EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: Eur. J. Org. Chem. 10.1002/ejoc.201601268

Link to VoR: http://dx.doi.org/10.1002/ejoc.201601268

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Stereoselective metal-free reduction of chiral imines in batch and in flow mode. A convenient strategy for the synthesis of chiral Active Pharmaceutical Ingredients.

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KEY TOPIC: Flow Chemistry – Chiral APIs

Abstract: A convenient, metal-free reduction of imines, bearing a very cheap and removable chiral auxiliary, allowed the synthesis of immediate precursors of chiral APIs (Active Pharmaceutical Ingredients), in batch and in flow mode, in high yields and almost complete stereocontrol. In the presence of an inexpensive and non toxic reducing agent, like trichlorosilane, and an achiral Lewis base such as *N*,*N*-dimethyl formamide, the formal synthesis of Rivastgmine and analogous compounds, calcimimetic NPS R-568 and a Rho kinases inhibitor was successfully accomplished. For the first time, both the diastereoselective imine reduction and the auxiliary removal were efficiently performed in (micro)-mesoreactors under continuous flow conditions, thus paving the way towards a development of a practical process in continuo for the synthesis of industrial relevant, biologically active, enantiopure *N*-alkyl amines.

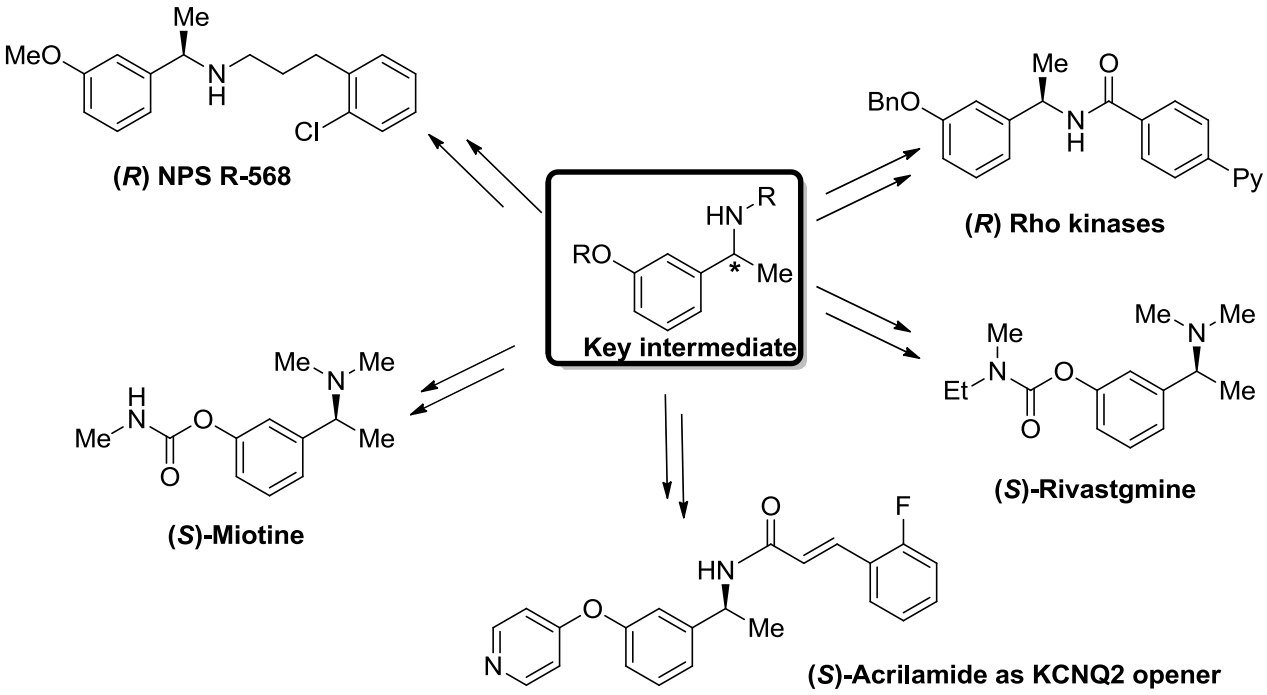
Keywords: stereoselective synthesis / mesoreactors / reduction / flow chemistry / active pharmaceutical ingredients

In the field of pharmaceuticals the industry is gradually progressing towards enantiopure formulations; currently, most of the newly introduced drugs are chiral and it is expected that nearly

95% of the pharmaceutical drugs would be chiral by 2020.[1] In this context, chiral amines are unanimously considered a class of paramount importance, due to their widespread diffusion in a plethora of compounds, not only of pharmaceutical interest, but also in agrochemicals, fragrances, and fine chemicals.[2] The reduction of C=N is one of the most widely used approach to synthesize chiral amines and the last ten years have witnessed the development of some successful catalytic enantioselective methods, either based on metal-promoted[3] or organocatalyzed[4] strategies.

However, when the industrial synthesis of a chiral pharmaceutical product must be planned, issues like chemical efficiency and robustness of the procedure, general applicability and economic considerations become crucially important. For these reasons, the application of many of the known chiral catalytic systems very often is not feasible and the use of inexpensive and readily available chiral auxiliaries becomes an attractive and economically competitive alternative. This holds true also for the synthesis of chiral amines,[5] that heavily relies on the diastereoselective reduction of *N*-functionalized imines with chiral, removable residues.[6]

We thought to take advantage of this approach to realize an efficient synthesis of both enantiomers of 1-(*m*-hydroxyphenyl)-ethylamine, a key intermediate for the preparation of several, valuable pharmaceutically active compounds (Scheme 1).



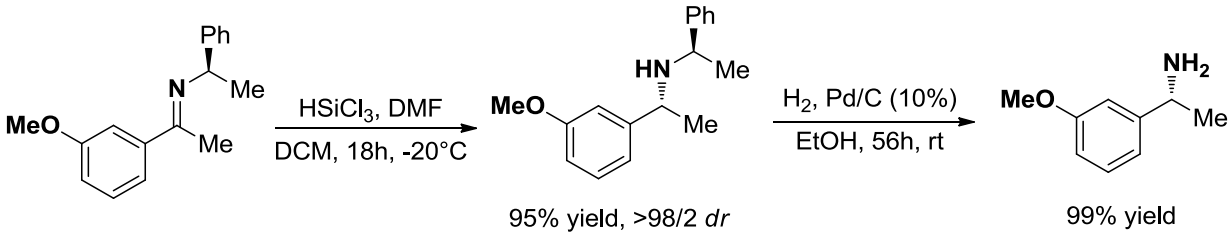
Scheme 1. Biologically active amines featuring the 1-(*m*-alcoxyphenyl)-ethylamine moiety.

Rivastgmine finds application in the treatment of mild to moderate dementia in Alzheimer's type and Parkinson diseases. Miotine, the first synthetic carbamate used clinically, is an anticholinesterase drug. ROCK inhibitors have proved to be efficacious in animal models of stroke,

inflammatory diseases, Alzheimer's disease and neuropathic pain, and therefore have potential for preventing neurodegeneration and stimulating neurodegeneration in various neurological disorders. (R)-NPS 568 is a calcimimetic compound used in the treatment of hyperparathyroidism, while Acrylamide (S)-A, a potent and efficacious KCNQ2 opener, is currently under study for the treatment of neuropathic pain, including diabetic neuropathy. The importance of *N*-alkyl chiral amines in medicinal chemistry, that encompasses a large variety of compounds with different biological activity, has been recently highlighted.[7]

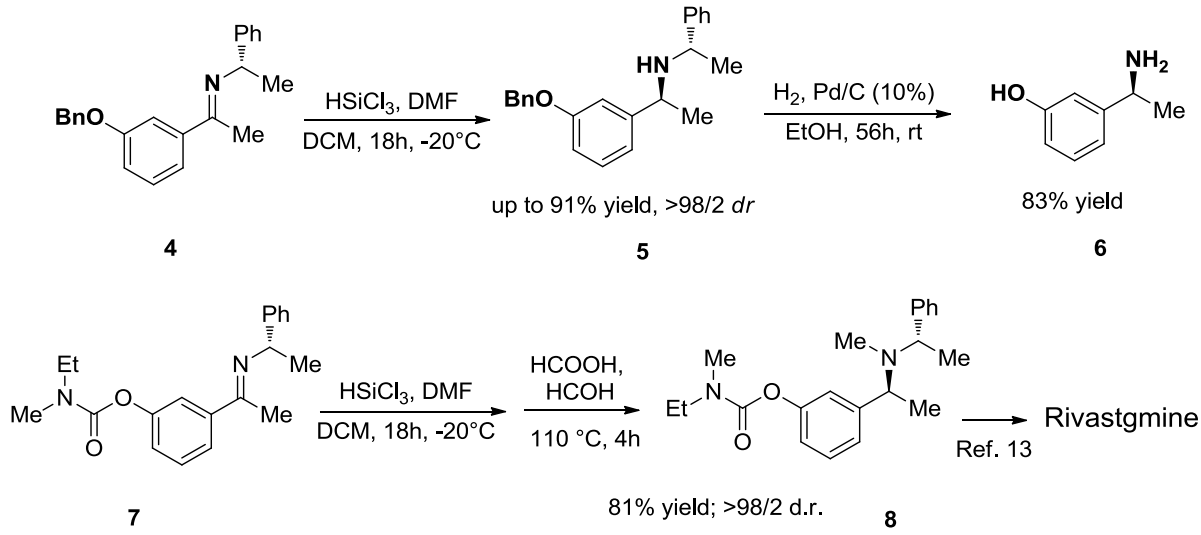
Our aim was not only to develop an efficient, metal-free reduction of imines bearing an inexpensive and easily removable chiral residue, but also to fulfil the transformation under continuous flow conditions.[8] Here we report, for the first time, a trichlorosilane mediated C=N reduction efficiently performed in (micro)-mesoreactors, followed by in flow *N*-deprotection in microfluidic device, to afford, virtually pure, both enantiomers of 1-(*m*-alkoxyaryl)-ethylamine derivatives, advanced precursors of several valuable APIs.[9]

Our investigation started with the in batch reduction of *N*-(1-(*R*)-phenylethyl)-ethan-1-(3-(methoxy)phenyl)-1-imine **1**,[10] that was successfully accomplished by using 3.5 mol eq. of trichlorosilane in the presence of 5 mol eq. of DMF, in dry DCM for 18 hours. The corresponding amine **2**, isolated in 95% yield virtually as single isomer,[11] went under Pd/C catalyzed hydrogenolysis in ethanol, affording in quantitative yield enantiomerically pure *(R)*-1-(3-methoxyphenyl)-ethylamine **3**, direct precursor of .the calcimimetic (R)-NPS 568 (Scheme 2).



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

Analogously, the reduction of the 3-benzyloxy protected imine **4** was accomplished in high yield and complete stereocontrol at -20 °C, in DCM (Scheme 3). It is possible to reduce the reaction time (6 hour), without appreciable changes in yield and stereoselectivity (Table 1). Additionally, we performed the transformation in toluene and anisole, considered eco-friendly solvents:[12] good yields (75%) and very high stereoselectivities (96:4 with anisole) were observed.



Scheme 3. In batch synthesis of *(S)*-1-(3-hydroxyphenyl)-ethylamine **6** and of amine **8**, immediate precursors of Rivastgmine and analogous derivatives.

The trichlorosilane-mediated reduction was effective also on the chiral imine **7**, featuring the carbamate group on the aromatic ring, and led to the isolation of *N*-methyl chiral amine **8** in 81% yield as a single isomer (>98/2 d.r.), immediate precursor to *(S)*-Rivastgmine.[13] To the best of our knowledge this is the first example of a stereoselective reduction of that class of imines, achieved in mild conditions, without observing any degradation of the carbamate moiety.

Table 1. In batch reduction of O-Bn protected chiral imine **4.**

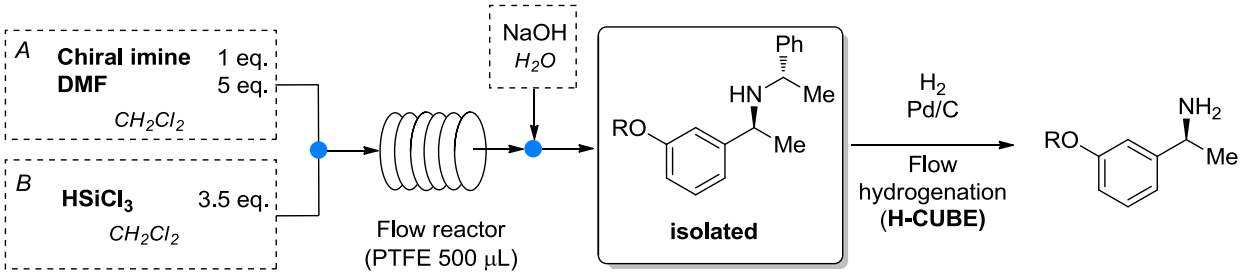
Entry	T (°C)	DMF (eq)	Solvent	Yield (%)[a]	d.r.[b]
1	0	10	DCM	85	92:8
2	-20	10	DCM	81	>98:2
3	0	5	DCM	91	92:8
4	-20	5	DCM	90	97:3
5[c]	-20	5	DCM	83	97:3
6	-20	5	Toluene	67	92:8
7	-20	5	Anisole	77	96:4

[a] Isolated yield; reaction time: 18h; [b] Determined by ^{1}H-NMR spectroscopy; [c] Reaction time: 6 h.

In the attempt to realize the one-step double deprotection of amine **5,** the hydrogenolysis was performed under the same, previously reported conditions: *(S)*-1-(3-hydroxyphenyl)-ethylamine **6** was isolated in 83% yield, after chromatographic purification, as pure enantiomer. The chiral amine represents a key intermediate for the synthesis of Rivastgmine, Miotine and KCNQ2 opener Acrylamide (S)-A, while its enantiomer is the immediate precursor of a very promising class of Rho-kinases inhibitors (Scheme 1).

Once the chemistry in batch has been successfully developed, we turned our attention to set up a continuous flow process.[14] The safe manufacturing of organic (chiral) intermediates under continuous flow conditions and, more in general, all the advantages that continuous processing may offer, are emerging topics, that can significantly impact 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 those valuable intermediates and no examples of "in flow" stereoselective imines reductions using $HSiCl_3$ as reducing agent.

A coil-reactor, realized by using 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 first preliminary studies (Scheme 4, see supporting information for pictures and further experimental details).



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

In the reduction of OBn protected imine **4,** operating with short residence time (5 minutes) at 15 °C in DCM, 70% yield was obtained, but a low diasteroisomeric ratio (90:10) was observed. As expected, at 0° C, with a residence time of 10 minutes, better results were achieved: 80% of yield and 93:7 *dr* were reached (Table 2). At -20 °C the continuous flow reduction afforded amine **5** in 75% yield and an almost complete stereoselection. Increasing the reaction concentration from 0.1 M to 0.5 M the reduction proceeds with comparable yields and stereoselectivity, thus demonstrating the possibility to further reduce the solvent volumes and realize a more sustainable process.

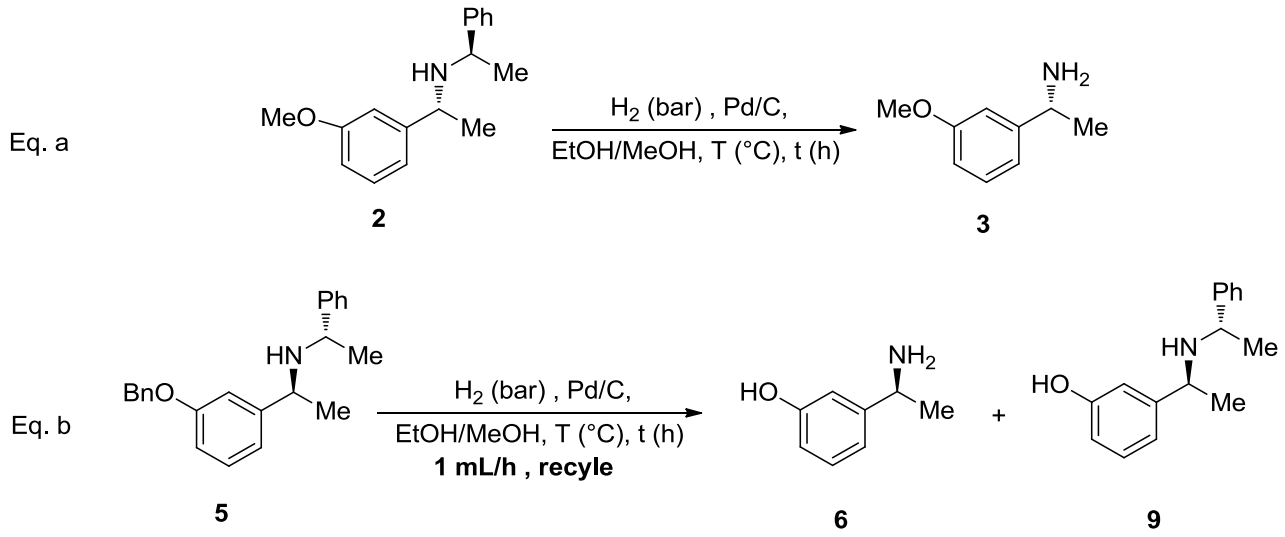
With the best conditions in our hands, the reduction of OMe functionalized ketoimine **1** and chiral imine **7**, direct precursor of the Rivastigmine was also investigated. Excellent results for chemical yield as for stereoselectivity were obtained in both cases (entries 6 and 7, Table 2).

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

Entry	R	Imine	T (°C)	Flow rate (μl/min)	Residence Time (min)	Yield (%)[a]	d.r.[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 given as average of five different samples collected at different times; reaction concentration: 0.1M; [b] Determined by ^{1}H-NMR spectroscopy; [c] Reaction concentration: 0.5M.

The continuous hydrogenolysis[16] of chiral amines was performed with a ThalesNano H-Cube Mini™, equipped with a 10% Pd/C cartridge and it was preliminarily studied on chiral amine **2** (eq. a, Scheme 5). At 50 °C and 50 bar no conversion was observed and the starting material was recovered unreacted; by rising the temperature to 80 °C and the pressure to 80 bar, chiral amine **3** was isolated in 70% yield. A further increase in temperature and pressure had no appreciable effects, while for longer reaction times 80% of conversion was obtained. In order to avoid too harsh conditions and to increase the yield, we decided to perform the reaction for longer times, using a closed loop system. In 2 hours the reaction gave a 95% of isolated yield at 80 bar and 90 °C, while at 70 °C, 6 hours were necessary to achieve 93% of yield, without any appreciable epimerization at the benzylic stereocenter (Table 3).



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

With the reaction conditions in our hands we explored the removal of the auxiliary in amine **5**. In this case the deprotection at 90 °C after 2 hours gave the O-debenzylated product **9** in 90% yield. After 4 hours of reaction at 80 °C, the desired chiral amine **6** was isolated in 70% yield, that was further increased up to 85% running the hydrogenolysis in continuo for 6 hours.

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

Entry	Amine	T (°C)	Flow rate (ml/min)	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 yield, reaction concentration: 0.1M; [b] Reaction run using a closed loop system; [c] Product **9** was obtained as major product in 90% yield.*

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

Experimental Section

General procedures for batch imines reduction with $HSiCl_3$: dry DMF (5 eq.) and a 0.9 M solution of the imine in dry solvent were introduced in a 10 mL round bottomed flask under N_2 atmosphere and further diluted in 2 mL of dry solvent. The mixture was cooled to the desired reaction temperature. A 1.6 M solution of $HSiCl_3$ (0.7 mmol, 3.5 eq.) in the selected solvent was added to the reaction mixture. After the desired time, the reaction was quenched with a of a 0.1 M solution of

NaOH until the basic pH was reached. The resulting slurry was stirred at room temperature for 10 minutes, then Na_2SO_4 was added as drying agent. The mixture was filtered over a celite pad and washed with CH_2Cl_2 (10 mL) and ethyl acetate (10 mL). The solvent was removed under reduced pressure and the diasteroisomeric ratio was evaluated on the crude mixture. The amines were purified by flash chromatography on silica gel or by crystallization.

General procedures for continuous flow imines reduction with $HSiCl_3$: The 500 μL coil-reactor at the desired temperature was fed with two 2.5 ml Hamilton gastight syringes, at the desired flow rate. Syringe A was filled with a solution of imine (1 mol eq.) and dry DMF (5 mol eq.) in dry DCM. Syringe B: was filled with a solution of $HSiCl_3$ in DCM. The concentration of the reagents in the syringes was fixed according to the desired concentration in the reactor.
The reaction mixture was collected into a one round bottomed flask, filled with a 0.1 M solution of NaOH at the same reaction temperature.
After the first volume was discharged, the steady-state conditions were reached; the reported yield values are given as average of five different samples collected at different times.

General procedure for batch amine deprotection:
To a 0.5 M solution of the amine in ethanol charged into a vial for high pressure hydrogenation (PARR instrument), 10% of Pd/C was added to the solution and the hydrogenation was carried out at 10 bar for 48 hours.
*Compound **3***: The ethanol suspension was filtered through a celite pad and washed with 50 mL of MeOH, the solution was then treated with 1 equivalent of a 2M solution of HCl in Et_2O. The solvents were removed under pressure. The residue was dissolved in DCM and treated with Amberlyst IRA-400 (OH-) resin in order to isolate the amine as neutral compound.
*Compound **6***: The ethanol suspension was filtered through a celite pad and washed with 50 mL of MeOH, the solvents were removed under pressure and the compound was obtained as neutral amine.

General procedure for H-Cube Mini deprotection:
For the synthesis of amine **6:** a 0.1M solution of the amine (1.51 mmol, 0.5 g) in ethanol (15 mL) was charged into a vial connected with the pump of the H CUBE Mini, equipped with a 30 mm cartridge of 10% Pd/C. The instrument was previously stabilized at the desired temperature and pressure and at 1 mL/min as flow rate. The reaction was run in a close loop for the desired time.

1-S-(3-hydroxy)-phenylethanamine

^{1}H NMR (300 MHz, MeOD) δ 7.19 (t, *J* = 8.1 Hz, 1H), 6.91–6.81 (m, 2H), 6.82–6.72 (m, 1H), 4.27–4.13 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 3H).

$[\alpha]_{D:}$ (c. 1 in methanol) = -22.1°

The spectroscopic data and the $[\alpha]_{D:}$ were in agreement with the literature. [17]

GC method: injector 200 °C; flow 2mL/min; temperature program 100 °C/hold 2 min.; 130 °C/rate 1 °C per min./hold 5 min; 170 °C/rate 2 °C per min/hold 5 min.: t_{ret}: 58.219 min.

Supporting Information. Synthesis of starting materials (ketones and ketoimines), synthesis of chiral amines **2**, **3, 5, 6** and **8**, detailed experimental procedures for reduction and hydrogenolysis procedures, characterization of compounds.

Acknowledgements. R.P. and D.B. acknowledge UNIMI for PhD fellowships. M.B. thanks CNR for the bilateral project FCT/CNR 2015-2016 (Ref. 441.00) "Exploring novel organocatalytic enantioselective reductions for accessing key drugs for neurodegenerative disease treatment". A.J.B. thanks bilateral project FCT/CNR 2015-2016 (Ref. 441.00).

References and Notes

[1] Reviews: a) P. J. Dunn, *Green Chem.* **2013**, *15*, 3099-3104; b) C. A. Busacca, D. R. Fandrick, J. J. Song, C. H. Senanayake, *Adv. Synth. Catal.* **2011**, *252*, 1825-1864; c) V. Farina, J. T. Reeves, C. H. Senanayake, J. J. Song, *Chem. Rev.* **2006**, *106*, 2734-2763.

[2] *Chiral Amine Synthesis: Methods, Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**.

[3] Recent general reviews on asymmetric hydrogenation: a) A. M. Palmer, A. Zanotti-Gerosa, *Current Opinion in Drug Discovery and Development* **2010,** *13*, 698; b) G. Shang, W. Li, X. Zhang. Transition Metal-Catalyzed Homogeneous Asymmetric Hydrogenation, in: *Catalytic Asymmetric Synthesis*, 3rd edn., I. Ojima Ed., Wiley, Hoboken, **2010**; c) for a special issue on hydrogenation and transfer hydrogenation see: M. J. Krische, Y. Sun, Eds. *Acc. Chem. Res.* **2007**, *40, 1237*-1419.

[4] For reviews on organocatalyzed enantioselective reductions see: a) M. Benaglia, A. Genoni, M. Bonsignore, Enantioselective organocatalytic reductions in *Stereoselective Organocatalysis: From C-C to C-heteroatom bond formation,* **(**Ed. R. Rios Torres) Wiley,

2012; b) S. Rossi, M. Benaglia, E. Massolo, L. Raimondi, *Catal. Science Technol.* **2014**, *9*, 2708-2723.

[5] For recent reviews on chiral amine synthesis: a) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753–819; b) N. Fleury-Br¦geot, V. de La Fuente, S. Castillýn, C. Claver, *ChemCatChem* **2010**, *2*, 1346–1371; c) for a review on fluorinated chiral compounds, including amines: J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, *111*, 455-529.

[6] For a pioneer work on the use of a-phenyl-ethylamine as auxiliary in imine reduction see: a) C. G. Overbergenr, N. P. Marullo, R. G. Hiskey *J. Am. Chem. Soc.* **1961**, *83*, 1374-1378; for other, representative metal-catalyzed reductions of *N*-1-phenylethyl imines see: b) M. B. Eleveld, H. Hogeveen, E. P. Schudde, *J. Org. Chem.* **1986**, *51*, 3635-3638; c) B. C. Ranu, A. Sarkar, A. Majee, *J. Org. Chem.* **1997**, *62*, 1841-1842; d) for a recent contribution on a sequential reductive amination-hydrogenolysis see T. C. Nugent, D. E. Negru, M. El-Shazly, D. Hu, A. Sadiq, A. Bibi, *Adv. Synth. Catal.* **2011**, *353*, 2085–2092 and references cited; for organocatalytic reductions of chiral imines, see: e) M. Fujii, T. Aida, M. Yoshihara, A. Ohno *Bull Chem. Soc. Jpn.* **1989**, *62*, 3845-3847; f) J. M. Farrell, Z. M. Heiden, D. W. Stephan, *Organometallics* **2011**, *30*, 4497-4500; g) S. Guizzetti, M. Benaglia, S. Rossi, *Org. Lett.* **2009**, *11*, 2928-2932; h) S. Guizzetti, M. Benaglia, C. Biaggi, G. Celentano, *Synlett* **2010**, 134-136.

[7] Reviews: a) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713–1760; b) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557–2590; for a recent contribution on the catalytic synthesis of *N*-alkyl chiral amines, see: V. N. Wakchaure, P. S. J. Kaib, M. Leutzsch, B. List, *Angew. Chem. Int. Ed.* **2015**, *54*, 11852–11856.

[8] Recent reviews: a) I. Atodiresei, C. Vila, M. Rueping, *ACS Catal*. **2015**, *5*, 1972-1985; b) A. Puglisi, M. Benaglia, R. Porta, F. Coccia, *Current Organocatalysis* **2015**, *2*, 79-101; c) R. Munirathinam, J. Huskens, W. Verboom, *Adv. Synth. Catal.* **2015**, *357*, 1093-1123; d) C. Rodríguez-Escrich, M. A. Pericàs, *Eur. J. Org. Chem*. **2015**, 1173-1188; some very recent examples of continuous flow synthetic methods: e) J-S. Poh, D. N. Tran, C. Battilocchio, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015,** *54*, 7920-7923; f) D. C. Fabry, M. A. Ronge, M. Rueping, *Chem. Eur. J.* **2015**, *21*, 5350-5354; g) D. N. Tran, C. Battilocchio, S-B. Lou, J. M. Hawkins, S. V. Ley, *Chem. Sci.* **2015**, *6*, 1120-1125.

[9] For examples of diastereoselective reductions aimed to the synthesis of Rivastigmine, see: a) ref. 6b; b) V. R. Arava, L. Gorentla, P. K. Dubey, *Der Pharma Chemica* **2011,** *3*, 426-433; c) see also ref. 13.

[10] For experimental details of the synthesis of ketones and chiral ketoimines, please see the Supporting Information.

[11] Different experimental conditions were studied; for example, the reduction at 0 °C afforded the product **2** in quantitative yield and 93/7 r.d.

[12] R. K. Henderson, C. Jemenez-Gonzalez, D. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fisher, J. Sherwood, S. P. Binks, A. D. Curzons, *Green Chem.* **2011**, *13***,** 854-862.

[13] H., Meng, Z. Fu-Li, X. Mei-Hua *Synth. Commun.* **2009**, *39*, 1527-1533.

[14] For the application of flow chemistry for multistep organic synthesis see: a) S. Newton, C. F. Carter, C. M. Pearson, L. C. Alves, H. Lange, P. Thansandote, S. V. Ley, *Angew. Chem. Int. Ed.* **2014**, *53,* 4915-4919; b) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17-57; c) M. Baumann, I. R. Baxendale, S. V. Ley, *Mol. Divers*. **2011**, *3*, 613-630. For some other recent, representative contributions see also: d) M. Chen, S. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52***,** 4247-4250 and e) I. R. Baxendale, S. V. Ley, A. C. Mansfield, C. D. Smith, *Angew. Chem. Int. Ed.* **2009**, *48***,** 4017-4021.

[15] Reviews on the synthesis of APIs under continuous flow conditions: a) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem. Int. Ed*. **2015**, *54*, 6688-6728; b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2-25.

[16] Review on continuous flow hydrogenation: P. J. Cossar, L. Hizartzidis, M. I. Simone, A. McCluskey, C. P. Gordon, *Org. Biomol. Chem*. **2015**, *13*, 7119-7130.

[17] W. Ou, S. Espinosa, H. J. Melendez, S. M. Farre, J. L. Alvarez, V. Torres, I. Martinez, K. Santiago, M. O. Marciales, *J. Org. Chem*. **2013**, *78*, 5314-5327.

Graphical Abstract

A metal-free diastereoselective reduction of chiral imines and chiral auxiliary removal were efficiently performed in mesoreactors. Continuous flow trichlorosilane-promoted C=N reduction in a coil reactor, followed by in flow *N*-deprotection in microfluidic device, afforded stereoisomerically pure both enantiomers of 1-(3-alkoxyphenyl)-ethylamine derivatives, advanced precursors of several valuable APIs.