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Stereoselective Metal-Free Reduction of Chiral Imines in Batch and Flow Mode: A Convenient Strategy for the Synthesis of Chiral Active Pharmaceutical Ingredients

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Abstract: The convenient, metal-free reduction of imines that contain an inexpensive and removable chiral auxiliary allowed for the synthesis of the immediate precursors of chiral active pharmaceutical ingredients (APIs). This protocol was carried out under batch and flow conditions to give the correspoding products in high yields with almost complete stereocontrol. In the presence of trichlorosilane, an inexpensive and nontoxic reducing agent, and an achiral Lewis base such as *N*,*N*-dimethylformamide, the formal syntheses of Rivastgmine, calcimimetic NPS R-568, and a Rho kinases inhibitor were successfully accomplished. For the first time, both the diastereoselective imine reduction and the auxiliary removal were efficiently performed in a micro- or mesoreactor under continuous-flow conditions, which paved the way towards the development of a practical process for the syntheses of industrially relevant, biologically active, enantiopure *N*-alkylamines.

Introduction

The pharmaceutical industry is gradually progressing towards enantiopure formulations. Most newly introduced drugs are chiral, and it is expected that approximately 95 % of pharmaceutical drugs will be chiral by 2020.[1] In this context, chiral amines are considered a class of paramount importance, because they are found in a plethora of compounds such as those of pharmaceutical interest as well as those developed for agrochemicals, fragrances, and fine chemicals.[2] The reduction of the C=N group is one of the most widely used approaches to synthesize chiral amines, and over the last ten years, successful catalytic enantioselective methods based on both metal-promoted[3] and organocatalyzed[4] strategies have been developed.

When an industrial synthesis of a chiral pharmaceutical product must be planned, however, issues such as the chemical efficiency and robustness of the procedure, its general applicability, and economic considerations become crucially important. For these reasons, the applications of many chiral catalytic systems are often not feasible, and the use of inexpensive and readily available chiral auxiliaries becomes an attractive and economic alternative. This also holds true for the synthesis of chiral amines[5] that rely heavily on the diastereoselective reduction of *N*-functionalized imines that contain removable chiral auxiliaries.[6] Taking these details into consideration, we proceeded to investigate an efficient synthesis for both enantiomers of 1-(*m*-hydroxyphenyl)ethylamine, a key intermediate in the preparation of several valuable pharmaceutically active compounds (Scheme 1).

Rivastgmine finds application in the treatment of mild to moderate dementia resulting from types of Alzheimer's and Parkinson diseases. Miotine, the first synthetic carbamate used clinically, is an anticholinesterase drug. Rho-associated protein kinase (ROCK) inhibitors have proved to be efficacious in animal models of stroke, inflammatory diseases, Alzheimer's disease, and neuropathic pain, and, therefore, have the potential to prevent the neurodegeneration and simulated neurodegeneration of various neurological disorders. (*R*)-NPS 568 is a calcimimetic compound that is used in the treatment of hyperparathyroidism, whereas acrylamide (*S*)-A, a potent KCNQ2 opener, is currently under study for the treatment of neuropathic pain, including diabetic neuropathy. The importance of chiral *N*-alkylamines in medicinal chemistry, which encompasses a large variety of compounds with differing biological activities, has been recently highlighted.[7]

Our goal was not only to develop an efficient, metal-free reduction of imines that contain an inexpensive and easily removable chiral auxiliary but also to achieve the transformation under continuous-flow conditions.[8] Herein we report a trichlorosilane-mediated C=N reduction efficiently performed in a micro- or mesoreactor followed by *N*-deprotection under flow conditions in a microfluidic device to afford both enantiomers of essentially pure 1-(*m*-alkoxyaryl)ethylamine derivatives, which are advanced precursors of several valuable active pharmaceutical ingredients (APIs).[9]

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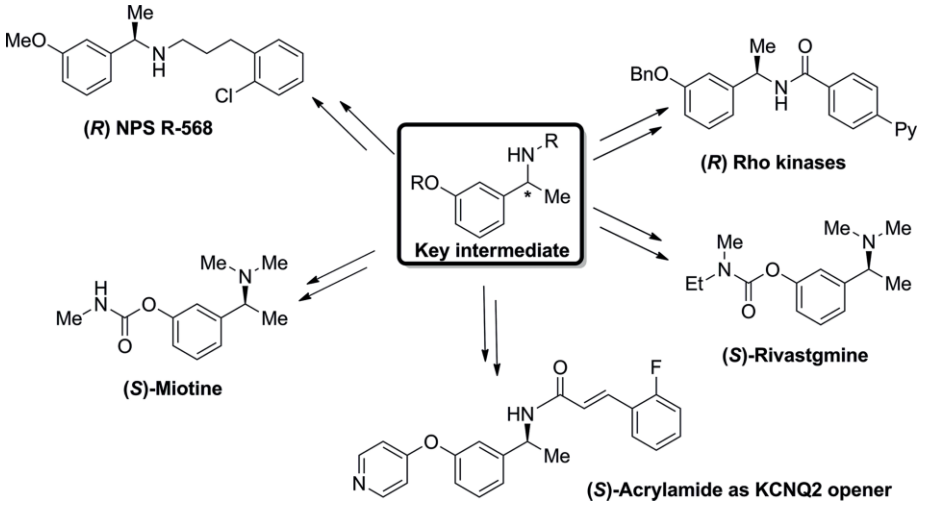
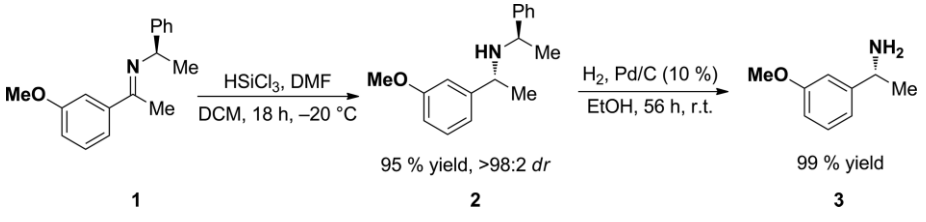


Scheme 1. Biologically active amines featuring the 1-(*m*-alkoxyphenyl)ethylamine moiety.

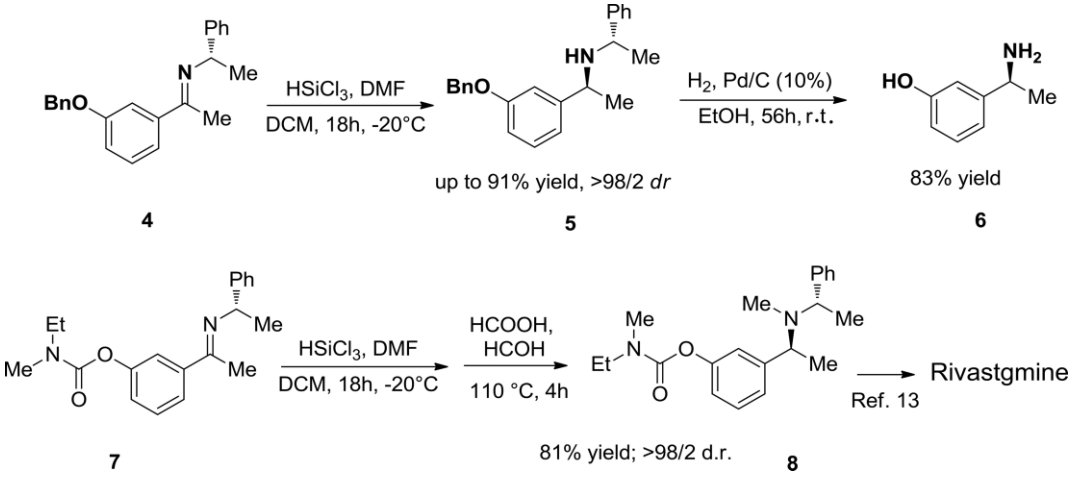
Results and Discussion

Our investigation began with the reduction of *N*-[1-(*R*)-phenylethyl]ethan-1-[3-(methoxy)phenyl]-1-imine (**1**) under batch conditions,[10] which was successfully accomplished by using 3.5 mol-equiv. of trichlorosilane in the presence of 5 mol-equiv. of *N*,*N*-dimethylformamide (DMF) in dry dichloromethane (DCM) for 18 h (Scheme 2). The corresponding amine **2**, which was isolated in 95 % yield as a single isomer,[11] was subjected to a Pd/C-catalyzed hydrogenolysis in ethanol to afford enantiomerically pure (*R*)-1-(3-methoxyphenyl)ethylamine (**3**) in quantitative yield, the direct precursor of calcimimetic (*R*)-NPS 568.

Similarly, the reduction of 3-benzyl-protected imine **4** was achieved in high yield and with complete stereocontrol at –20 °C in DCM (Scheme 3). A series of experiments showed that it was possible to reduce the reaction time from 18 to 6 h without an appreciable change to the yield or stereoselectivity (Table 1, Entry 5). Additionally, we performed the transforma-



Scheme 2. Synthesis of (*R*)-1-(3-methoxyphenyl)ethylamine (**3**), the direct precursor of (*R*)-NPS 568.



Scheme 3. Under batch conditions, the synthesis of (*S*)-1-(3-hydroxyphenyl)ethylamine (**6**) and amine **8**, immediate precursors of rivastgmine and analogous derivatives.

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tion in toluene and anisole, both eco-friendly solvents,[12] and good product yields (e.g., 77 %) with high stereoselectivities (96:4 with anisole) were observed.

Table 1. Reduction of benzyl-protected chiral imine **4** under batch conditions.

Entry	*T* [°C]	DMF [equiv.]	Solvent	Yield [%][a]	*dr*[b]
1	0	10	DCM	85	92:8
2	–20	10	DCM	81	>98:2
3	0	5	DCM	91	92:8
4	–20	5	DCM	90	97:3
5[c]	–20	5	DCM	83	97:3
6	–20	5	toluene	67	92:8
7	–20	5	anisole	77	96:4

[a] Isolated yields are provided. The reaction time was 18 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction time was 6 h.

The trichlorosilane-mediated reduction of chiral imine **7**, which features a carbamate group on the aromatic ring, was also effective and led to the isolation of chiral *N*-methylamine **8**, an immediate precursor to (*S*)-rivastgmine, in 81 % yield as a single isomer [>98:2 diastereomeric ratio (*dr*)].[13] To the best of our knowledge, this is the first example of a stereoselective reduction of this class of imines under mild conditions without any degradation of the carbamate moiety.

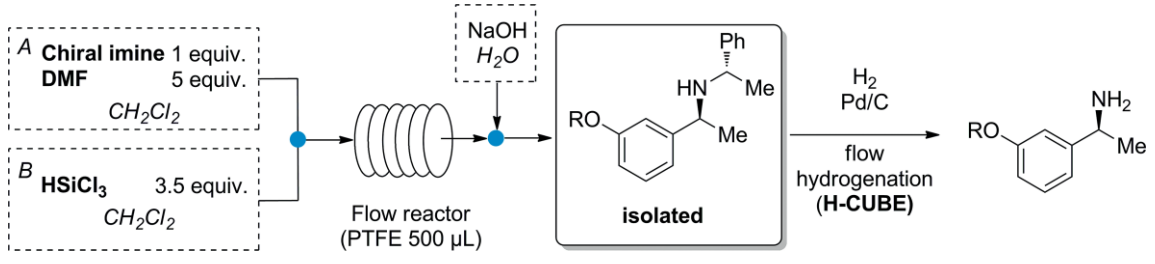
In the attempt to realize the one-step double deprotection of amine **5**, a hydrogenolysis reaction was performed under the previously reported conditions to give (*S*)-1-(3-hydroxyphenyl)ethylamine (**6**) in 83 % yield as a pure enantiomer after chromatographic purification. This chiral amine represents a key intermediate in the syntheses of rivastgmine, miotine, and the KCNQ2 opener acrylamide (*S*)-A, whereas its enantiomer is the immediate precursor of a very promising class of Rho-kinases inhibitors (Scheme 1).

Once the chemistry under batch conditions was successfully developed, we turned our attention to examine a continuous-flow process.[14] The safe manufacturing of organic (i.e., chiral) intermediates under continuous-flow conditions and, more in general, all of the advantages that continuous processing may offer are emerging topics that can have a significant impact on the synthesis of APIs.[15] Therefore, the development of a continuous-flow process for the preparation of both enantiomers of 1-(*m*-alkoxyphenyl)ethylamine derivatives is an attractive option. As far as we know, there are no reports of continuous-flow processes for the synthesis of these valuable intermediates and no examples of in-flow stereoselective reductions of imines that use $HSiCl_3$ as a reducing agent.

A coil reactor, realized by using polytetrafluoroethylene (PTFE) tubing (1.58 mm outer diameter, 0.58 mm inner diameter, 1.89 m length, 500 µL effective volume) coiled in a bundle and immersed in a bath cooled to the desired temperature, was employed for our preliminary studies (Scheme 4, see Supporting Information for figures and further experimental details).

The continuous-flow reduction of Bn-protected imine **4** was carried out in DCM at 15 °C with a short residence time (5 min) to give a good 70 % yield of the product but with a low diastereomeric ratio (90:10; Table 2, Entry 1). As expected, better results were achieved at 0 °C with a residence time of 10 min, which provided an 83 % yield of the product with 93:7 *dr* (Table 2, Entry 3). At –20 °C, the continuous-flow reduction afforded amine **5** in 81 % yield with almost complete stereoselection (Table 2, Entry 4). Increasing the concentration of the reduction reaction from 0.1 to 0.5 M gave comparable yields and stereoselectivity, which thus demonstrates the possibility to further reduce the solvent volumes and attain a more sustainable process (Table 2, Entry 5).

With the optimal conditions at hand, the reductions of MeO-functionalized ketoimine **1** and chiral imine **7**, a direct precursor of rivastigmine, were also investigated. Excellent chemical yields as well as stereoselectivities were obtained in both cases (Table 2, Entries 6 and 7).



Scheme 4. Continuous-flow reduction of chiral imines and removal of the chiral auxiliary by continuous-flow hydrogenation to afford pure primary amines.

Table 2. Reduction of chiral imines **1**, **4**, and **7** under continuous-flow conditions.

Entry	R	Imine	*T* [°C]	Flow rate [µL min^{-1}]	Residence time [min]	Yield [%][a]	*dr*[b]
1	Bn	**4**	15	50	5	70	90:10
2	Bn	**4**	0	50	5	57	96:4
3	Bn	**4**	0	25	10	83	93:7
4	Bn	**4**	–20	25	10	81	98:2
5[c]	Bn	**4**	0	25	10	75	96:4
6	Me	**1**	–20	25	10	82	95:5
7	CONMeEt	**7**	–20	25	10	80	98:2

[a] Yields are averages of five different samples collected at different times. The concentrations of the reactions were 0.1 M. [b] Determined by ^{1}H NMR spectroscopy. [c] Reaction concentration was 0.5 M.

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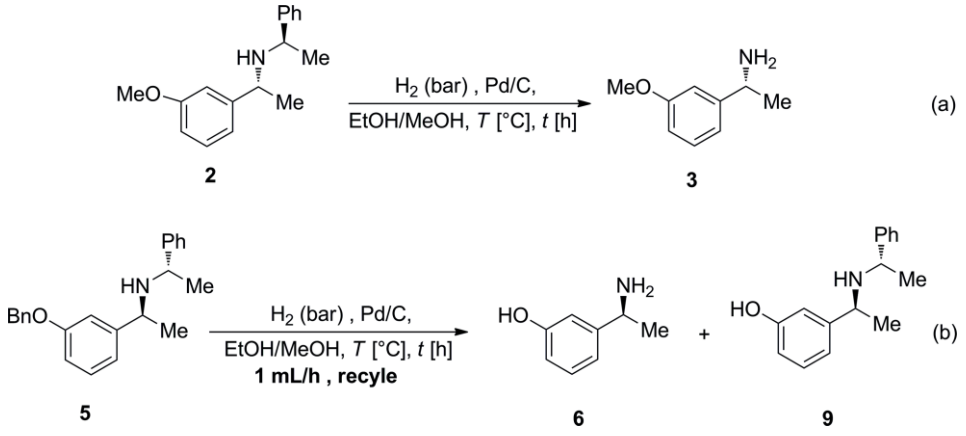

Scheme 5. Continuous-flow deprotection of amines **2** and **5** to afford chiral primary amines.

The continuous hydrogenolysis[16] of the chiral amines was then performed with a ThalesNano H-Cube Mini™ that was equipped with a 10 % Pd/C cartridge. First, the reaction of chiral amine **2** [Scheme 5, Equation (a)] was examined at 50 °C and a pressure of 50 bar, but no conversion was observed, and the starting material was recovered from the reaction mixture (Table 3, Entry 1). By increasing the temperature to 80 °C and the pressure to 80 bar, chiral amine **3** was isolated in 70 % yield (Table 3, Entry 2). A further increase in temperature and pressure had no appreciable effect, but with the additional increase in the reaction time, an 80 % conversion was obtained (Table 3, Entry 4). To avoid too harsh conditions and to increase the yield, we decided to perform the reaction over a longer period of time by using a closed-loop system. After 2 h at 80 °C and a pressure of 80 bar, the reaction gave an isolated product yield of 95 % (Table 3, Entry 5), but carrying out the reaction at 70 °C and a pressure of 70 bar required 6 h to achieve a 93 % yield without any appreciable epimerization at the benzylic stereocenter of the product (Table 3, Entry 6).

Table 3. Continuous-flow hydrogenolysis reaction of chiral amines **2** and **5**.

Entry	Amine	*T* [°C]	Flow rate [mL min^{-1}]	Pressure [bar]	Reaction time [min]	Yield[a] [%]
1	**2**	50	1	50	10	n.r.
2	**2**	80	1	80	10	70
3	**2**	95	0.5	95	20	70
4	**2**	95	0.3	95	23	80
5[b]	**2**	80	1	80	120	95
6[b]	**2**	70	1	70	360	93
7[b]	**5**	90	1	80	120	90[c]
8[b]	**5**	80	1	80	240	70
9[b]	**5**	80	1	80	360	85

[a] Isolated yields are provided. The concentrations of the reactions were 0.1 M. n.r. = no reaction. [b] Reactions were run by using a closed-loop system. [c] Product **9** was obtained in 90 % yield as the major product.

With the reaction conditions in hand, we then explored the removal of the chiral auxiliary in amine **5**. After 2 h at 90 °C, the deprotection of amine **5** occurred to give *O*-debenzylated product **9** in 90 % yield (Table 3, Entry 7). After the reaction had proceeded at 80 °C for 4 h, the desired chiral amine **6** was isolated in 70 % yield, which was further increased to 85 % yield by running the hydrogenolysis reaction under continuous-flow conditions for 6 h (Table 3, Entries 8 and 9).

Conclusions

We have developed an efficient protocol for the synthesis of both enantiomers of 1-(*m*-hydroxyphenyl)ethylamine, a key intermediate in the preparation of several valuable pharmaceutically active compounds. For the first time, stereoselective trichlorosilane-mediated reduction reactions were successfully performed in a mesoreactor followed by continuous flow hydrogenolysis reactions to afford enantiomerically pure 1-(3-alkoxyphenyl)ethylamines in good yields in short reaction times and reduced solvent volumes. The development of a highly efficient "all flow" multistep, sequential procedure that starts from a ketone and includes the reductive amination and deprotection steps to afford enantiomerically pure pharmaceutically relevant amines is currently under investigation.

Experimental Section

General Procedure for the Reduction of Imines with $HSiCl_3$ under Batch Conditions: Dry DMF (5 equiv.) and a 0.9 M solution of the imine in dry solvent were added to a 10 mL round-bottom flask under N_2 and further diluted with dry solvent (2 mL). The mixture was cooled to the desired reaction temperature. A 1.6 M solution of $HSiCl_3$ (0.7 mmol, 3.5 equiv.) in the selected solvent was added to the reaction mixture. After the desired time, the reaction was quenched with NaOH (0.1 M solution) until a basic pH was reached. The resulting slurry was stirred at room temperature for 10 min, and then Na_2SO_4 was added as a drying agent. The mixture was filtered through a pad of Celite, and the filter cake was washed with CH_2Cl_2 (10 mL) and ethyl acetate (10 mL). The solvent was removed under reduced pressure, and the diastereomeric ratio of the crude mixture was determined. The amines were purified by flash chromatography on silica gel or by crystallization.

General Procedures for the Reduction of Imines with $HSiCl_3$ under Continuous-Flow Conditions: At the desired temperature, the 500 μL coil reactor was fed by using two 2.5 mL Hamilton gastight syringes at the desired flow rate. Syringe A was filled with a solution of the imine (1 mol-equiv.) and dry DMF (5 mol-equiv.) in dry DCM.

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Syringe B was filled with a solution of $HSiCl_3$ in DCM. The concentrations of the reagents in the syringes were set according to the desired concentration in the reactor. The reaction mixture was collected in a round-bottom flask, which was filled with NaOH (0.1 M solution) at the same reaction temperature. After the first amount was discharged, the steady-state conditions were reached. The reported yields are given as an average of five different samples collected at different times.

General Procedure for Deprotection of Amine under Batch Conditions: To a 0.5 M solution of the amine in ethanol in a vial for high-pressure hydrogenation (Parr instrument) was added 10 % of Pd/C, and the hydrogenation was carried out at 10 bar for 48 h.

Compound 3: The general procedure above was employed. The resulting ethanol suspension was filtered through a pad of Celite, and the filter cake was washed with MeOH (50 mL). The filtrate was then treated with HCl (2 M in Et_2O, 1 equiv.). The solvents were removed under reduced pressure, and the resulting residue was dissolved in DCM. The solution was treated with Amberlyst IRA-400 (OH^-) resin to isolate the amine as a neutral compound.

Compound 6: The general procedure above was employed. The resulting ethanol suspension was filtered through a pad of Celite, and the filter cake was washed with MeOH (50 mL). The filtrate was concentrated under reduced pressure to give the compound as a neutral amine.

General Procedure for H-Cube Mini Deprotection of Amine. Preparation of (1*S*)-(3-Hydroxyphenyl)ethanamine (6): A 0.1 M solution of the amine (0.5 g, 1.51 mmol) in ethanol (15 mL) was added to a vial connected to the pump of the H-CUBE Mini, which was equipped with a 30 mm cartridge of 10 % Pd/C. The instrument was previously stabilized at the desired temperature and pressure and at a flow rate of 1 mL min^{-1}. The reaction was run in a close-loop system for the desired time. ^1H NMR (300 MHz, CD_3OD): δ = 7.19 (t, J = 8.1 Hz, 1 H), 6.91–6.81 (m, 2 H), 6.82–6.72 (m, 1 H), 4.27–4.13 (m, 1 H), 1.51 (d, J = 6.8 Hz, 3 H) ppm. $[\alpha]_D^{25}$ = –22.1 (c = 1, methanol). The spectroscopic data and the optical rotation are in agreement with those in the literature.[17] GC method [(injector: 200 °C; flow rate: 2 mL min^{-1}; temperature: program 100 °C (hold 2 min), 130 °C at a rate of 1 °C min^{-1} (hold 5 min); 170 °C at a rate of 2 °C min^{-1} (hold 5 min)]: t_R = 58.219 min.

Supporting Information (see footnote on the first page of this article): Synthesis of starting materials (ketones and ketoimines); synthesis of chiral amines **2**, **3**, **5**, **6**, and **8**; detailed experimental procedures for the reduction and hydrogenolysis procedures; and characterization data of compounds.

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Keywords: Reduction · Amines · Chiral auxiliaries · Flow chemistry · Microreactors

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