

## **2. LITERARY BACKGROUND**

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Chemical reactions in the tank reactor have a number of disadvantages, including, for example, the difficulty of scale-up and the inhomogeneity of the macrokinetic (mixing, dosing) and microkinetic (concentration, temperature, pressure) parameters of the process.

The solution to the above problems can be the application of flow chemistry technologies. Due to its larger surface area compared to batch tank reactors, outstanding temperature control and efficient mixing can be achieved.<sup>2</sup>

Compounds containing benzimidazole (**10**) and tricyclic benzimidazole (**30**) moieties (Figure 1) play a key role in many indications of drug discovery due to their broad range of biological activity.<sup>3</sup> There are many literature examples of the preparation of these compounds by batch technology, but it has been found that the processes employed so far have many disadvantages, such as often low production, corrosive, toxic reagents, high temperature and long reaction times.<sup>4</sup> Flow chemistry as an innovative technology offers the opportunity to alleviate the above disadvantages of batch reactions, especially with regard to reaction time and the exclusion of toxic reagents. For the benzimidazole derivatives there is only a limited number of methods have been published, which are difficult to implement in the pharmaceutical industry.<sup>5</sup> To the best of our knowledge, compounds containing tricyclic benzimidazole backbone (**30**) have not been prepared yet using flow chemical technology.

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(2) Schwalbe, T.; Autze, V.; Wille, G. *Chimia (Aarau)*. **2002**, *56* (11), 636–646.

(3) Nofal, Z. M.; Soliman, E. A.; El-Karim, S. S. A.; El-Zahar, M. I.; Srour, A. M.; Sethumadhavan, S.; Maher, T. J. *Drug Res. (Stuttg)*. **2011**, *68* (4), 519–534.

(4) Rathod, C. P.; Rajurkar, R. M.; Thonte, S. S. *Indo Am. J. Pharm. Res.* **2013**, *3* (2), 2323–2329.

(5) Sauks, J. M.; Mallik, D.; Lawryshyn, Y.; Bender, T.; Organ, M. *Org. Process Res. Dev.* **2014**, *18*, 1310–1314.

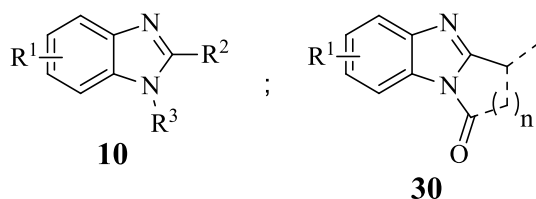


Figure 1: General structure of benzimidazole and tricyclic benzimidazole derivatives

The importance of *N*-protected *cis*-4-aminocyclohexanol backbone compounds (Figure 2, **38**) lies in its versatile use. On the one hand, it can be incorporated into the target compound skeleton by a simple *O*-substitution,<sup>6</sup> and on the other hand, if the *trans* diastereomeric derivative is responsible for the desired biological effect, it can be obtained, for example, by a  $S_N2$ -type reaction.<sup>7</sup>

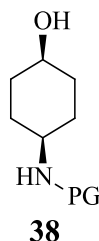


Figure 2: General structure of *N*-protected *cis*-4-aminocyclohexanols

There are many examples in the literature for the preparation of **38**. One of the most commonly used processes is the catalytic hydrogenation of phenol derivatives,<sup>8</sup> the other is the reduction of 4-aminocyclohexanone derivatives.<sup>9</sup> The main disadvantage of these processes is that without the use of expensive auxiliary reagents, the diastereomeric selectivity is low and the proportion of *cis* and *trans* product are approximately 1:1, so that the desired isomer can only be obtained by further purification steps, more often by recrystallization or chromatography. The stereoselectivity of the reaction can be clarified if the position is already fixed in the structure of the starting material. In the case of the *N*-protected 2-oxa-3-azabicyclo[2.2.2]oct-5-ene cycloadducts, the oxygen and nitrogen atoms are in *cis* position so

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- (6) Hwang, S. H.; Weckler, A. T.; Zhang, G.; Morisseau, C.; Nguyen, L. V.; Fu, S. H.; Hammock, B. D. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3732–3737.
- (7) Tawaraishi, T.; Sakauchi, N.; Hidaka, K.; Yoshikawa, K. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 3067–3072.
- (8) Li, H.; Wang, Y.; Lai, Z.; Huang, K.; Li, H.; Wang, Y.; Lai, Z.; Huang, K. *ACS Catal.* **2017**, *7*, 4446–4450.
- (9) Hutchins, R. O.; Su, W.-Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *48* (20), 3412–3422.
- (10) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32* (43), 6077–6080.

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that the *cis* product can be obtained with 100% selectivity when cleaving the N-O bond.<sup>10</sup> To the best of our knowledge, the *cis*-selective synthesis of *N*-protected 4-aminocyclohexanols has not been accomplished by continuous flow chemistry.

### **3. EXPERIMENTAL METHODS**

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During continuous flow experiments, solutions of the starting materials were transported using KNAUER HPLC pumps, acylation reactions were performed in an Asia loop reactor (internal volume is 4 or 16 mL), hydrogenations were performed in an H-Cube Pro (Thalesnano<sup>®</sup>) apparatus, and in the case of nitroso Diels-Alder reaction, an Omnifit column was used for the MnO<sub>2</sub> charge. Nitrogen was applied above the starting material solutions to ensure inert conditions. The CEM Discover Microwave reactor was used to optimize the acylation reactions.

Starting materials for continuous flow experiments were prepared using batch conditions or purchased (Sigma Aldrich, Combi-Blocks), purified by column or flash chromatography (CombiFlash<sup>®</sup>) or by recrystallization. The purity of the compounds was checked by gas chromatography or liquid chromatography coupled mass spectroscopy. The structures of the compounds were confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy.

### **4. RESULTS AND DISCUSSION**

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#### 4.1 Design of a benzimidazole ring system by one-pot reductive cyclization method using continuous flow system

Our goal was to carry out the nitro group reduction and ring closure steps in one reactor system, which required the careful selection of critical reaction parameters such as catalyst, temperature, and solvent. In order to optimize the process, the synthesis of 2-methylbenzimidazole (**51**) from 2-nitroacetanilide (**52**) was chosen as a model reaction (Figure 3). It was found that when the experiment was carried out in acetic acid solvent with a 30 mm 10% Pd/C catalyst charge at 150 °C, besides the desired ring closure, the ring was also saturated, whereby 2-methyl-4,5,6,7-tetrahydro-1*H*-benzo[*d*]imidazole (**53**) was prepared with 98% selectivity.

Because with the modification of temperature and residence time parameters we couldn't reach the selectivity for **51**, hereafter we focused on the selectivity of poisoned catalysts instead of the 10% Pd/C catalyst. In the case of the sulfur poisoned 5% Pt/C catalyst, which is widely used in the industry, the desired 2-methylbenzimidazole (**51**) could be obtained with >99% selectivity at 150 °C and 20 bar.

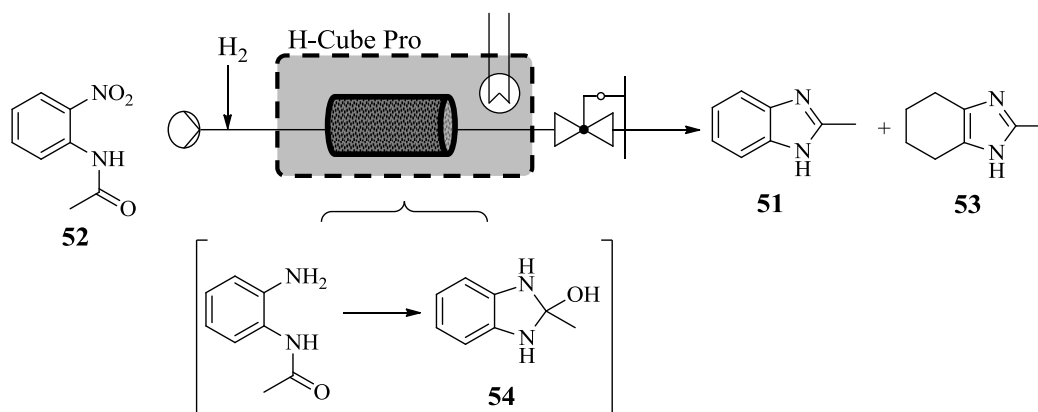


Figure 3: Schematic diagram of continuous flow synthesis of 2-methylbenzimidazole (**51**)

In the next step, the temperature dependence of the dehydration was investigated. The results indicate that the H-Cube Pro should be run at its maximum temperature of 150 °C, because conversion decreases significantly with the decrease of temperature.

In order to make our process suitable for coupling to other flow reactions, we aimed to determine the minimum required acetic acid content while maintaining selectivity. Based on the results of the measurements, it was found that dehydration with 36% conversion was achieved using 100% ethanol solvent, but complete conversion could be achieved in 50 v/v% acetic acid-ethanol solvent mixture.

#### 4.1.1 Application of the optimized flow chemical system for reductive ring closure of substituted 2-nitroacetanilide derivatives

In the following, we investigated the tolerance of the optimized method towards substituted 2-nitroacetanilide derivatives (**55a-i**) useful in synthetic chemistry (Figure 4). Based on the experimental results it can be stated, that in the cases of functional groups sensitive to reductive cleavage (MeO (**56a**), CN (**56b**), CBz (**56c**), Br (**56d**), Cl (**56e**)) and to acidic medium (Boc (**56f**), piperidine (**56g**), morpholine (**56h**) and pyrrolidine (**56i**)) had outstanding selectivities (82-99%).

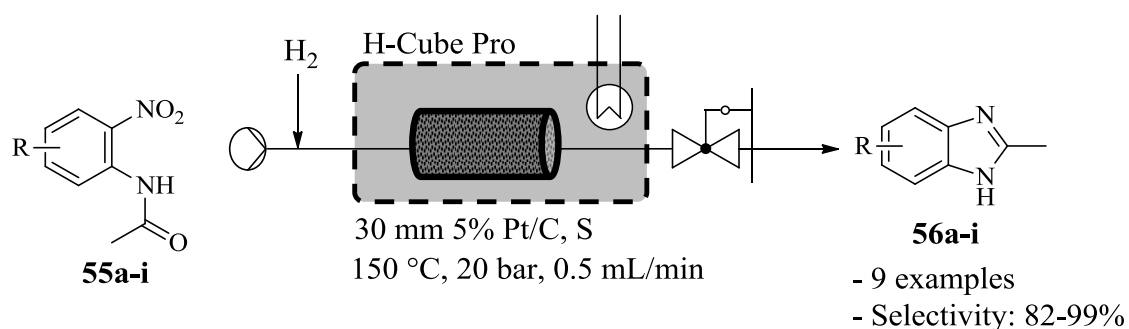


Figure 4: Extension of the continuous reductive cyclization method to substituted *N*-acetyl-2-aminonitrobenzene (**55a-i**) derivatives

#### 4.1.2 Attempts to integrate acylation and reductive ring closure of 2-nitroaniline (**57**)

The next challenge was to integrate acylation of 2-nitroaniline (**57**) with the continuous reductive ring closure process discussed above (Figure 5). Based on the results we can establish, that it is possible to obtain a complete selectivity of 99% by acylation at 200 °C with 3 equiv. acetic anhydride. It has been found that at this temperature the use of the catalyst is not required and that no byproduct is formed despite the excess of acetic anhydride.

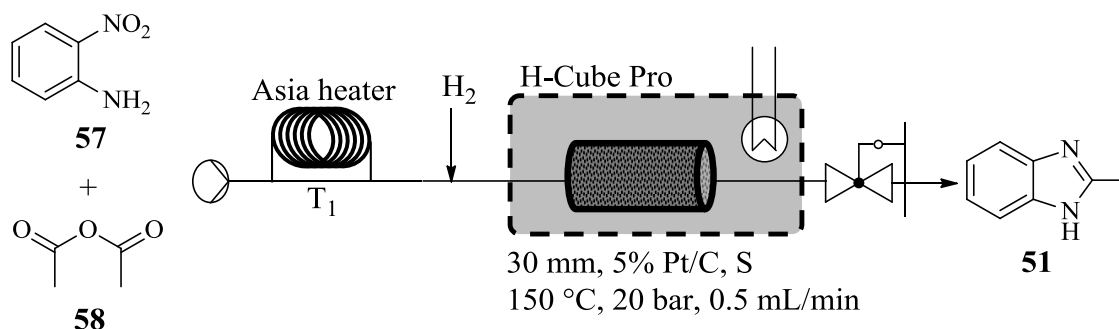


Figure 5: Integration of the acylation step with the continuous flow hydrogenation

#### 4.2 Preparation of benzimidazole lactams by reductive ring closure in a flow chemistry system

In developing a novel process for the preparation of the title compounds, we started with the optimization of reductive ring closure using continuous flow technology. The experiments were performed under conditions optimized for reductive ring closure of 2-methylbenzimidazole (30mm 5% Pt/C, S; 20 bar, 150 °C, 0.5 mL/min) using H-Cube Pro device.

#### 4.2.1 Investigation of reductive ring closure with dicarboxylic acids among *N*-acylated 2-nitroaniline derivatives

As starting materials we investigated 4-[(2-nitrophenyl)amino]-4-oxobutanoic acid (**60**) and 5-[(2-nitrophenyl)amino]-5-oxopentanoic acid (**61**) (Figure 6) and cyclic imide unit containing derivatives such as 1-(2-nitrophenyl)pyrrolidine-2,5-dione (**62**) and 1-(2-nitrophenyl)piperidine-2,6-dione (**63**) (Figure 7).

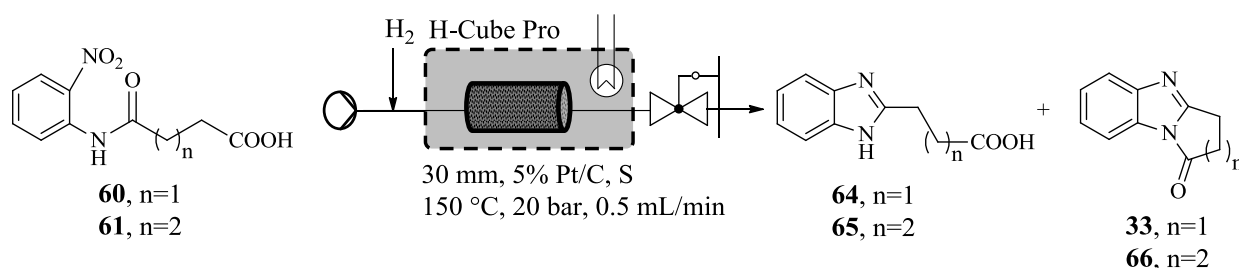


Figure 6: Continuous flow synthesis of benzimidazole derivatives from  $\omega$ -[(2-nitrophenyl)amino]- $\omega$ -oxoalkanoic acid

Based on these experiments, 3-(1*H*-benzo[*d*]imidazol-2-yl)propanoic acid (**64**) (94%) and 4-(1*H*-benzo[*d*]imidazol-2-yl)butanoic acid (**65**) (93%) can also be prepared with good selectivity. Due to the acidic medium and the high temperature, the dehydration step is also favored so that tricyclic lactam derivatives are also produced in a minimum amount (**33**, **66**).

Subsequently, the above reaction was repeated with starting materials containing the cyclic imide units (**62**, **63**) (Figure 7).

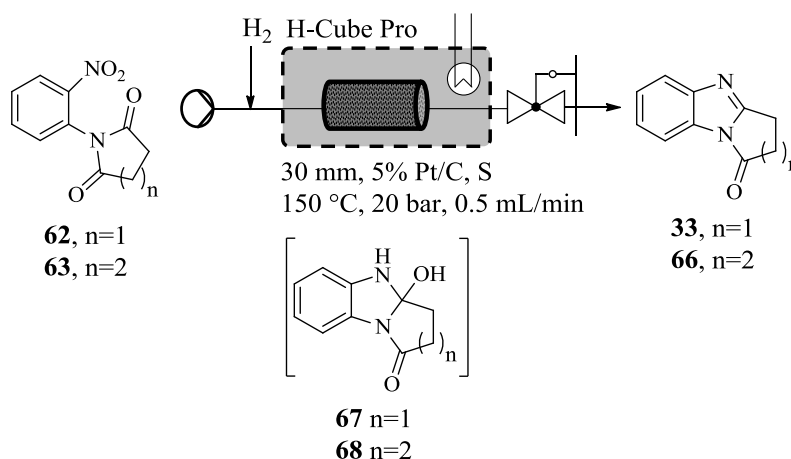


Figure 7: Schematic diagram of continuous flow synthesis of benzimidazole lactams

The desired product (**33**, **66**) was obtained with the best selectivity at a minimum flow rate of 0.3 mL/min (94% **33**, 86% **66**). Further, based on our experimental results, we have found that at the reaction conditions there is an equilibrium between lactam and open forms.

#### 4.2.2 Continuous flow production of tricyclic benzimidazole derivatives in a linked system

Following optimization of the reductive ring closure, production of **33** from **60** was attempted by coupled thermal lactam formation (Figure 8). Based on our results, two main conclusions can be drawn. Higher temperatures increase the ratio of **33** in the product mixture, but modification of reaction time at the same temperature does not cause a significant change in product selectivity. At 150 °C, lactam formation is negligible (2-4%), but at 250 °C, the maximum temperature of the Asia heater, the amount of **33** can be significantly increased (64-60%).

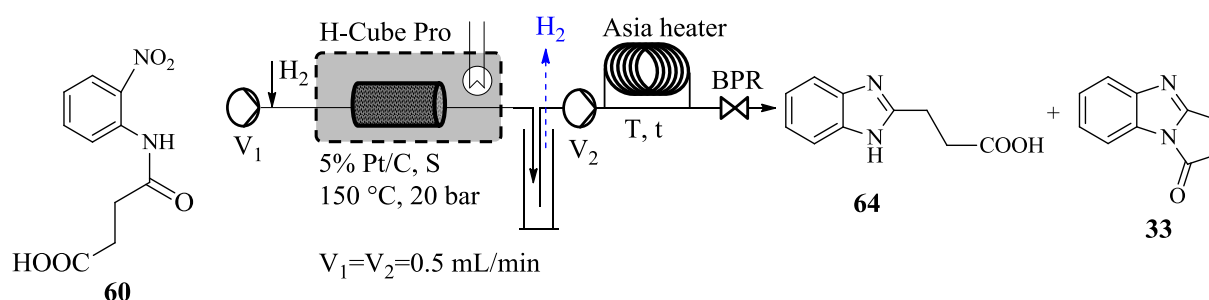


Figure 8: Integration of the thermal ring closure step with the continuous flow hydrogenation

Our next goal was to integrate the acylation step into the flow system. Optimal parameters for acylation were determined under batch conditions in a microwave reactor, using temperature of 200 °C and 30 minutes reaction time (Figure 9). In the light of past experiences and considerations, we have opted for toluene as solvent. Acetic acid was used as catalyst and cosolvent and its effect on product selectivity was investigated by varying its volume percentage (0-100 v/v%).

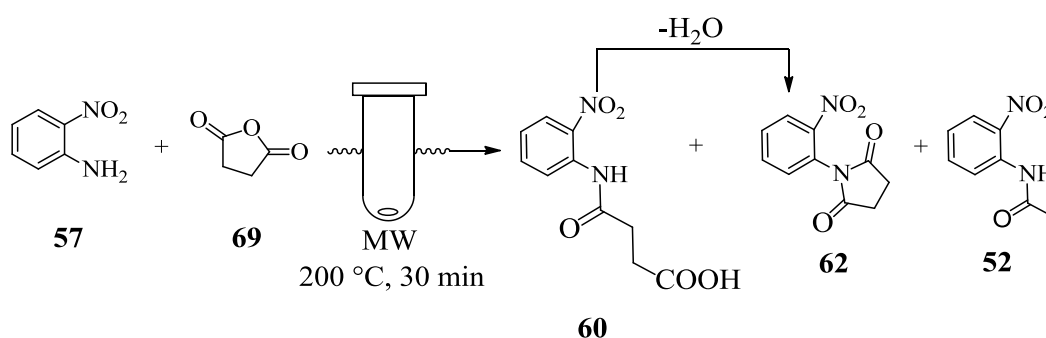


Figure 9: Optimization of condensation of 2-nitroaniline and succinic anhydride in microwave reactor

The results obtained show that by increasing the acetic acid ratio, the main product (**60**) is converted to the product (**62**) by dehydration. In addition, with higher acetic acid content, the

formation of a mixed anhydride of succinic anhydride and acetic acid is favored, leading to an increasing formation of 2-nitroacetanilide (**52**) (100 v/v% acetic acid, 69% **52**).

It can be stated that the desired product (**60**) can be prepared in the 80 v/v% toluene to 20 v/v% acetic acid solvent system with the most favorable selectivity (20 v/v% acetic acid, 89% **60**).

In order to avoid the formation of mixed anhydride mentioned above and thus the formation of by-product **52**, an attempt was made to replace acetic acid. Unfortunately, the addition of stronger acids than acetic acid resulted an intense precipitation, which, due to the risk of plugging, precludes its integration into the flow system. Subsequently, the effectiveness of the highly acidic Amberlyst XN-1010 ion exchange resin containing sulfonic acid groups on its surface was investigated. Surprisingly, the succinimide product (**62**) can be prepared with almost complete selectivity (96%) at 200 °C. However, white needle crystals were observed in the product mixture, which precluded integration of the method into the flow system.

Based on the experience gained in microwave optimization of acylation, acetic acid catalyzed system was chosen for integration into the flow system. A schematic diagram of our flow system coupled with acylation and reductive ring closure is shown in Figure 10. A solution of **57** and **69** in 20 v/v% acetic acid and 80 v/v% toluene was pumped into a heated reactor module directly connected to the H-Cube Pro<sup>®</sup> continuous flow hydrogenator.

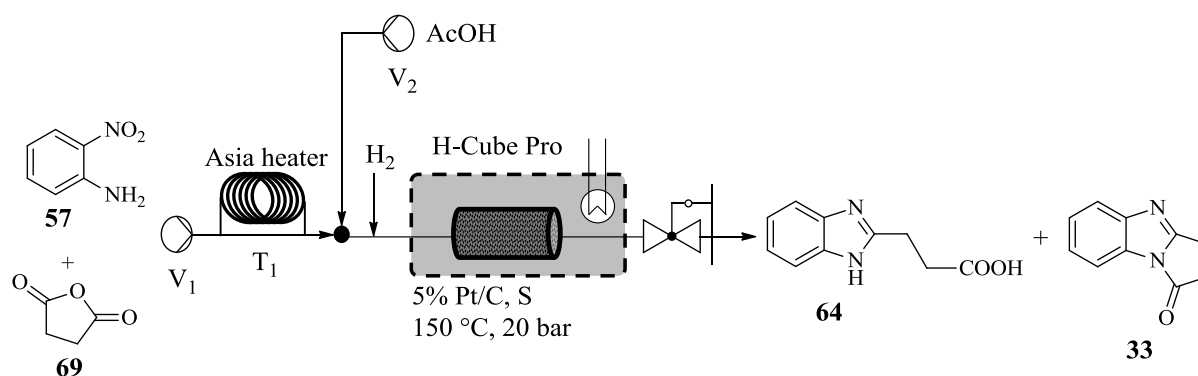


Figure 10: Integration of the acylation step with the continuous flow hydrogenation

LC-MS results show large amounts of by-products formation during the hydrogenation step. In addition we can say, that higher residence time (32 minutes, 35% **33**) and excess of succinic anhydride (6 equiv., **69**, 47% **33**) favored the formation of **33**.

In order to avoid side reactions, the acetic acid content was increased by the addition of glacial acetic acid through a T-mixer after the acylation step. The most appropriate parameters for the preparation of **64** (72%) were 3 equivalents of **69**, 30 minutes of acylation reaction time and 80% acetic acid content during reductive ring closure step.

#### 4.3. Diastereoselective synthesis of *N*-protected *cis*-4-aminocyclohexanols in flow chemistry

##### 4.3.1 Optimization of reductive ring opening using *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate starting material (**73**)

As a first step, our goal was to optimize the conditions for reductive ring opening on an H-Cube Pro continuous device. To achieve this, the synthesis of Boc protected *cis*-4-aminocyclohexanol (**75**) starting from *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (**73**) was selected as model reaction (Figure 11).

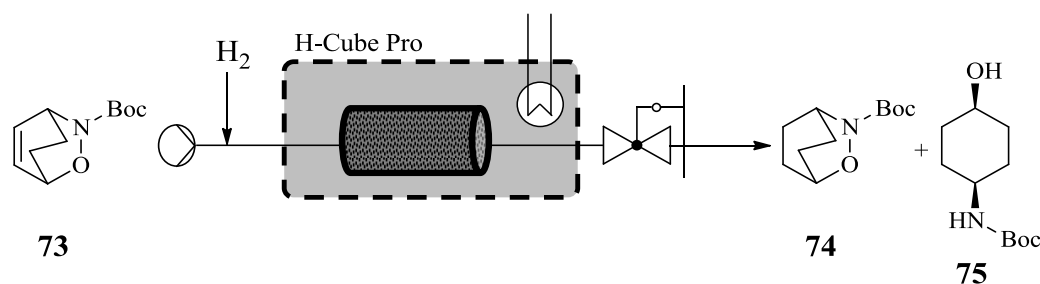


Figure 11: Schematic diagram of continuous flow reductive ring opening of *tert*-butyl 2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (**73**)

On a wide temperature scale ( $T=25$ - $150$  °C), the activity and selectivity of three catalyst charges were compared. These were 10% Pd/C, 5% Ru/C and Raney-nickel catalysts. In order to make the process compatible with the nitroso Diels-Alder (NDA) reaction, we first investigated the reductive ring opening in absolute tetrahydrofuran solvent under a nitrogen atmosphere. The results show that the saturation of the olefin bond occurs at 25 °C in the case of all three catalysts. In the case of 10% Pd/C and 5% Ru/C catalysts, cleavage of the N-O bond occurs only upon heating, but no significant selectivity for either **74** or **75** products was achieved. Raney-nickel catalyst charge had outstanding activity already at 25 °C for cleavage of N-O bond (13% **75**), and at 75 °C gave almost complete selectivity of the expected Boc protected *cis*-4-aminocyclohexanol (>99%, **75**).

After optimization, the need for inert conditions was investigated. The optimum conditions defined above were used in the experiments, with the only change being the use of normal, non-stabilized tetrahydrofuran and atmospheric air. Surprisingly, only about 1% of the

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expected product (**75**), 57% of the reduced bicyclic intermediate (**74**), and 42% of the starting material (**73**) remained in the product mixture. It is believed that in these experiments, the water content of the solvent and traces of hydroperoxide due to the decomposition of unstabilized tetrahydrofuran were responsible for the deactivation of the catalyst.<sup>11</sup>

#### 4.3.2 Attempts to integrate nitroso Diels-Alder cycloaddition and reductive ring opening

The next step was to integrate the NDA reaction to continuous flow reductive ring opening. Since it is most practical to separate the oxidant and the reaction mixture at the same time with the reaction, the conversion of the hydroxamic acid to the nitroso reagent is carried out in a packed column by heterogeneous MnO<sub>2</sub> oxidation. A schematic drawing of the flow system we have assembled is shown in Figure 12.

A solution of 1,3-cyclohexadiene (**48**) and *N*-Boc-hydroxylamine (**77**) under an inert atmosphere in anhydrous and peroxide free tetrahydrofuran was mixed in a "T" mixer and passed through an MnO<sub>2</sub> filled Omnifit column at 25 °C. The resulting reaction mixture was directly connected to H-Cube Pro (30 mm Raney-nickel Catalyst, 75 °C, 20 bar, 0.5 mL/min). In our experiments, 1.1 equivalents of cyclohexadiene (**48**) achieved complete conversion (>99% **75**).

Upon repeated measurements, unexpected deactivation of the catalyst was observed, which, according to the literature, was most likely caused by the possible dissolution of the manganese ions in the reaction mixture. The reaction mixture dripping from the Omnifit column was analyzed by atomic absorption spectroscopy, which showed a content of 15 ppm manganese. To ensure consistent product quality over time, a commercially available SiliaMetS AMPA manganese ion selective chelator was charged after the MnO<sub>2</sub> charge. With this modification, the deactivation of the Raney-nickel catalyst was no longer observed during the measurement period (3 hours). In the next step, the capacity of the 5g MnO<sub>2</sub> charge was measured over time. The conversion to **78** was determined by measuring the GC of the samples taken every 30 minutes. It can be stated that full conversion can be reached for 6 hours to get **78**.

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(11) Gleason, W. S.; Lewiston, N. Deactivation of Catalysts. United States Patent Office 2,810,666, **1957**.

Finally, to demonstrate the applicability of our process, a number of *N*-protected hydroxylamine derivatives were converted to *N*-protected *cis*-4-aminocyclohexanol, also important in synthetic chemistry (Figure 12, **79-82**).

Excellent selectivity (>99%) was obtained starting from acetyl hydroxamic acid. Good selectivity (90%) was also achieved for the benzyl carbamate protecting group, suggesting that the groups sensitive to reductive cleavage show high stability under the conditions of our optimized process.

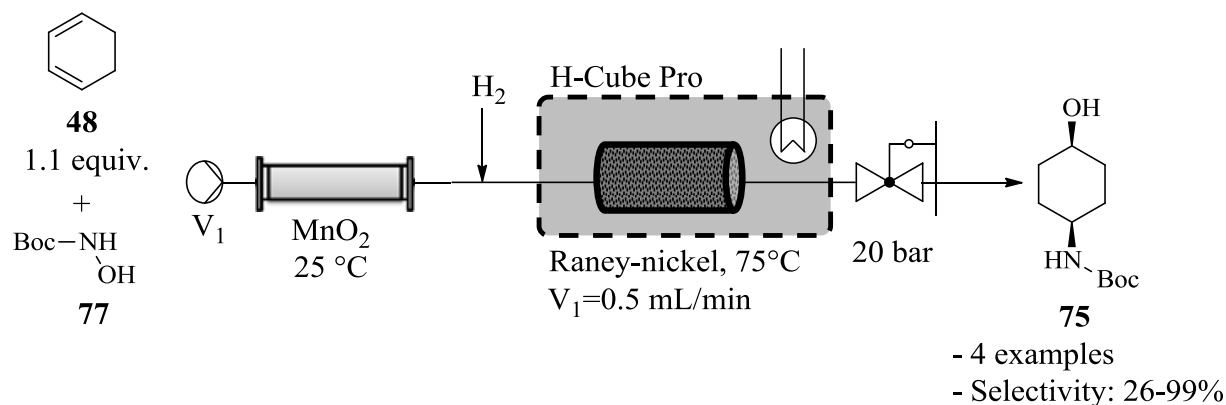


Figure 12: Extension of the continuous reductive ring opening method to additional *N*-protected *cis*-4-aminocyclohexanol (**79-82**) derivatives

Due to considerable degradation lower selectivity could be reached in the case of compounds with Fmoc (66%) and 1,1-dimethylurea protecting group (26%).

## 5. THESES

1. For the first time, the continuous flow synthesis of 2-methylbenzimidazole was accomplished by one-pot reductive intramolecular ring closure starting from 2-nitroacetanilide. It has been found, that the developed method allows the preparation of corresponding benzimidazole derivatives wearing functional groups sensitive towards reductive cleavage and acidic medium with outstanding selectivities (82-99%). (III., V., VIII.)
2. We successfully integrated the acetylation step of 2-nitroaniline for continuous flow hydrogenation to provide the desired 2-methylbenzimidazole product in 100% selectivity. It has been found that the rate of intramolecular ring closure under the reaction conditions used is higher than that of the acetylation, so despite the excess acetic anhydride, no diacetylated by-product is formed. (III., V., VIII.)
3. We have successfully extended the novel continuous-flow technology for the preparation of the benzimidazole ring framework to lactam type tricyclic benzimidazole derivatives. Starting

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from the  $\omega$ -[(2-nitrophenyl)amino]- $\omega$ -oxoalkanoic acids,  $\omega$ -(1*H*-benzo[*d*]imidazol-2-yl)alkanoic acids were prepared with outstanding selectivities (93-94%), and from the cyclic imide unit containing starting materials also good selectivities could be achieved (86-94%). (I., IX.)

4. With the help of a microwave equipment, we have optimized the condensation of 2-nitroaniline with succinic acid making it feasible to implement into our flow system. We realised foremost that fine tuning of the acetic acid ratio is necessary to achieve both proper conversion and good product selectivity. The optimized parameters were successfully applied to our new flow chemical system, which, after fine-tuning, yielded 3-(1*H*-benzo[*d*]imidazol-2-yl)propanoic acid with good selectivity. (I., IX.)

5. For the first time, diastereoselective synthesis of *N*-protected *cis*-4-aminocyclohexanol derivatives starting from *N*-protected 2-oxa-3-azabicyclo[2.2.2]oct-5-ene was carried out under continuous flow conditions. (II., IV., VII.)

6. For the first time, a continuous flow synthesis of *N*-protected *cis*-4-aminocyclohexanols, starting from 1,3-cyclohexadiene and the corresponding *N*-protected hydroxamic acid, was carried out by integrating the nitroso Diels-Alder reaction to the continuous flow reductive ring opening step. The coupled procedure was successfully used to prepare 4 other *N*-protected *cis*-4-aminocyclohexanol derivatives (26->99%). (II., IV., VII.)

7. We realised foremost that the continuous synthesis of *N*-protected *cis*-4-aminocyclohexanols requires the use of a stabilized THF solvent, inert medium, and chelating agent for manganese to avoid deactivation of the Raney-nickel catalyst. (II., IV., VII.)

## **6. APPLICATION OPTIONS**

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Thanks to the continuous hydrogenation process we have developed, reductive ring closure, starting from 2-nitroacetanilide derivatives, has been selectively carried out under mild reaction conditions. As a result, a new pathway has been opened for the production of benzimidazole and tricyclic benzimidazole based drug intermediates sensitive to acidic media or reductive cleavage.

The continuous flow reductive ring opening process, which has been developed for the synthesis of *N*-protected *cis*-4-aminocyclohexanol derivatives, allows isomer-selective preparation of these important drug-intermediate building block derivatives. The *N*-protected 2-oxa-3-azabicyclo[2.2.2]oct-5-ene cycloadducts used as starting materials for the synthesis are available commercially in a limited and expensive manner, thus integration nitroso Diels-

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Alder cycloaddition with hydrogenation step improves the economics of the process and the extensibility for wide range of derivatives. Due to the new coupled process, the starting materials for the synthesis are the cheap and readily available 1,3-cyclohexadiene and the stable *N*-protected hydroxamic acids.

## **7. PUBLICATIONS**

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### 7.1 Publications related to the dissertation

- I. Szabó, B.; Szakter, K.; Thurner, A.; Faigl, F.; Éles, J.; Greiner, I. A Novel, Domino Synthesis of Tricyclic Benzimidazole Derivatives Using Continuous Flow. *Period. Polytech. Chem. Eng.*, **2020**, *64* (1), 1–8. (Impact factor (2019): 1.382; Author ratio: 80%). <https://doi.org/10.3311/PPch.14275>.
- II. Szabó, B.; Tamás, B.; Faigl, F.; Éles, J.; Greiner, I. Diastereoselective synthesis of *cis-N*-Boc-4-aminocyclohexanol with reductive ring opening method using continuous flow. *Journal of Flow Chemistry*, **2019**, *9* (1), 13-17. (Impact factor (2018): 2.277; Author ratio: 90%). <https://doi.org/10.1007/s41981-018-00028-3>.
- III. Szabó, B.; Faigl, F.; Éles, J.; Greiner, I. A Novel One-Pot Benzimidazole Ring Formation via a Continuous Flow Selective Reductive Cyclization Method. *Curr. Org. Chem.* **2018**, *22* (19), 1940–1944. (Impact Factor (2018): 2.029; Author ratio: 100%). <https://doi.org/10.2174/1385272822666180829100850>.
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## 7.2 Publications not related to the dissertation

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## 7.3 Oral presentations related to the dissertation

- VII. Szabó, B.P.; Tamás, B.; Faigl, F.; Éles, J. *Cisz-4-aminociklohexanol származékok redukív gyűrűnyitások módszerrel történő diasztereoselektív előállítása áramlásos kémiai rendszerben, 41. Kémiai Előadói Napok, Szeged, 2018.*
- VIII. Szabó, B.P.; Faigl, F.; Éles, J. Benzimidazol származékok szelektív, one-pot áramlásos kémiai szintézise, *40. Kémiai Előadói Napok, Szeged, 2017.*

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- X. Hergert, T.; Mátravölgyi, B.; Szabó, B.; Faigl, F.; Éles, J.; Greiner, I. A Multistep Flow Synthesis of the Key Intermediate of Terbinafine. *Conference on Frontiers in Organic Synthesis Technology*, Budapest, 2019.10.16-18.