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Solid supported chiral *N*-picolylimidazolidinones: recyclable catalysts for the enantioselective, metal- and H₂-free reduction of imines in batch and in flow mode.[#]

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[#] Dedicated to Prof. Cesare Gennari on the Occasion of his 65th Birthday

Abstract: A new class of solid supported chiral imidazolidinones organocatalysts for the catalytic reduction of imines with trichlorosilane was developed. Polystyrene proved to be a more effective support than silica in terms of both chemical and stereochemical efficiency. Even with a loading as low as 1 mol % the best performing supported catalyst showed a remarkable activity and stereocontrol ability, promoting the reduction with stereoselectivities reaching 98% e.e. and in most cases ranging between 90-95% e.e. The general scope of the methodology and the good recyclability of the immobilized catalyst were demonstrated. The polystyrene-anchored chiral catalyst was also used to prepare packed bed reactors for the continuous flow synthesis of chiral amines, that were obtained in excellent yields and enantioselectivities. By exploiting the chiral organocatalytic reactor, the in-flow stereoselective synthesis of a common, immediate precursor of rivastigmine, of the calciomimetic (R)-NPS 568 and of Acrylamide (S)-A, currently under study for the treatment of neuropathic pain, was successfully accomplished.

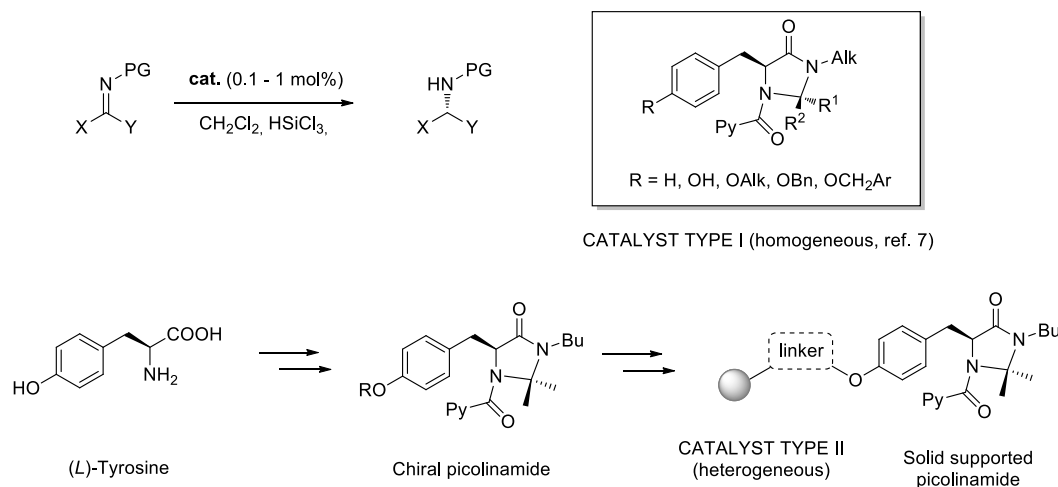
Keywords: Supported catalysts, chiral amines, catalytic reactors, imine reduction, asymmetric catalysis.

Chiral amines are very important pharmacophore that can be found in several biologically active molecules and agrochemical compounds. The reduction of ketamines either by metal-catalyzed hydrogenation^[1] or by organocatalytic methodologies^[2] is a very convenient strategy to access to this class of molecules. Among the available catalytic methods, the stereoselective reduction of imines with trichlorosilane (HSiCl_3) promoted by chiral Lewis bases has been investigated by several research groups and has proved to be very efficient.^[3] The possibility to use in a catalytic continuous flow process a very cheap, readily available and atoxic reagent like HSiCl_3 is extremely attractive, in view of a large scale preparation of enantiopure amines of industrial interest.^[4] The immobilization of the chiral catalyst would allow not only to recycle the heterogenized chiral catalytic species in the in-batch reaction,^[5] but also to assembly a catalytic reactor to be employed in the enantioselective reduction under continuous flow conditions^[6] with the catalyst permanently residing in the reactor.

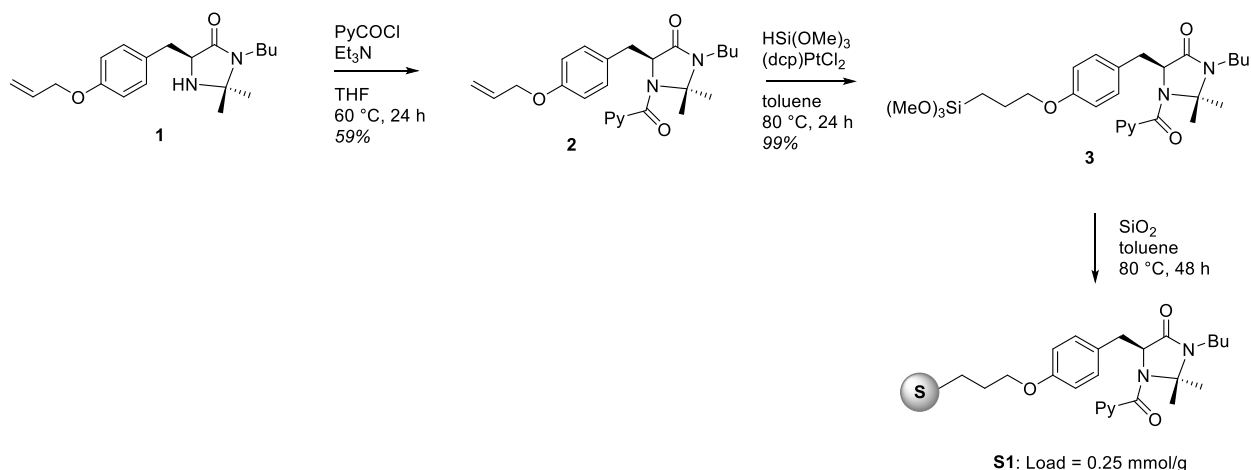
We have recently reported a new class of highly active chiral Lewis bases, able to promote the reduction of a wide variety of imines with low catalyst loading (down to 0.1% mol), occurring in quantitative yields and enantioselectivities usually higher than 90% (Figure 1, catalyst type I).^[7]

Here we report the immobilization of this new class of imidazolidinone-based picolinamides and their use in the enantioselective $\text{C}=\text{N}$ bonds reduction; despite it was often observed that the heterogenization of chiral catalysts led to a decreased catalytic efficiency, in the present study the polymer-support Lewis base of choice showed a remarkable behavior, even at 1 mol % loading, promoting the reaction in high yields and stereoselectivities up to 98 % e.e.. Not only the recyclability was demonstrated under batch conditions, but, for the first time, a chiral organocatalytic reactor for the enantioselective, trichlorosilane-mediated imine reduction under continuous flow conditions was successfully prepared and employed for the in-flow synthesis of chiral amines, including advanced intermediates of pharmaceutically relevant compounds.^[8]

For the preparation of the supported picolinamide, we started from (*L*)-Tyrosine to build up the chiral scaffold and exploited the phenolic residue as site to anchor the catalyst onto a solid support (Figure 1, catalyst type II).

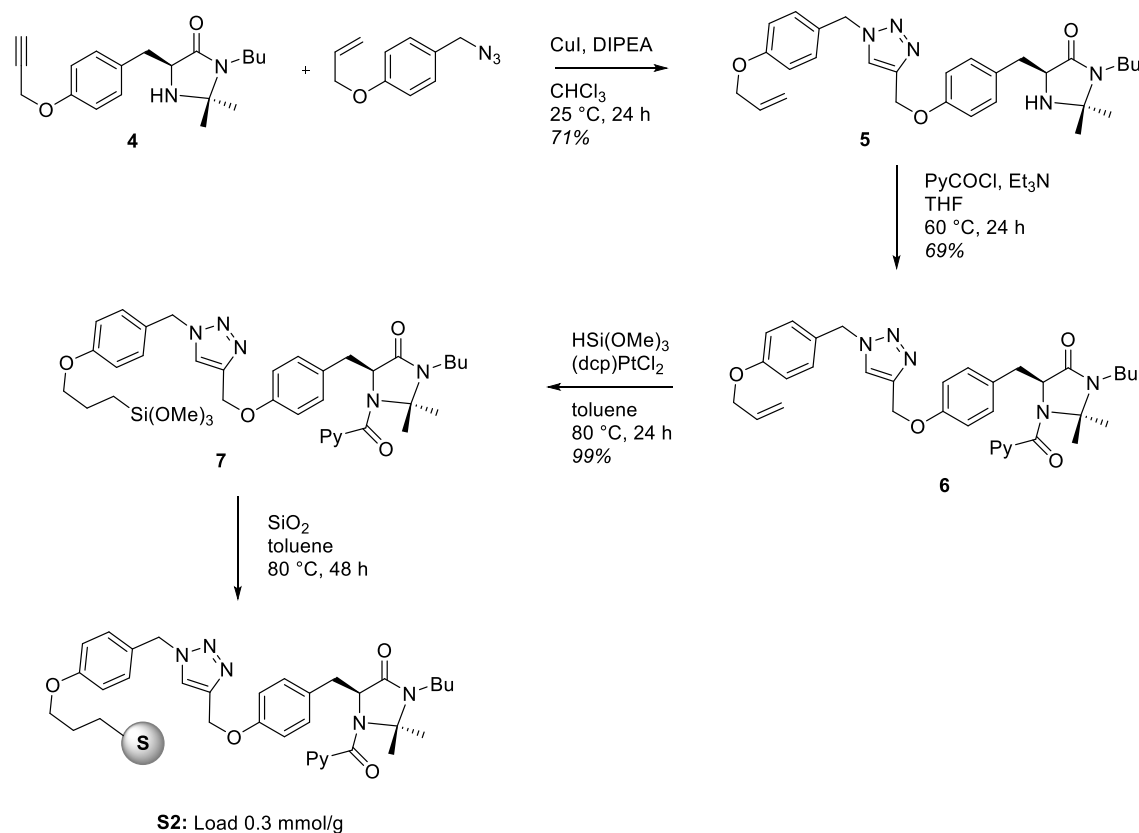
Figure 1. General synthetic strategy for the preparation of solid supported picolinamides.

The synthesis of silica supported picolinamide involved the preparation of *O*-allyl protected picolinamide **2** starting from the known intermediate **1** (Scheme 1).^[9] Compound **2** was then converted into the corresponding trimethoxysilyl derivative **3**, that was grafted onto commercially available SiO₂ (Apex Prepsil Silica Media 8 μm) to afford the silica-supported catalyst **S1** (loading: 0.25 mmol/g, as determined by weight difference).

Scheme 1. Synthesis of silica supported catalyst **S1**.

Another silica supported picolinamide, featuring a longer linker between the catalyst's active site and the solid support, was also synthesized (Scheme 2). Starting from imidazolidinone **4**,^[10] a click reaction with 1-(allyloxy)-4-(azidomethyl)benzene gave compound **5** that was then converted into the corresponding picolinamide **6**. Platinum catalyzed hydrosilylation with $\text{HSi}(\text{OMe})_3$ followed by grafting onto commercially available SiO_2 (Apex Prepsil Silica Media 8 μm) afforded the immobilized catalyst **S2** (load = 0.3 mmol/g).

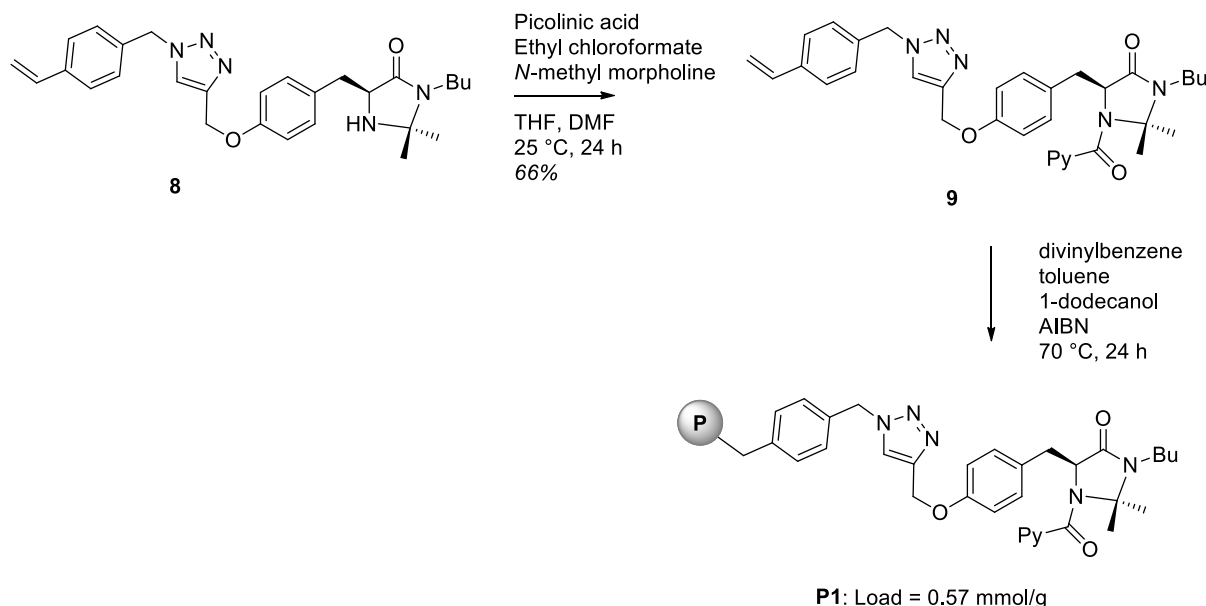
Scheme 2. Synthesis of silica supported catalyst **S2**.



The synthetic strategy for the preparation of the polymer supported catalyst takes advantage of the known imidazolidinone **8**^[10] featuring a styrene moiety to be employed in the polymerization step of the synthesis. Intermediate **8** was converted into the corresponding picolinamide **9** by reaction with picolinic acid and ethylchloroformate in the presence of *N*-methyl morpholine as a base. Monomer **9**

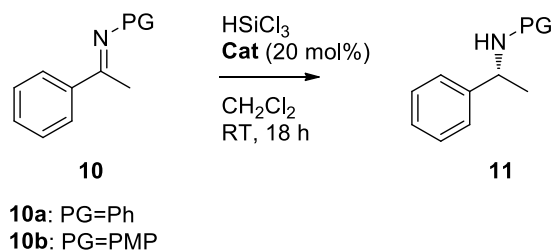
was then polymerized by AIBN-promoted radical copolymerization with divinylbenzene as co-monomer, in the presence of toluene and 1-dodecanol as porogens (Scheme 3). The loading of **P1** was evaluated to be 0.57 mmol/g, based on the stoichiometry of polymerization reaction.

Scheme 3. Synthesis of polymer supported catalyst **P1**.



The trichlorosilane-mediated reduction of imines *N*-phenyl **10a** and *N*-PMP (p-methoxyphenyl) protected **10b** derived from acetophenone was chosen as model reaction to test the solid supported catalysts (Table 1).

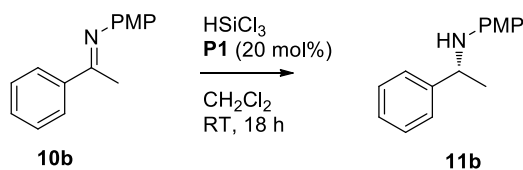
Catalyst **S1** promoted the reduction of both substrates in excellent yields and very good enantioselectivities (entries 1 and 2). The presence of a longer linker as in catalyst **S2** did not improve the chemical efficiency, but had a detrimental effect on the stereoselectivity, that was markedly reduced (entries 3 and 4). Polystyrene supported picolinamide **P1** proved to be the best catalytic system, affording the desired products (**11a** and **11b**) in very good yields and excellent stereoselectivities (97% e.e., entries 5 and 6).

Table 1. Catalyst screening.

Entry ^a	Catalyst	PG	Yield (%) ^b	ee (%) ^c
1	S1	Ph	97	82
2	S1	PMP	98	86
3	S2	Ph	70	21
4	S2	PMP	95	75
5	P1	Ph	92	97
6	P1	PMP	94	97

a) Reaction conditions: imine (0.1 mmol), HSiCl₃ (0.5 mmol), DCM(1 mL). b) Isolated yield after chromatography. c) Enantiomeric excess was determined by HPLC on chiral stationary phase; the absolute configuration was confirmed by comparison with literature data, see ref. 7.

On the basis of these preliminary investigations, **P1** was selected for further studies (Table 2).

Table 2. Screening of catalyst loading.

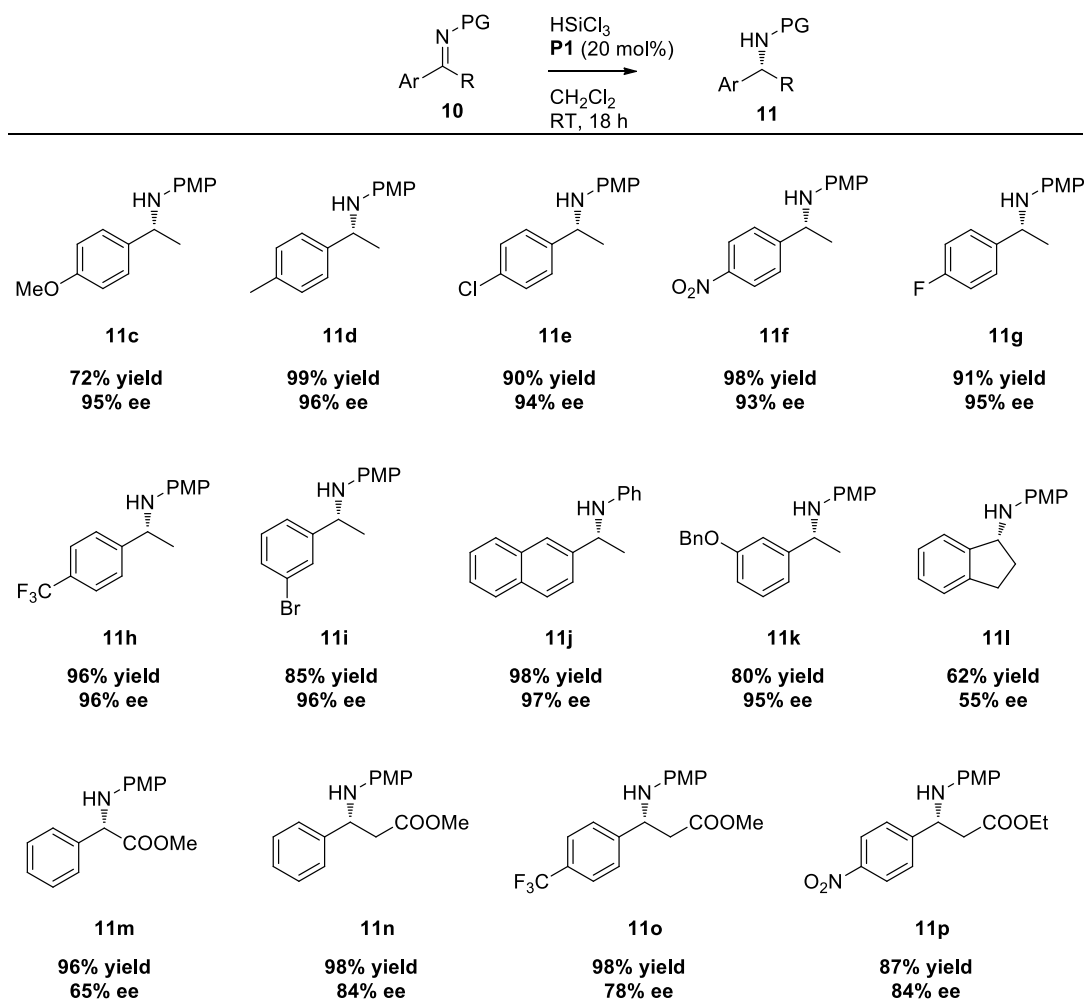
Entry ^a	P1 (mol%)	Yield (%) ^b	ee (%) ^c
1	20	94	97
2	10	94	96
3	5	92	95
4	5 ^d	82	94
5	1	96	95
6	1 ^d	46	93

a) Reaction conditions: imine (0.1 mmol), HSiCl₃ (0.5 mmol), DCM(1 mL). b) Isolated yield after chromatography. c) Enantiomeric excess was determined by HPLC on chiral stationary phase. d) Reaction time: 4h.

Remarkably, the amount of the supported catalyst could be reduced to just 1 mol%, without an appreciable loss of the chemical or stereochemical activity (Table 2, entry 1 vs entry 5). When reaction time was reduced to 4 hours, a loading of 5 mol% of **P1** was sufficient to afford chiral amine **11b** in 82% yield and 94% e.e., thus confirming the excellent chemical behavior of the heterogenized chiral Lewis base.

The general scope of the reaction was then studied. Different *C*-aryl substituted imines were reacted with HSiCl_3 in the presence of polymer-supported catalyst **P1** (Scheme 4).

Scheme 4. Reaction scope.

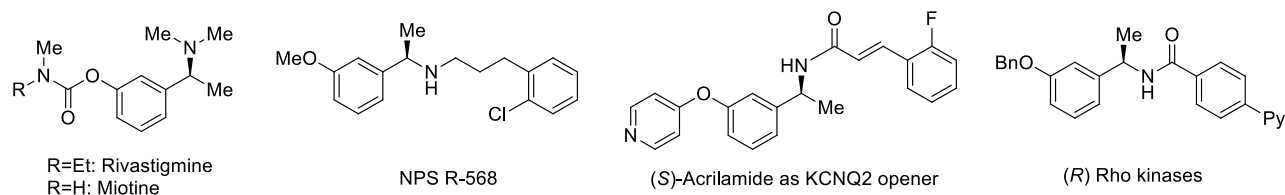


Substrates bearing both electron withdrawing (**11e-11i**) and electron donating groups (**11c**, **11d**, and **11j**) were reduced in very good yields and excellent e.e., up to 97%. Notably, amine **11k**, a direct precursor of rivastigmine (see below, Figure 2), was obtained in 80% yield and 95% e.e.. In all cases, the supported catalyst showed to behave like the non-immobilized catalyst under homogeneous conditions, and afforded the products with the (R) absolute configuration, thus suggesting that polymer-supported **P1** promotes the reduction according to the same mechanism proposed for the homogeneous catalyst.^[7]

The α -amino ester **11m** was obtained in 96% yield and only 65% e.e., β -amino esters **11n**, **11o** and **11p**, precursors of chiral β -lactams, were isolated in quantitative yields and good e.e., up to 84%.

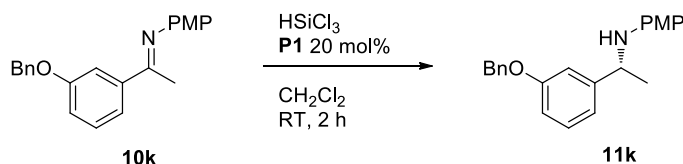
In order to demonstrate the practical applicability of the heterogeneous catalyst **P1**, both its recovery and recycle were studied in the reduction of imine **10k**, a key common intermediate for the preparation of several, pharmaceutically relevant molecules (Figure 2).

Figure 2. Some biologically active chiral amines featuring 3-alcoxyaryl residue.



With a two hours reaction time for each cycle, the same immobilized catalyst could be used for seven reaction cycles, affording a constant yield, typically ranging between 80 and 85%, and a reproducible, high level of enantioselectivity, of about 94% e.e. (Table 3).^[11]

Table 3. Recycling experiments.

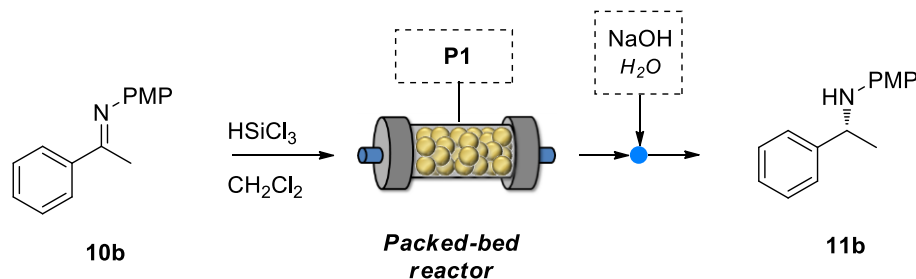


Cycle ^a	Yield (%) ^b	ee (%) ^c
1 st	80	94
2 nd	81	94
3 rd	80	94
4 th	79	93
5 th	87	93
6 th	84	90
7 th	76	87

a) Reaction time of each cycle: 2 hours. b) Isolated yield. c) E.e. was determined by HPLC on chiral stationary phase

Polystyrene supported catalyst **P1** was then employed for the fabrication of packed bed reactors, required for developing an efficient and convenient continuous flow reduction of imines with HSiCl_3 . **P1** (0.3 g) was packed into a stainless-steel HPLC column (*l*: 6 cm, *id*: 0.4 cm, *V*: 0.75 mL). A 0.05 M solution of **10b** and HSiCl_3 in CH_2Cl_2 was pumped into the reactor through a syringe pump at 0.4 mL/h (res time: 30 min) at room temperature. The outcome of the reactor was collected into a flask containing NaOH 10% solution and the product isolated by extraction and solvent evaporation. After the first two operating hours, the product was collected at 1 h intervals and analyzed in order to determine the conversion and the ee. Results of the continuous flow experiments are reported in Table 4.

Table 4. Continuous flow synthesis of amine **11b**.



Entry	Running time (min)	Yield (%) ^a	ee (%) ^b
1	0-120	92	85
2	120-180	94	83
3	180-240	93	81
4	240-300	94	80
5	300-360	94	75
6	360-420	94	73

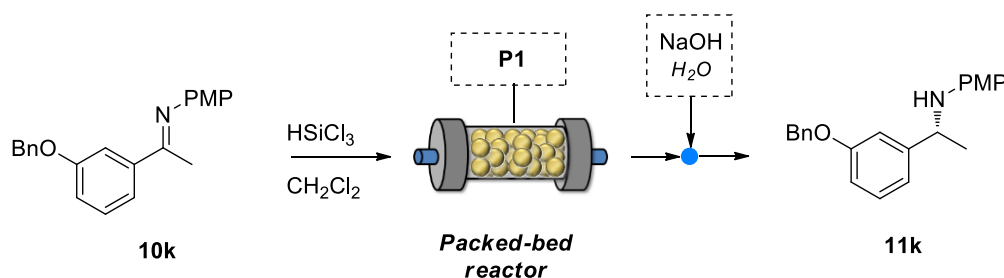
a) Isolated yield after chromatography. b) Enantiomeric excess was determined by HPLC on chiral stationary phase

As reported in Table the flow system was stable for seven hours, producing chiral amine **11b** in excellent yield (always higher than 90%) and good e.e.. The stereoselectivity of the process slightly decreased with time, probably because of a very slow, but constant, partial degradation of the imidazolidinone ring of the catalyst.^[12]

Then, we decided to study the in-flow synthesis of a valuable compound such as 1-(*m*-benzyloxyphenyl)-ethylamine **11k**, precursors, among others, of rivastigmine, of the calciomimetic (R)-NPS 568 and of Acrylamide (S)-A, currently under study for the treatment of neuropathic pain (Figure 2).^[13]

By employing the packed-bed reactor **P1** the continuous flow process afforded chiral amine **11k** in 82% yield and 83% e.e. for the first three operation hours (Scheme 5). The chiral amine was continuously produced for other 2 hours with similar yield and enantioselectivity, while, in the course of the sixth hour, a process of comparable yield and a minimally decreased selectivity was observed (79% yield and 77% e.e).^[14]

Scheme 5. Continuous flow synthesis of amine **11k**.



Entry	Running time (min)	Yield (%) ^a	ee (%) ^b
1	0-180	82	83
2	180-300	80	81
3	300-360	79	77

a) Isolated yield after chromatography. b) Enantiomeric excess was determined by HPLC on chiral stationary phase

In conclusion, a new class of solid supported chiral Lewis bases for the catalytic reduction of imines with trichlorosilane was studied. Polystyrene-immobilized catalysts promoted the reaction in very high enantioselectivities for a wide variety of substrates, up to 97% e.e. The possibility to decrease the catalyst's loading down to 1 mol % and to recycle the catalyst six times was demonstrated. The polymer-supported catalyst of choice was used to prepare packed bed reactors for the synthesis of chiral amines under continuous flow conditions and applied to the preparation of an advanced precursor of important pharmaceutically active compounds. The combination of catalytic reactors with recently developed synthetic and analytical devices for the in-flow processes, will offer new unforeseen and readily exploitable opportunities for the automated synthesis of complex molecules.^[15]

Experimental Section

General procedure for batch reaction

Supported catalyst (0.02 mmol) and imine (0.1 mmol) were introduced into a vial and dissolved in dry CH_2Cl_2 (1 mL) under inert atmosphere. HSiCl_3 (1 M solution in CH_2Cl_2 , 5 equiv.) was added at 0°C and then the reaction was stirred at room temperature for 18 hours. After this reaction time the supported catalyst was removed by filtration and washed with dichloromethane. The organic layer was treated with NaOH 10% aq. until basic pH = 9. The organic layer was collected, dried with Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel. The enantiomeric excess was determined by HPLC on chiral stationary phase.

General procedure for continuous flow reaction

A 0.05 M mixture of imine (0.1 mmol) and HSiCl_3 (5 equiv.) in dry CH_2Cl_2 (2 mL) was charged into a 2.5 mL SGE gas tight syringe and fixed on a syringe pump. The syringe was connected to the packed bed reactor and flushed at the indicated flow rate. The reactor was then washed with pure CH_2Cl_2 at the same flow rate. The outcome of the reactor was collected into a flask containing NaOH 10% solution. After phase separation and concentration the product was isolated. At predetermined intervals of time the product was collected and analyzed. The yield was determined by chromatography and the ee was determined on HPLC on chiral stationary phase.

Supporting Information. Synthesis of catalysts, substrates, general procedures for batch and flow synthesis, products characterization, NMR spectra and HPLC traces.

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References and Notes

- [1] For general reviews on asymmetric hydrogenation, see: a) A. M. Palmer, A. Zanotti-Gerosa, *Current Opinion in Drug Discovery and Development*, **2010**, *13*, 698; b) for a special issue on hydrogenation and transfer hydrogenation see: M. J. Krische, Y. Sun, Y. Eds., *Acc. Chem. Res.* **2007**, *40*, 1237; c) for reviews on metal-catalyzed hydrogenation of imines and heteroaromatic systems see: N. Fleury-Bregeot, V. de la Fuente, S. Castillon, C. Claver, *Chem. Cat. Chem.* **2010**, *2*, 1346; d) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557.
- [2] 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; c) for two recent reviews on Bronsted acids-catalyzed reactions, including C=N reductions, see: D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9407 and d) T. Akiyama, K. Mori, *Chem. Rev.* **2015**, *115*, 9277.
- [3] Reviews: a) S. Guizzetti, M. Benaglia, *Eur. J. Org. Chem.*, **2010**, 5529-5541; b) S. Jones, C. J. A. Warner, *Org. Biomol. Chem.*, **2012**, *10*, 2189-2200. For selected, recent contributions not included in previous reviews: c) L. Chen, C. Wang, L. Zhou, J. Sun, *Adv. Synth. Catal.* **2014**, *356*, 2224-2230; d) X.-Y. Hu, M.-M. Zhang, C. Shu, Y.-H. Zhang, L.-H. Liao, W.-C. Yuan, X.-M. Zhang, *Adv. Synth. Catal.* **2014**, *356*, 3539-3544; e) C. Wang, X. Wu, L. Zhou, J. Sun, *Org. Biomol. Chem.*, **2015**, *13*, 577-582; f) J. Ye, C. Wang, L. Chen, X. Wu, L. Zhou, J. Sun, *Adv. Synth. Catal.* **2016**, *358*, 1042-1048.; g) A. Chelouan, R. Recio, L. G. Borrego, E. Álvarez, N. Khiar, I. Fernandez, *Org. Lett.*, **2016**, *18*, 3258-3261. For pioneer works with aminoacid-derived catalysts see: h) A. V. Malkov, A. Mariani, K. N. MacDougall, P. Kočovský, *Org. Lett.* **2004**, *6*, 2253-2256; i) A. V. Malkov, M. Figlus,

S. Stončius, P. Kočovský, *J. Org. Chem.* **2009**, *74*, 5839-5849; j) A. V. Malkov, A. J. P. S. Liddon, P. Ramírez-López, L. Bendová, D. Haigh, P. Kočovský, *Angew. Chem. Int. Ed.*, **2006**, *45*, 1432-1435; see also reviews, ref. [3a-b].

[4] Reviews on the synthesis of APIs under continuous flow conditions: a) B. Gutmann, D. Cantillo, D.; C. O. Kappe, *Angew. Chem. Int. Ed.* **2015**, *54*, 6688; b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res. Dev.* **2016**, *20*, 2-25; c) for a comprehensive review on the synthesis of natural products in flow see: J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849.

[5] a) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401; b) M. Gruttadauria, F. Giacalone, R. Noto, *Chem. Soc. Rev.*, **2008**, *37*, 1666; c) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 418; d) M. Benaglia, *Recoverable and Recyclable Catalysts*, Wiley-VCH, Weinheim, **2009**; e) C. Jimeno, S. Sayalero, M. A. Pericàs, in *Catalysis by Metal Complexes, Vol. 33: Heterogenized Homogeneous Catalysis for Fine Chemicals Production*, (Eds.: Barbaro, P.; Liguori, F.), Springer, Berlin, **2010**, pp. 123 –170; f) N. Haraguchi, S. Itsuno, *Polymeric Chiral Catalyst Design and Chiral Polymer Synthesis*, John Wiley & Sons, **2011**; g) *RSC Green Chemistry, No. 15: Enantioselective Homogeneous Supported Catalysis* (Ed.: R. Sebesta), RSC, Cambridge, **2012**.

[6] For recent reviews on stereoselective catalytic reactions in flow see: a) T. Tsubogo, T. Ishiwata, S. Kobayashi, *Angew. Chem. Int. Ed.*, **2013**, *52*, 6590; b) A. Puglisi, M. Benaglia, V. Chirolì, *Green Chem.* **2013**, *15*, 1790; c) I. Atodiresei, C. Vila, M. Rueping, *ACS Catal.* **2015**, *5*, 1972; d) R. Munirathinam, J. Huskens, W. Verboom, *Adv. Synth. Catal.* **2015**, *357*, 1093; e) C. Rodríguez-Escrich, M. A. Pericàs, *Eur. J. Org. Chem.*, **2015**, 1173. For a few selected, recent contributions not included in the reviews: f) J. Izquierdo, C. Ayats, A. H. Henseler, M. A. Pericàs, *Org. Biomol. Chem.*, **2015**, *13*, 4204; g) H. Liu, J. Feng, J. Zhang, P. S. Miller, L. Chena, C.-Y. Su, *Chem. Sci.*, **2015**, *6*, 2292; h) R. J. Ingham, C. Battilocchio, D. E. Fitzpatrick, E. Sliwinski, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 144; i) P. Llanes, C. Rodríguez-Escrich, S. Sayalero, M. A. Pericàs, *Org. Lett.* **2016**, *18*, 6292. See also j) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature*, **2015**, *520*, 329.

[7] D. Brenna, R. Porta, E. Massolo, L. Raimondi, M. Benaglia, *ChemCatChem* **2017**, DOI: 10.1002/cctc.201700052.

[8] Recently we reported the use of solid supported Cinchona alkaloid-based Lewis bases as catalysts in the imine reduction, that showed good chemical activity but moderate enantioselectivity; in a very

preliminary study, a packed bed reactor employed in a continuous flow reaction suffered from poor enantioselectivity and very low stability: a) S. D. Fernandes, R. Porta, P. C. Barrulas, A. Puglisi, A. J. Burke, M. Benaglia, *Molecules* **2016**, *21*, 1182; b) for a pioneer paper on the use of catalytic columns employing immobilized Cinchona alkaloid derivatives, see: A. M. Hafez, A. E. Taggi, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 10853.

[9] A. Puglisi, M. Benaglia, R. Annunziata, V. Chiroli, R. Porta, A. Gervasini, *J. Org. Chem.* **2013**, *78*, 11326.

[10] R. Porta, M. Benaglia, A. Puglisi, A. Mandoli, A. Gualandi, P. G. Cozzi, *ChemSusChem*, **2014**, *7*, 3534.

[11] The supported catalyst showed to be highly efficient for a limited operating time; when recycling experiments were conducted for 20 hours for each cycle, amine **11k** was obtained as racemic mixture already at the 2nd run (40 hours of activity, overall).

[12] For previous studies on the immobilization of chiral imidazolidinones and their recyclability see: a) M. Benaglia, G. Celentano, M. Cinquini, A. Puglisi, F. Cozzi, *Adv. Synth. Catal.* **2002**, *344*, 149; b) S. A. Selkälä, J. Tois, P. M. Pihko, A. M. P. Koskinen, *Adv. Synth. Catal.* **2002**, *344*, 941; c) Y. Zhang, L. Zhao, S. S. Lee, J. Y. Ying, *Adv. Synth. Catal.* **2006**, *348*, 2027; d) J. Y. Shi, C. A. Wang, Z. J. Li, Q. Wang, Y. Zhang, W. Wang, *Chem. Eur. J.* **2011**, *17*, 6206; e) S. Guizzetti, M. Benaglia, J. S. Siegel, *Chem. Commun.* **2012**, *48*, 3188; f) P. Riente, J. Yadav, M. A. Pericàs, *Org. Lett.* **2012**, *14*, 3668-3671; g) V. Chiroli, M. Benaglia, F. Cozzi, A. Puglisi, R. Annunziata, G. Celentano, *Org. Lett.* **2013**, *15*, 3590; h) V. Chiroli, M. Benaglia, A. Puglisi, R. Porta, R. P. Jumde, A. Mandoli, *Green Chem.* **2014**, *16*, 2798 and ref. [10]; i) S. Ranjbar, P. Riente, C. Rodriguez-Esrich, J. Yadav, K. Raminemi, M. A. Pericàs, *Org. Lett.* **2016**, *18*, 1602-1605.

[13] 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 recent, in flow synthesis exploiting mesoreactor technology of important chiral pharmaceutical amine derivatives, see: c) D. Brenna, M. Benaglia, R. Porta, S. D. Fernandes, A. J. Burke, *Eur. J. Org. Chem.* **2016**, doi:10.1002/ejoc.201601268; d) D. Brenna, M. Pirola, L. Raimondi, A. J. Burke, M. Benaglia, *Bioorg. Med. Chem.* **2017**, DOI: 10.1016/j.bmc.2017.01.023.

[14] For experimental details of the in-batch and in-flow synthesis of the chiral amines and their characterization, please see the Supporting Information.

[15] Review: S. V. Ley, D. E. Fitzpatrick, R. J. Ingham, R. M. Myers, *Angew. Chem. Int. Ed.* **2015**, *54*, 3449. For a few, representative, recent examples of continuous flow synthetic applications for multistep organic synthesis: b) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17; c) M. Chen, S. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 4247; d) 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; e) J.-S. Poh, D. N. Tran, C. Battilocchio, J. M. Hawkins, S. V. Ley, *Angew. Chem. Int. Ed.* **2015**, *54*, 7920; f) D. C. Fabry, M. A. Ronge, M. Rueping, *Chem. Eur. J.* **2015**, *21*, 5350; g) D. N. Tran, C. Battilocchio, S.-B. Lou, J. M. Hawkins, S. V. Ley, *Chem. Sci.* **2015**, *6*, 1120.

Graphical Abstract

A new recyclable, polystyrene supported catalyst of wide general applicability, promoted the trichlorosilane-mediated imine reduction with a remarkable activity, even with a loading as low as 1 mol %; excellent stereocontrol ability, up to 98% e.e. was observed, in most cases ranging between 90-95% e.e. By exploiting packed bed chiral organocatalytic reactors, the in-flow stereoselective synthesis of chiral amines, precursors of valuable APIs, was accomplished in satisfactory yields and enantioselectivities.

