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Advanced Synthesis & Catalysis

Expanding the Toolbox of Heterogeneous Asymmetric Organocatalysts: Bifunctional Cyclopropenimine Superbases for Enantioselective Catalysis in Batch and Continuous Flow

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In memory of Professor Giancarlo Fantin

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Abstract: A strategy for the immobilization of chiral 2,3-bisaminocyclopropenium salt (pre-catalyst) onto polystyrene and silica supports is presented together with a suitable procedure for the conversion into the corresponding cyclopropenimine superbase catalysts. The activity and recyclability of polystyrene- and silica-supported cyclopropenimines were initially tested under batch conditions in a model Michael addition detecting comparable efficiencies but a superior stability of the latter heterogeneous catalyst (5 cycles, accumulated TON of 27.1). The preferred silica-supported cyclopropenimine behaved very similarly to the soluble counterpart in the reaction of glycine imine with different Michael acceptors (48–92% yield; 60–98% *ee*) and it could be utilized as packing material for the fabrication of fixed-bed mesoreactors (pressure-resistant stainless-steel columns). Continuous-flow experiments were performed with satisfactory long-term stability (24 h on stream) with unaltered conversion efficiency and enantioselectivity.

Keywords: asymmetric catalysis; Brønsted base; C-C coupling; flow chemistry; heterogeneous catalysis; immobilization; Michael addition; organocatalysis; packed-bed reactor

Introduction

According to Caubère definition,[1] organic superbases are neutral compounds with basicity greater than Proton-sponge® (pK_{BH+} 18.8 in MeCN), which are characterized by the structural combination of two different types of basic functionalities. To date, the list of compounds belonging to this class of Brønsted bases is quite narrow and it mainly includes, in order of increasing basicity, amidines, guanidines, cyclopropenimines, iminophosphoranes-phosphazenes, and azaphosphatranes (Figure 1).[2] In particular, the strong basicity of cyclopropenimines (pK_{BH+} ~26 in MeCN) is attributable to the presence of the latent, aromatic 2π-electron cyclopropenium ion, which is generated by protonation of the head imino nitrogen and further stabilized by delocalization of the three nitrogen lone pairs.[3] Organic superbases are complementary to inorganic bases with advantageous properties such as better solubility in organic media, good moisture

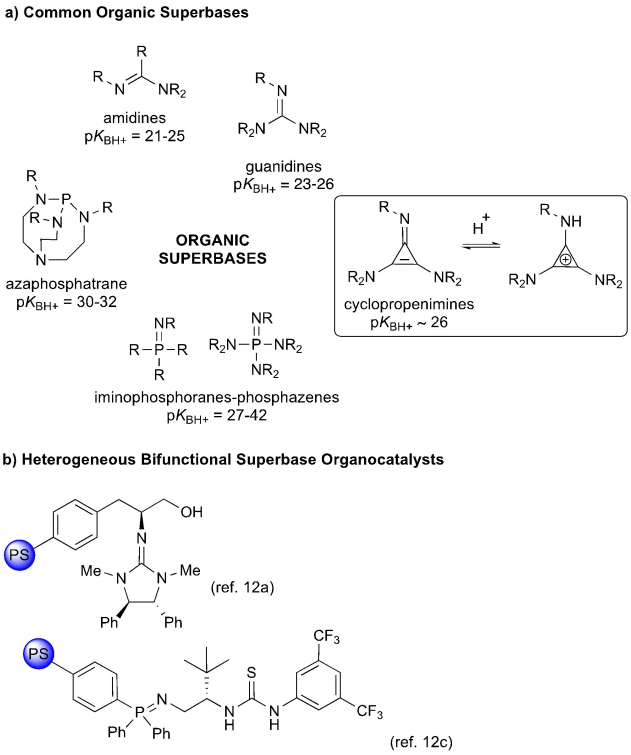


Figure 1. Structures and pK_{BH+} values (MeCN) of organic superbases and known bifunctional heterogeneous superbase organocatalysts for asymmetric catalysis.

resistance, decreased nucleophilicity, countercation coordination ability by the protonated conjugated acid and, importantly, the possibility to induce stereoselectivity. In recent years, chiral versions of organic superbases have been emerging as effective Brønsted base catalysts in enantioselective reactions by HOMO activation of pronucleophiles with high pK_a values, which are generally unreactive towards Brønsted bases employed so far.[4] Excellent results in terms of stereoselectivity have been obtained by exploiting synergistic mechanisms by installing H-bonding donor groups on the catalyst structure.[5] Indeed, bifunctional superbase organocatalysts have been successfully engaged in a number of asymmetric processes, including Michael,[6] Mannich,[7] oxyamination,[8] and cycloaddition[9] reactions. Nevertheless, the field of asymmetric catalysis mediated by organic superbases is still in its infancy compared to other organocatalytic activation modes such as Lewis base, Brønsted acid, and counterion catalysis;[10] thus, further improvements are needed especially regarding the ease of access to superbases, whose preparation and purification are sometimes complicated by their inherent strong reactivity. Organocatalyst heterogenization may offer unique opportunities in this direction by facilitating the catalyst handling and recycling, with the advantage of the simple product/catalyst separation and the possible adaptability to flow chemistry.[11] To the best of our knowledge, the immobilization of bifunctional chiral superbases have been achieved for guanidine- and iminophosphorane-derived organocatalysts[12] recording, however, high levels of stereoselectivity only with the second type of supported catalysts (Figure 1).[12c]

Actually, preserving in heterogeneous phase the reactivity and stereoinduction ability of chiral organocatalysts is a challenging goal at the forefront of catalysis, which mainly depends on the linker nature,[13] the solvent effect[14] and, ultimately, on the choice of the solid matrix.[15] In continuation of our research on asymmetric organocatalysis in heterogeneous conditions,[16] we herein report on the immobilization onto polystyrene and silica gel of chiral 2,3-bisaminocyclopropenimine (Lambert catalyst),[17] which is a privileged bifunctional organocatalyst for highly enantioselective Michael,[6e,18] Mannich,[7c] and [3+2] cycloaddition reactions (Figure 2).[9c] Once we established the comparable, high efficiency of both polystyrene- and silica-supported cyclopropenimines in model Michael additions (yield >90%; *ee* up to 98%), the greater stability (recyclability) of the silica-based catalyst was exploited to demonstrate for the first time the compatibility of asymmetric organo-superbase catalysis with a continuous-flow setup through the fabrication and long-term operation of the corresponding packed-bed mesoreactor.

Results and Discussion

Our study commenced with the synthesis of the polystyrene-supported version of the Lambert catalyst, that was initially approached adopting the same strategy developed for the preparation of the homogeneous counterpart (Schemes 1 and 2).[6e] Accordingly, 4-bromo-D-phenylalaninol **1** was readily obtained by reduction of the corresponding commercially available amino acid;[19] then, the Suzuki-Miyaura cross-coupling of **1** with 4-vinylphenylboronic acid **2** was deeply investigated under different conditions with $PdCl_2(PPh_3)_2$ catalyst to introduce the styryl functionality, which was necessary for the copolymerization of the expected adduct **3** with styrene (STY) and divinylbenzene (DVB) leading to the polymer-sup-

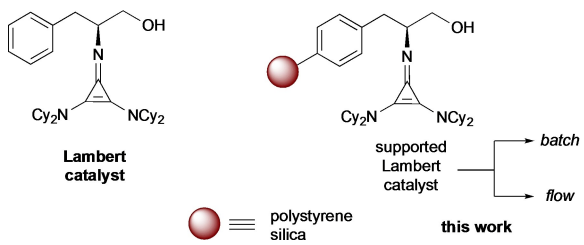
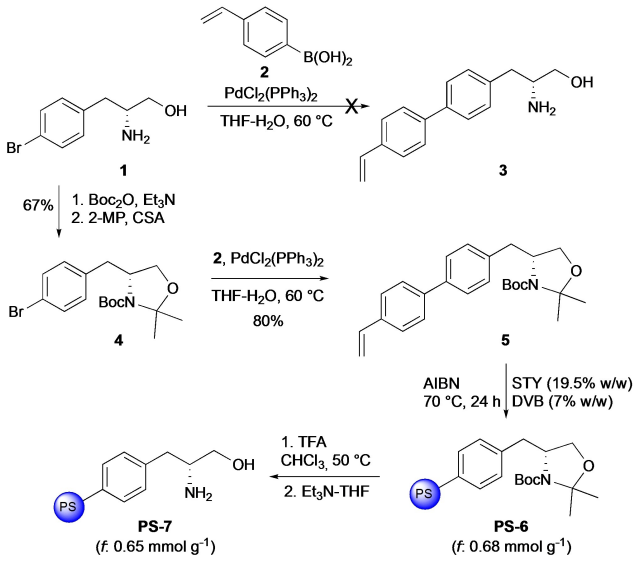
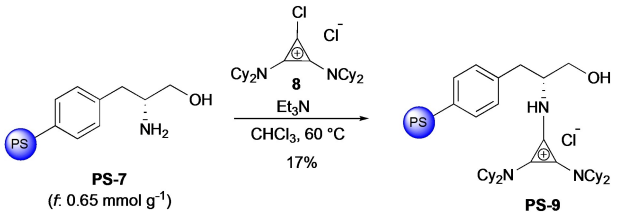


Figure 2. Lambert catalyst and heterogeneous versions thereof.



Scheme 1. Synthesis of polystyrene-supported D-phenylalaninol **PS-7**.



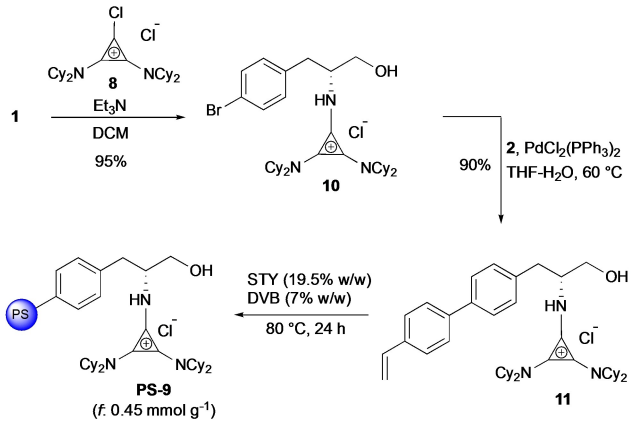
Scheme 2. Ineffective approach to the synthesis of polystyrene-supported cyclopropenium salt pre-catalyst **PS-9**.

ported phenylalaninol **PS-7** (Scheme 1). Unfortunately, any attempt to obtain the styryl derivative **3** failed because of the formation of a gummy, unmanageable reaction mixture, which was likely due to uncontrolled Pd-catalyzed homopolymerization of **3**. Hence, we reasoned that protection of the amino alcohol functionality of **1** could suppress Pd complexation, which was assumed to be responsible for the *in situ* formation of Pd species capable to promote the self-oligomerization of **3**.[20] Indeed, the *N*-Boc oxazolidine-protected derivative **4**, which was easily obtained from **1** by standard chemistry, underwent Suzuki-Miyaura coupling with **2** under $PdCl_2(PPh_3)_2$ catalysis affording the styryl adduct **5** in satisfactory 80% isolated yield. After a brief polymerization study, macroporous **PS-6** was then prepared with a satisfactory loading of oxazolidine units (*f*: 0.68 mmol g^{-1}) using the optimal reaction mixture, which was composed of STY (19.5% w/w), DVB (7% w/w), the co-monomer **5** (13% w/w), 1-dodecanol (50% w/w) and toluene (10% w/w) as the porogens, and AIBN (0.1% w/w) as the radical initiator. Deprotection of triturated **PS-6** was finally carried out with TFA/chloroform followed by treatment with Et_3N/THF to give the target polymer-supported phenylalaninol **PS-7** (Scheme 1).

In agreement with the Lambert protocol,[6e] the heterogeneous chiral amino alcohol **PS-7** was coupled with bis(dicyclohexylamino)cyclopropenium chloride **8**[17b] exploring different reaction conditions (variation of base, solvents, temperature, and excess **8**; Scheme 2).[21] Disappointingly, the lower reactivity of **PS-7** compared to homogeneous phenylalaninol could not be compensated by the increase of temperature (60 °C vs. RT), the larger amount of **8** (up to 5 equiv.), and the use of a good swelling solvent ($CHCl_3$), which provided the target cyclopropenium salt pre-catalyst **PS-9** in only 17% conversion, as determined by quantitative ^{1}H NMR analysis (internal standard) of the supernatant solution.

A more effective route to **PS-7** was investigated by considering the homogeneous coupling of **8** with 4-bromo-phenylalaninol **1** to give the cyclopropenium salt **10**, followed by Suzuki-Miyaura cross-coupling with boronic acid **2** and subsequent co-polymerization of the resulting styryl derivative **11** with STY and DVB (Scheme 3). Actually, this approach proved to be practicable since the cyclopropenium salt **11** could be obtained in high yield (85% over two steps) and used as crude material in the polymerization to **PS-9** (80 °C, 24 h). Elemental analysis of this resin confirmed a satisfactory loading of cyclopropenium units (*f*: 0.45 mmol g^{-1}), while a control experiment with an authentic sample of **10** (toluene, 80 °C, 24 h) confirmed the maintenance of the structural integrity of the chiral amino alcohol functionality under the quite harsh conditions of the cross-coupling and polymerization steps (^{1}H NMR analysis; see the Experimental Section for details).

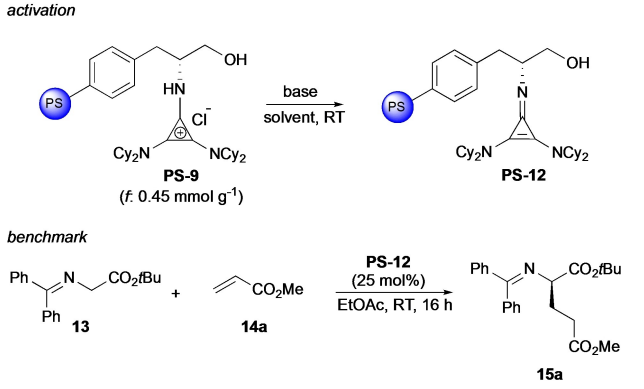
Next, formation of the cyclopropenimine superbase catalyst **PS-12** was considered by testing different activation conditions and using the Michael reaction of glycine imine **13** with methyl acrylate **14a** as the



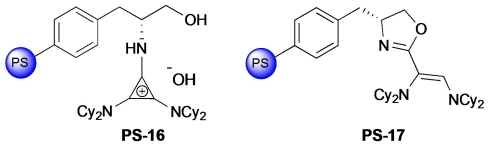
Scheme 3. Effective approach to the synthesis of polystyrene-supported cyclopropenium salt pre-catalyst **PS-9**.

benchmark (Table 1). Hence, by mimicking in the heterogeneous phase the activation protocol optimized for the homogenous Lambert catalyst,[6e] **PS-9** was initially suspended in a 0.5 M aqueous NaOH-THF (1:1) mixture and subsequently washed with several portions of THF and EtOAc to remove any trace of hydroxyl anion, which could be eventually responsible for a racemic background reaction. Unfortunately, application of the supposed **PS-12** (25 mol%) generated under the above conditions to the model **13**/**14a** coupling resulted in no formation of the expected Michael adduct **15a** (entry 1). Reasonably, excess water of the activation procedure consumed the *in situ* generated superbase **PS-12** producing the unactive cyclopropenium hydroxide **PS-16**; as a matter of fact, this side-reaction can be avoided in the homogeneous phase because deprotonation of the soluble cyclopropenium pre-catalyst occurs at the organic solvent/water interface in a separation funnel.[6e] Promisingly, utilization of anhydrous conditions (DCM, RT, 1 h) in combination with DBU (3 equiv.) as organic base furnished at least a portion of active **PS-12** since formation of the target product **15a** could be achieved in very poor yield (6%) but with good enantiomeric excess (92% *ee*; entry 2). Increasing the excess of DBU to 20 equivalents (entry 3) and the use of the stronger TBD base in DCM or THF slightly improved the outcome of the model reaction (entries 4 and 5), thus suggesting still a partial activation of **PS-7**. The rise in temperature (50 °C, TBD, THF) determined a marked decrease of conversion efficiency of the so-generated **PS-12** (entry 6); in agreement with Lambert's proposal,[6e] this result was explained by preferential formation of undesired oxazolidine **PS-17** via internal deprotonation of the pendant hydroxyl group and subsequent cyclization triggered by the temperature increase. Similar unsatisfactory outcomes were also detected with *n*-BuLi or NaHMDS (3 equiv.) as the bases (entries 7–8). Optimal conditions for **PS-12** generation were finally achieved with complete reproducibility by treating **PS-7** with 0.05 M LiOH in anhydrous MeOH (RT, 1 h); gratifyingly, by this activation procedure, **PS-12** (25 mol%) promoted the formation of adduct **15a** in almost quantitative yield and 98% *ee* (EtOAc, RT, 16 h; entry 9).

Table 1. Optimization of catalyst **PS-12** formation and its activity in the model Michael reaction.[a]



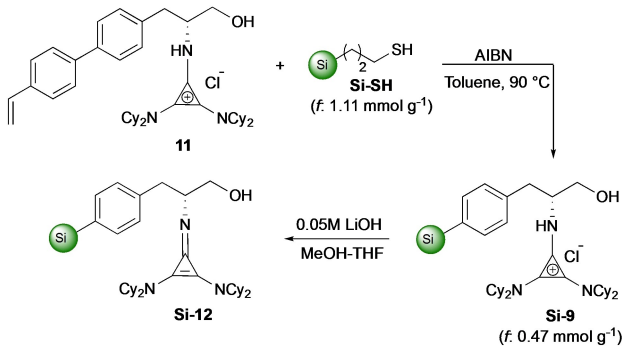
Entry	Base	Solvent	**15a** (%)[b]	*ee* (%)[c]
1	0.5 M NaOH	H_2O-THF	–	–
2[d]	DBU	DCM	6	92
3[e]	DBU	DCM	18	93
4[e]	TBD	DCM	30	96
5[e]	TBD	THF	28	95
6[e,f]	TBD	THF	5	84
7[d]	*n*-BuLi	THF	7	88
8[d]	NaHMDS	THF	9	84
9	0.05 M LiOH	MeOH	> 95	98



[a] Activation: **PS-9** (100 mg, 0.045 mmol); benchmark: **13** (0.07 mmol), **14a** (0.21 mmol), **PS-12** (0.017 mmol based on **PS-9** loading), EtOAc (1.5 mL).
[b] Detected by ^{1}H NMR analysis of reaction mixture.
[c] Determined by chiral stationary phase HPLC.
[d] Base (0.14 mmol).
[e] Base (9.00 mmol).
[f] Activation of **PS-9** at 50 °C.

At the beginning of this study we were aware of the strict structural requirements to guarantee activity, stability, and enantioinduction ability of the homogeneous Lambert catalyst, including the key intramolecular CH···O interaction between the dicyclohexylamino and hydroxyl groups in the ground state of the catalyst.[17b] On the other hand, it is well known that the nature of support may deeply affect the activity and selectivity of heterogeneous (organo)catalysts because of unfavorable interactions between the catalytic active sites and the solid surface.[15] Hence, the matrix effect was also explored by considering the immobilization of Lambert cyclopropenimine onto silica gel through thiol-ene coupling (TEC)[22] of the styryl cyclopropenium salt **11** with the suitably prepared mercaptopropyl silica gel **Si-SH**[16b] (Scheme 4). By this strategy, heterogeneous pre-catalyst **Si-9** was readily obtained (AIBN, 90 °C, 16 h) with a satisfactory level of functionalization (*f*: 0.47 mmol g^{-1}) and subsequently converted into the corresponding cyclopropenimine free base **Si-12** by application of the same protocol optimized for the polystyrene-supported analogue **PS-9** (0.05 M LiOH in anhydrous MeOH, RT, 1 h).

The catalytic activity and recyclability of the newly prepared heterogeneous cyclopropenimine superbases **PS-12** and **Si-12** were duly investigated (Table 2). As previously mentioned, **PS-12** (25 mol%) afforded the Michael adduct **15a** in quantitative yield and 98% *ee* in

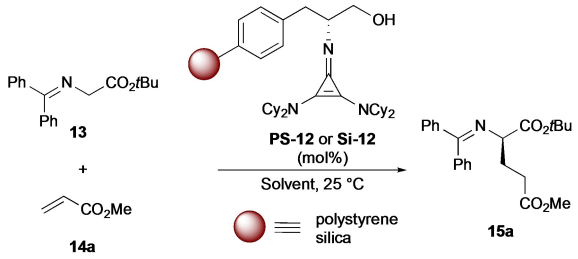


Scheme 4. Synthesis of silica-supported cyclopropenium salt pre-catalyst **Si-9** and cyclopropenimine superbase **Si-12**.

16 h using EtOAc as the solvent (entry 1). With the aim to improve the conversion efficiency of **PS-12**, the solvent effect was also examined (entries 2–5). The diffusion and adsorption of reactive species over the matrix surface is, in fact, strictly dependent on the reaction medium, affecting the catalytic performance of immobilized (organo)catalysts significantly.[14] A brief screening of aprotic solvents with different polarity confirmed EtOAc as the best performing medium. Additionally, the increase of temperature to 45 °C left the reaction conversion almost unchanged but determined a rather lower enantioselectivity (95% *ee*, entry 6).

In parallel experiments (entries 7–9), we found that the silica-supported cyclopropenimine **Si-12** (25 mol%) behaved quite similarly to **PS-12**, as the adduct **15 a** was formed in quantitative yield and 98% *ee* using EtOAc as the preferred solvent (entry 7). Gratifyingly, this result validated our catalyst design criteria based on utilization of a quite flexible spacer to maintain the local molecular structure of the chiral cyclopropenimine moiety and avoid disruption of the transition state organization by H-bonding with the free hydroxyl groups of the silica support. Notably, a significant difference in reusability was observed for **PS-12** and **Si-12**. Recycling tests were performed by treating the recovered catalyst with 0.05 M LiOH (MeOH) to completely restore the active cyclopropenimine free base after each run (poorer results were detected with the simply washed and filtered catalyst). Indeed, while the enantioinduction ability of both **PS-12** and **Si-12** was kept almost unaltered after five runs, the conversion efficiency of **PS-12** markedly decreased after the first recycle (68%, entry 10); by contrast, **Si-12** could be reused five times without considerable deactivation (entry 13).[23] In addition, the extension of the reaction time to 24 h allowed the reduction of **Si-12** loading to 15 mol% with little variation of reaction yield (entry 14) and maintenance of recycling performance (entries 15 and 16). Overall, these results indicated **Si-12** as the more effective heterogeneous bifunctional superbase organocatalyst with an accumulated turnover number (TON) of 27.1 (Figure 3). Remarkably, the catalytic

Table 2. Activity and recyclability test with **PS-12** and **Si-12**.[a]



Entry	Catalyst (mol%)	Solvent	Time (h)	**15 a** (%)[b]	*ee* (%)[c]
1	**PS-12** (25)	EtOAc	16	>95	98
2	**PS-12** (25)	THF	16	51	98
3	**PS-12** (25)	Toluene	16	70	52
4	**PS-12** (25)	DCM	16	10	68
5	**PS-12** (25)	Et_2O	16	27	98
6[d]	**PS-12** (25)	EtOAc	16	>95	95
7	**Si-12** (25)	EtOAc	16	>95	98
8	**Si-12** (25)	Toluene	16	43	74
9	**Si-12** (25)	Et_2O	16	>95	97
10[e]	**PS-12** (25)	EtOAc	16	68	98
11[f]	**PS-12** (25)	EtOAc	16	17	95
12[e]	**Si-12** (25)	EtOAc	16	92	98
13[f]	**Si-12** (25)	EtOAc	16	83	98
14	**Si-12** (15)	EtOAc	24	92	98
15[e]	**Si-12** (15)	EtOAc	24	90	98
16[f]	**Si-12** (15)	EtOAc	24	77	98
17[g]	**Si-12** (15)	EtOAc	24	91	98
18[h]	**Si-12** (15)	EtOAc	24	93	98

[a] Reaction conditions: **13 a** (0.07 mmol), **14 a** (0.21 mmol), solvent (0.5–1.5 mL).
[b] Detected by ^{1}H NMR analysis of the crude reaction mixture.
[c] Determined by chiral stationary phase HPLC.
[d] Reaction performed at 45 °C
[e] First recycle.
[f] Forth recycle.
[g] Reaction run with catalyst stored at 0 °C for one week.
[h] Gram-scale experiment: **13 a** (3.39 mmol).

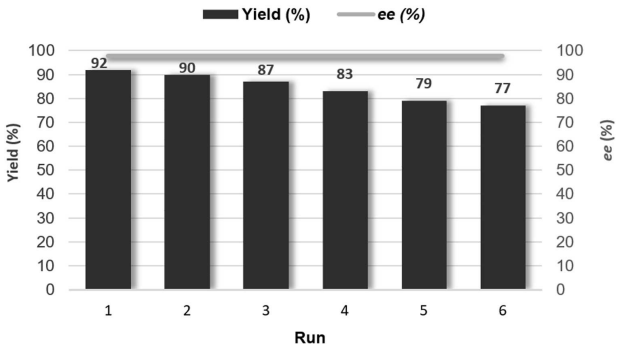


Figure 3. Recycling experiments (**13**/**14a** coupling with 15 mol% of **Si-12**).

activity of **Si-12** remained unchanged over several days when kept at 0 °C, as confirmed by a control reaction promoted by a sample of **Si-12** stored in the fridge for one week (entry 17). Finally, the successful gram-scale experiment of entry 18 indicated the potential of **Si-12** for practical applications.

The structural analysis of the stable silica-supported pre-catalyst **Si-9** was performed by FTIR spectroscopy (Supporting Information) and by a preliminary high-resolution magic angle spinning (HR-MAS) NMR study based on the direct comparison with a homogeneous precursor. Figure 4a illustrates the ^{1}H NMR

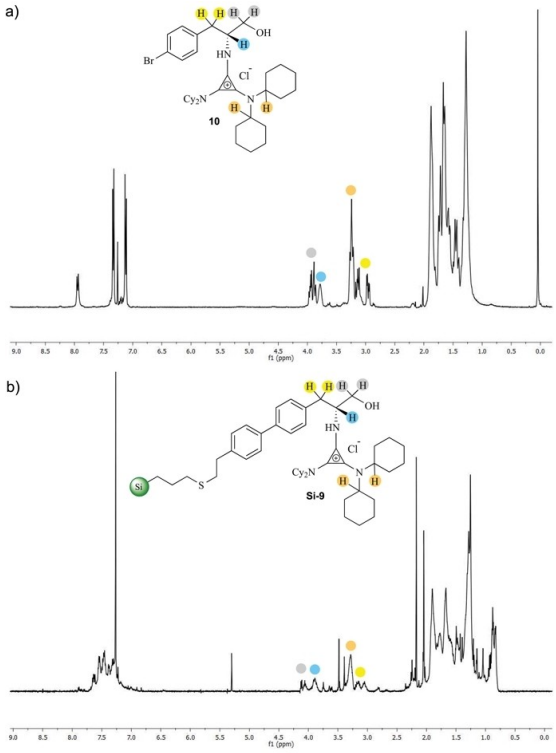


Figure 4. ^{1}H NMR spectrum ($CDCl_3$) of **10** (a); CPMG filtered ^{1}H HR-MAS-NMR spectrum ($CDCl_3$) of **Si-9** (b).

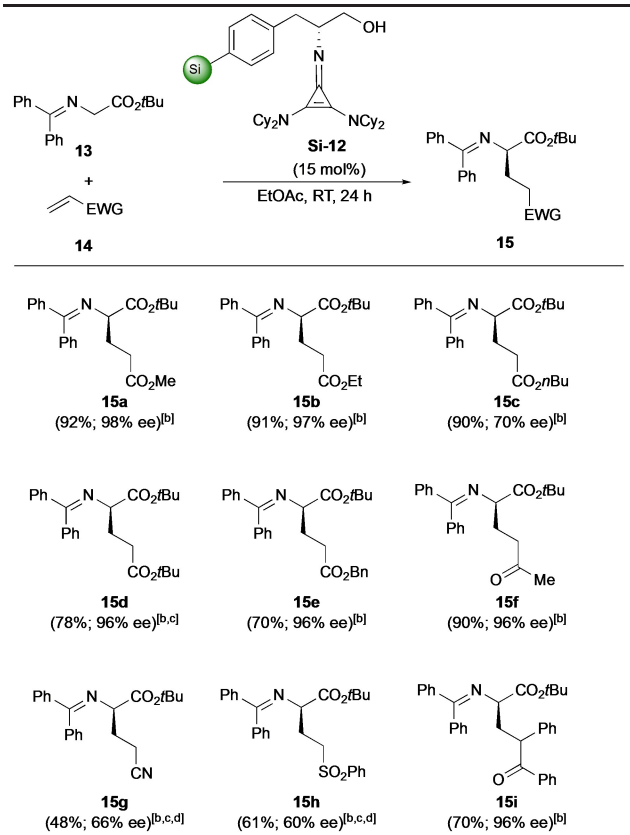
spectrum of the soluble cyclopropenium salt **10** and the assignment of the diagnostic signals associated to the protons of the alaninol and cyclohexyl units ($\delta =$ 4.0–2.5 ppm). The CPMG filtered ^{1}H HR-MAS-NMR spectrum of **Si-9** (Figure 4b) displays a high degree of homology with that of **10**, thus allowing to confirm the covalent immobilization of the cyclopropenium moiety on support through the thioether linkage. The complete activation of **Si-9** by the optimized basic procedure was confirmed by ^{1}H HR-MAS-NMR analysis of **Si-12**, detecting the expected upfield shift of the alaninol diagnostic peaks (Supporting Information). Formation of the cyclopropenimine unit on support was further demonstrated by argentometric titration,[24] which did not reveal any significant amount of chloride anion left in **Si-12** (Experimental Section).

In analogy with the homogeneous study, the catalytic performance of **Si-12** was tested in the reaction of glycine imine **13** with different Michael acceptors **14a–i** (Table 3). Satisfyingly, heterogeneous **Si-12** behaved very similarly to the soluble Lambert catalyst in all the substrate combinations investigated (comparable results in terms of yield and enantioselectivity were also detected for **PS-12**). Indeed, ethyl, *n*-butyl, *t*-butyl, and benzyl acrylates effectively participated in the conjugate addition furnishing the products **15b–e** in good to high yields and with excellent enantioselectivities apart from **15c** (70% *ee*). Methyl vinyl ketone, acrylonitrile, and phenyl vinyl sulfone afforded the corresponding adducts **15f**, **15g** and **15h** in lower yields but still satisfactory enantioselectivities (60–96% *ee*). Finally, chalcone resulted a suitable substrate as well yielding **15i** as a sole diastereoisomer (d.r. > 19:1) with high enantioselectivity (96% *ee*).

Asymmetric catalysis promoted by heterogeneous organo-superbases in continuous-flow (CF) regime is a completely unexplored area of research, which may offer new opportunities for the efficient production of high added-value chiral molecules such as enantioenriched synthons and active pharmaceutical ingredients (APIs).[11]

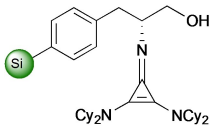
Therefore, driven by our experience in process intensification by fabrication of organocatalytic fixed-bed mesoreactors,[16] we next investigated the transition of the model Michael addition from batch to continuous-flow conditions. Accordingly, the silica-supported cyclopropenimine **Si-12** (loading 0.47 mmol g^{-1}) was selected as the packing material (pore size 60 Å, particle size ~50 mm, superficial area 500 m^2 g^{-1}) in virtue of its superior stability compared to the polystyrene analogue. Then, the mesoreactor **R** was fabricated by slurry packing **Si-12** (EtOAc as solvent) into a pressure-resistant stainless-steel column (length 10 cm, 0.46 cm internal diameter); the hold-up (dead) volume (V_0) and the total porosity (ε_{tot}) of reactor **R** were determined by pycnometry measurements, thus permitting the calculation of the residence time at different flow rates (Table 4).

Table 3. Scope of the Michael addition of glycine imine **13** with different acceptors **14** catalyzed by **Si-12** under batch conditions.[a]



[a] Reaction conditions: **13** (0.10 mmol), **14** (0.30 mmol), EtOAc (0.5 mL).
[b] In bracket: isolated yield and enantiomeric excess as determined by chiral stationary phase HPLC.
[c] Reaction time: 48 h.
[d] **Si-12**: 25 mol%.

Table 4. Main features of packed-bed mesoreactor **R**.

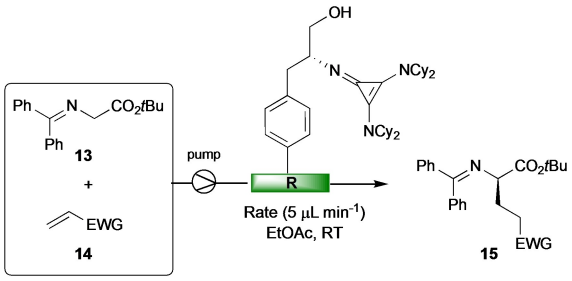


Si-12 [g][a]	V_G [mL][b]	V_o [mL][c]	Total Porosity[d]	Time [min][e]	*p* [bar][f]
1.50	1.66	1.16	0.70	116	5

[a] Loaded catalyst: calculated by difference with catalyst amount in the residual slurry solution.
[b] Geometric volume (V_G) of the stainless-steel column.
[c] Void volume (V_0) determined by pycnometry.
[d] Total porosity $\varepsilon_{tot} = V_0/V_G$.
[e] Residence time (t_0) calculated at 10 µL min^{-1}.
[f] Backpressure measured at 50 µL min^{-1} (RT, EtOAc).

Flow experiments were aimed at reaching complete conversion of glycine imine **13** in single pass-flow mode to facilitate the purification of the adduct **15 a** by simple evaporation of the solvent and excess acrylate **14 a** (Table 5). After some experimentation, the optimal turnover frequency (TOF) was achieved by pumping a solution in EtOAc of **13** (0.04 M) and **14 a** (0.12 M) with a flow rate of 5 µL min^{-1} (**15 a**: 0.43 mmol$_{prod}$ d^{-1} mmol$_{cat}^{-1}$; entry 1). While a quite long residence time (t_0 = 232 min) was required to get full consumption of imine **13** (steady-state regime in ~5 h), the mesoreactor **R** could be operated for additional 24 h with unaltered values of conversion efficiency (>95%) and enantioselectivity (98% *ee*; Figure 5-blue line). After that time, however, a progressive loss of productivity was observed (~50% conversion at 48 h). Importantly, the catalytic activity of the packing material **Si-12** could be completely restored by feeding **R** with a 0.05 M solution of LiOH in anhydrous methanol, as confirmed by the subse-

Table 5. Continuous-flow production of Michael addition products **15**.[a]



Entry	**13** (*c* [M])	**14** (*c* [M])	**15** (conv.[%])[b]	*ee* (%)[c]	TOF[d]
1	0.04	**14 a** (1.20)	**15 a** (>95)	98	0.43
2[e]	0.04	**14 a** (1.20)	**15 a** (95)	98	0.41
3	0.04	**14 b** (1.20)	**15 b** (95)	97	0.41
4	0.04	**14 c** (1.20)	**15 c** (92)	70	0.4
5	0.03	**14 d** (1.20)	**15 d** (90)	96	0.29
6	0.03	**14 e** (1.20)	**15 e** (91)	96	0.29

[a] See the Experimental section for a description of the flow apparatus.
[b] Instant conversion in the steady-state regime as determined by ^{1}H NMR analysis
[c] Determined by chiral stationary phase HPLC.
[d] Turnover frequency (TOF) is measured in mmol$_{prod}$ d^{-1} mmol$_{cat}^{-1}$.
[e] Experiment run with regenerated **R** (see the Experimental Section for details).

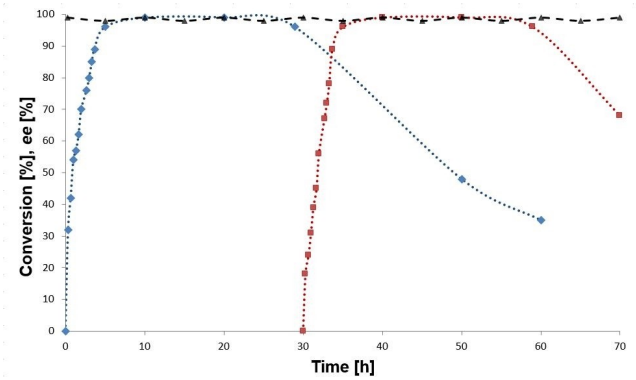


Figure 5. Long-term stability experiment (**13/14 a** coupling). Conversion [%], dotted line; *ee* [%], dashed line. In blue color: experiment run with fresh packing material **Si-12**. In red color: experiment run with regenerated packing material **Si-12**.

quent **13/14 a** coupling performed with the regenerated reactor (entry 2; Figure 5-red line). Satisfyingly, the selected acceptors **14 b–e** also reacted with glycine imine **13** with high instant conversions (>90%) by suitably adjusting the initial reagent concentrations (flow rate: 5 μL min^{-1}; entries 3–6).

Conclusion

In summary, we have presented polystyrene- and silica-supported versions of the valuable cyclopropenimine Lambert catalyst, which have been demonstrated to be active in Michael additions with levels of enantioselectivity comparable to those achieved with the homogeneous counterpart. Crucial for the success of our research has been the identification of suitable conditions for the conversion of the cyclopropenium salt pre-catalyst into the active cyclopropenimine promoter in the heterogeneous phase. A good recyclability of the silica-based catalyst was detected in batch experiments, thus paving the way for its utilization as packing material of fixed-bed mesoreactors for the continuous-flow production of Michael adducts with high enantiomeric purity. To the best of our knowledge, the application of heterogeneous superbase organocatalysts in stereoselective flow processes is unprecedented in the literature; therefore, we believe that the herein disclosed silica-supported Lambert catalyst might represent a new opportunity for further progress in the field of asymmetric Brønsted base catalysis.

Experimental Section

General Information. All moisture-sensitive reactions were performed under an argon atmosphere using oven-dried glassware. Solvents were dried over a standard drying agent and freshly distilled prior to use. Reactions were monitored by TLC on silica gel 60 F_{254} with detection by charring with potassium permanganate or phosphomolybdic acid. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Optical rotations were measured at 25±2 °C in the stated solvent; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} (concentration *c* given as g/100 mL). ^{1}H (300 MHz), ^{1}H (400 MHz), ^{13}C (101 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ solution at room temperature. The chemical shifts in ^{1}H and ^{13}C NMR spectra were referenced to trimethylsilane (TMS). Peak assignments were aided by ^{1}H-^{1}H COSY and gradient HMQC experiments. Enantiomeric excess (*ee* %) was evaluated by HPLC using Lux amylose 2 column. CPMG filtered ^{1}H HR-MAS NMR experiments were registered in $CDCl_3$ at 499.84 MHz Larmor frequency and 2 KHz spinning frequency with Agilent DD2 NMR System, PremiumCompact superconducting magnet 11.7 Tesla (54-mm bore, 500 MHz 1H) equipped with an Agilent Nanoprobe. FT-IR analyses were performed using the Bruker Instrument Vertex 70. Elemental analyses were performed using a FLASH 2000 series CHNS/O analyzer (ThermoFisher Scientific). ESI-MS routine analyses were performed in positive ion mode with samples dissolved in 10 mM solution of ammonium formate in 1:1 MeCN/H_2O. For high resolution mass spectrometry (HRMS), the compounds were analyzed in positive ion mode using an Agilent 6520 HPLC-Chip Q/ TOF-MS (nanospray) with a quadrupole, a hexapole, and a time-of-flight unit to produce the spectra. The capillary source voltage was set at 1700 V; the gas temperature and drying gas were kept at 350 °C and 5 L min^{-1}, respectively. The MS analyzer was externally calibrated with ESI–L low concentration tuning mix from m/z 118 to 2700 to yield accuracy below 5 ppm. Accurate mass data were collected by directly infusing samples in 40/60 H_2O/ACN 0.1% TFA into the system at a flow rate of 0.4 μL min^{-1}. All commercially available compounds were used as received. Amino alcohol **1** was synthetized following a literature procedure.[19] Chloro[bis(dicyclohexylamino)]cyclopropenium chloride **8** was synthetized following a literature procedure.[17b] Mercaptopropyl silica gel was prepared according to a literature procedure.[16b]

***tert*-Butyl (*R*)-4-(4-bromobenzyl)-2,2-dimethyloxazolidine-3-carboxylate (4)**. Amino alcohol **1** (1.35 g, 5.87 mmol) was dissolved in anhydrous THF (15.0 mL, 0.40 M) in an oven dried round bottom flask and the solution was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. Triethylamine (0.80 mL, 8.87 mmol) was added, and the reaction was cooled to 0 °C. Later, an anhydrous solution of di(*tert*)-butyl dicarbonate in THF (3 mL, 1.75 M, 5.87 mmol) was added and the reaction was allowed to reach room temperature. The formation of the product was monitored through ^{1}H NMR and after 3 h the solvent was removed under vacuum. The residue was taken up with dichloromethane (10 mL), washed with $NaHCO_3$ saturated solution (3×20 mL) and dried. After the solution was filtered, removal of the solvent afforded the Boc-protected amino alcohol *tert*-butyl (*R*)-(1-(4-bromophenyl)-3-hydroxypropan-2-yl)carbamate (1.72 g, 88%) as an amorphous white solid with spectroscopic data in accordance with the literature.[4]

The protected amino alcohol (952 mg, 2,88 mmol) was then dissolved in anhydrous dichloromethane (20 mL) under inert atmosphere and the solution was cooled to 0 °C. Later, 2-methoxypropene (0.69 mL, 7.21 mmol) and camphorsulfonic acid (67 mg, 0.29 mmol) were added and the reaction was allowed to stir at 0 °C for almost 2 h until complete by NMR

analysis. The mixture was sequentially washed with $NaHCO_3$ saturated solution (15 mL) and water (15 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give compound **4** (853 mg, 80%) as a yellowish oil. $[\alpha]_D = 35.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 2H, ArH), 7.09 (m, 2H, ArH), 4.12–3.87 (m, 1H, $NCHBnCH_2O$), 3.79 (dd, $J = 9.2$, 5.5 Hz, 1H, $NCHBnCH_2O$), 3.71 (d, $J = 9.2$ Hz, 1H, $NCHBnCH_2O$), 3.19 (s, 1H, CH_2Ph), 3.16–2.98 (m, 1H, CH_2Ph), 2.63 (dd, $J = 12.9$, 10.3 Hz, 1H), 1.59–1.44 (m, 15H, $C(CH_3)_3$, $NC(CH_3)_2O$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1*, 137.4, 131.7* (2 C), 131.0 * (2 C), 120.4*, 94.1*, 80.2*, 65.7*, 58.9, 39.0 *, 28.4* (3 C), 26.9*, 24.5* (* signals appear as doublet due to the presence of conformers). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{16}BrNO$ 269.0415; found: 269.0456.

***tert*-Butyl (*R*)-2,2-dimethyl-4-((4′-vinyl-[1,1′-biphenyl]-4-yl) methyl)oxazolidine-3-carboxylate (5)**. Protected amino alcohol **4** (0.60 g, 1.62 mmol), $PdCl_2(PPh_3)_2$ (57 mg, 0.08 mmol, 5 mol%), 4-vinyl phenylboronic acid **2** (0.36 g, 2.43 mmol), and potassium phosphate (0.69 g, 3.24 mmol) were loaded into a glass vial. Subsequently, freshly distilled THF (10 mL) was added, followed by degassed water (3.4 mL). The mixture was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. Later, the vial was sealed, and the reaction mixture was stirred at 60 °C. After 6 h, an additional amount of 4-vinyl phenylboronic acid (0.20 g, 1.35 mmol) and $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol) was added. The mixture was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times and let stirring at 60 °C for 16 h. The reaction was then cooled to room temperature, quenched with water (7.0 mL), and extracted with EtOAc (2 × 7.0 mL). The combined organic phases were dried over Na_2SO_4, concentrated, and purified by flash silica column chromatography (9:1 cyclohexane: EtOAc) to give **5** (570 mg, 80%) as a pale yellow amorphous solid. $[\alpha]_D = 31.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, $J = 8.0$ Hz, 4H, ArH), 7.48 (d, $J = 8.0$ Hz, 2H, ArH), 7.37–7.26 (m, 2H, ArH), 6.75 (dd, $J = 17.5$, 11.0 Hz, 1H, $ArCHCH_2$), 5.79 (d, $J = 17.5$ Hz, 1H, $PhCHCH_2$), 5.27 (d, $J = 11.0$ Hz, 1H, $ArCHCH_2$), 4.25–3.94 (m, 1H, $NCHBnCH_2O$), 3.81 (d, $J = 3.1$ Hz, 2H, $NCHBnCH_2O$), 3.36–3.04 (m, 1H, CH_2Ph), 2.82–2.61 (m, 1H, CH_2Ph), 1.62–1.44 (m, 15H, $C(CH_3)_3$, $NC(CH_3)_2O$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.8*, 140.2, 139.0, 138.9, 137.8, 136.5, 129.8* (2 C), 127.2 (2 C), 127.1 (2 C), 126.7 (2 C), 114.0, 94.2*, 79.8*, 66.2*, 59.3, 39.4*, 28.7* (3 C), 27.0*, 23.4 (* signals appear as doublet due to the presence of conformers). HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{20}H_{23}NO$ 293.1780; found: 293.1731.

(**PS-6**). A homogeneous mixture of styryl derivative **5** (0.30 mg, 0.76 mmol), styrene (0.61 mL, 5.30 mmol), divinylbenzene (0.21 µL, 1.51 mmol), toluene (0.30 mL, 2.83 mmol), 1-dodecanol (1.57 mL, 7.06 mmol), and AIBN (10 mg, 0.06 mmol) was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was then poured into a glass column sealed at both ends (placed in vertical position) and heated at 60 °C in a standard oven for 16 h. After cooling of the reaction column, the glass was broken, and the resulting monolith **PS-6** was triturated to obtain a yellow powder. This powder was suspended in THF (5.0 mL) and centrifuged with portions of THF (4 × 5.0 mL). The composition of the collected supernatants was analyzed by ^1H NMR to confirm the full incorporation of the monomer **5** into the polymer. After vacuum drying (0.1 mbar, 40 °C, 6 h), **PS-6** resin was further submitted to elemental and FT-IR analyses. Elemental analysis (%) found: N 0.95 (*loading* = 0.68 mmol g^{-1}); FT-IR (KBr) ν 1699 (C=O), 1602 (C=C) cm^{-1}.

(**PS-7**). **PS-6** (0.30 g, *loading* = 0.68 mmol g^{-1}) was suspended in a 1:1 $CHCl_3$: TFA mixture (10 mL) and stirred at 50 °C for 4 days. After cooling, the solvent was removed under vacuum. The resin was suspended in THF (5.0 mL) and sequentially centrifuged with portions of THF (3 × 7.0 mL), 1:1 THF:Et_3N (3 × 7.0 mL), 1:1 THF:EtOH (3 × 7.0 mL), THF (1 × 7.0 mL) and *n*-hexane (1 × 7.0 mL). After vacuum drying (0.1 mbar, 40 °C, 6 h), **PS-7** resin was further submitted to elemental and FT-IR analyses. Elemental analysis (%) found: N 0.92 (*loading* = 0.65 mmol g^{-1}); FT-IR (KBr): ν 3580 (N–H), 3424 (O–H) cm^{-1}. Furthermore, complete deprotection has been corroborated by mean Kaiser test on the resin. Accordingly, **PS-7** (2 mg) was suspended in 1 mL of deionized water followed by 1 mL of acetate buffer (pH = 5.5). The resulting suspension was sonicated for 15 minutes; Then, 1 mL of a solution of KCN in pyridine (0.03 M) and 1 mL of a solution of phenol (0.04 M) was added and the suspension was heated at 120 °C for 10 minutes. After that, 1 mL of ninhydrin solution (5% in EtOH) was added and heated for additional 10 minutes. The suspension was allowed to cool and 5 mL of the EtOH/water solution (3:2 v/v) was added. The solid was separated by centrifugation and the resulting supernatant was analyzed by UV-vis spectrometer. The primary amine loading was obtained by matching the Abs of genuine sample with the calibration curve (benzylamine as standard) following the protocol reported by Krueger.[21] Kaiser test (*loading* = 0.62 mmol g^{-1}).

(**PS-9**). *Route A* (Scheme 2). **PS-7** (80 mg, *loading* = 0,65 mmol g^{-1}) was suspended in anhydrous $CHCl_3$ followed by the addition of cyclopropenium salt **8** (39 mg, 0,10 mmol) and stirred at 60 °C. After 16 h triethylamine (17 µL, 0.12 mol) was added and stirred at 60 °C for three days. After cooling, the resulting **PS-9** was centrifugate and washed with THF (3 × 9.0 mL) and *n*-hexane (1 × 9.0 mL). The composition of the collected supernatants was analyzed by ^1H NMR. After vacuum drying (0.1 mbar, 40 °C, 6 h), **PS-7** resin was further submitted to elemental and FT-IR analyses. Elemental analysis (%) found: N 1.10 (*loading* = 0.13 mmol g^{-1}); FT-IR (KBr): ν 3582 (N–H), 3424 (O–H) cm^{-1}.

Route B (Scheme 3). A homogeneous mixture of styryl derivative **11** (533 mg, 0.76 mmol), styrene (0.35 mL, 3.05 mmol), divinylbenzene (0.12 mL, 0.87 mmol), toluene (0.21 mL, 2.64 mmol), 1-dodecanol (1.09 mL, 7.03 mmol), and AIBN (7.0 mg, 0.04 mmol) was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was then poured into a glass column sealed at both ends (placed in vertical position) and heated at 80 °C in a standard oven for 24 h. After cooling of the reaction column, the glass was broken, and the resulting monolith **PS-9** was triturated to obtain a yellow powder. This powder was suspended in THF (5.0 mL) and centrifuged with portions of THF (4 × 5.0 mL). The composition of the collected supernatants was analyzed by ^1H NMR to confirm the full incorporation of the monomer **11** into the polymer **PS-9**. After vacuum drying (0.1 mbar, 40 °C, 6 h), **PS-9** resin was further

submitted to elemental and FT-IR analyses. Elemental analysis (%) found: N 1.95 (*loading* = 0.45 mmol g^{-1}); FT-IR (KBr): ν 3585 (N–H), 3421 (O–H) cm^{-1}.

(*R*)-2-((2,3-Bis(dicyclohexylamino)cycloprop-2-en-1-ylidene) amino)-3-(4-bromophenyl)propan-1-ol hydrochloride salt (10). The amino alcohol **1** (300 mg, 1.30 mmol) was dissolved in anhydrous dichloromethane (13.0 mL) followed by the addition of chloro[bis(dicyclohexylamino)]cyclopropenium chloride **8** (0.51 g, 1.18 mmol) and the solution was stirred at room temperature for 16 h. Then, the crude reaction mixture was washed with 1.0 M HCl (3 × 15 mL), dried with anhydrous sodium sulfate and concentrated in vacuo to yield cyclopropenimine hydrochloride salt **10** at least 90% pure (^{1}H NMR analysis) as a white amorphous solid (0.81 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.8 Hz, 1H, NH), 7.33 (d, J = 8.2 Hz, 2H, ArH), 7.12 (d, J = 8.2 Hz, 2H, ArH), 3.92 (m, 2H, $NCHBnCH_2OH$), 3.78 (bs, 1H, $NCHBnCH_2OH$), 3.24 (m, 4H, NCyH), 3.14 (dd, J = 13.8, 9.4 Hz, 1H, CH_2Ph), 2.96 (dd, J = 13.8, 5.0 Hz, 1H, CH_2Ph), 1.94–1.19 (m, 40H, NCyH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 131.4 (2 C), 131.3 (2 C), 120.2, 117.1, 114.8 (2 C), 64.1, 61.7, 59.5 (4 C), 37.7, 32.4 (4 C), 32.2 (4 C), 25.7 (4 C), 25.7 (4 C), 24.6 (4 C). ESI MS (642.4): 642.2 (M−Cl).

Thermal stability of **10**. Adduct **10** (20 mg, 0.03 mmol) was loaded into a glass vial. Subsequently, anhydrous THF (2.0 mL) was added. The mixture was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. Later, the vial was sealed, and the reaction mixture was stirred at 80 °C for 20 h. Then, the crude reaction mixture was concentrated *in vacuo* to yield cyclopropenimine hydrochloride salt **10** whose 1H NMR was identical to that of the authentic sample before thermal treatment.

(*R*)-2-((2,3-Bis(dicyclohexylamino)cycloprop-2-en-1-ylidene) amino)-3-(4′-vinyl-[1,1′-biphenyl]-4-yl)propan-1-ol hydrochloride salt (11). Adduct 10 (600 mg, 0.90 mmol), $PdCl_2(PPh_3)_2$ (30 mg, 0.04 mmol, 5 mol%), 4-vinyl phenylboronic acid 2 (268 mg, 1.8 mmol), and potassium phosphate (384 mg, 1.81 mmol) were loaded into a glass vial. Subsequently, freshly distilled THF (6.5 mL) was added, followed by degassed water (2.1 mL). The mixture was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. Later, the vial was sealed, and the reaction mixture was stirred at 80 °C for 16 h. The reaction was then cooled to room temperature and the layers separated. The combined organic phases were dried over Na_2SO_4, concentrated, and purified by washing with Et_2O (2 × 3 mL) to give 11 (554 mg, 90%) at least 90% pure (^{1}H NMR analysis) as a dark yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66–7.40 (m, 6H, ArH), 7.29 (d, J = 8.2 Hz, 2H, ArH), 6.74 (dd, J = 17.6, 10.8 Hz, 1H, $ArCHCH_2$), 5.78 (d, J = 17.6 Hz, 1H, $ArCHCH_2$), 5.27 (d, J = 10.8 Hz, 1H, $ArCHCH_2$), 4.07 (m, 1H, $NCHBnCH_2OH$), 3.90 (m, 2H, $NCHBnCH_2OH$, $NCHBnCH_2OH$), 3.26 (dd, J = 16.1, 7.8 Hz, 4H, NCyH), 3.19–2.97 (m, 2H, CH_2Ph), 1.98–1.13 (m, 40H, NCyH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.0, 138.8, 137.4, 136.5, 132.0* (2 C), 129.9* (2 C), 128.6* (2 C), 126.7* (2 C), 117.1, 115.7, 114.9, 114.0, 63.9, 61.8, 59.4(4 C), 58.3,38.3, 33.0 (4 C), 32.3* (4 C), 26.6 (4 C), 25.6* (4 C), 24.7 (4 C) (*signals appear as doublet due to the presence of conformers). ESI MS (666.5): 664.2 (M−Cl).

(PS-12). Cyclopropenimine supported-catalyst **PS-12** was obtained by suspending the corresponding hydrochloride salt **PS-9** (80 mg, *loading* = 0.45 mmol g^{-1}) in 0.05 M LiOH solution in MeOH (2.0 mL). The mixture was stirred at room temperature for 30 minutes. Then the solution was centrifugated and the catalyst was suspended in a fresh portion of 0.05 M LiOH solution in MeOH (2.0 mL). The mixture was stirred at room temperature for other 30 minutes. After centrifugation and removal of the basic solution, the resin was sequentially washed with MeOH (2 × 9.0 mL), THF (3 × 9.0 mL) and EtOAc (1 × 9.0 mL). Later, after drying, activated polystyrene supported cyclopropenimine superbase **PS-12** was directly used as catalyst. Elemental analysis (%) found: N 1.94 (*loading* = 0.45 mmol g^{-1}); FT-IR (KBr) ν 3306 (O–H), 2924 (C–H) cm^{-1}.

(Si-9). A stirred solution of **11** (240 mg, 0.35 mmol), 3-mercaptopropyl silica gel (266 mg, 0.24 mmol, *loading* = 1.11 mmol g^{-1}), AIBN (39 mg, 0.24 mmol), and anhydrous toluene (2.0 mL) was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred and heated to 90 °C overnight. After cooling to room temperature, the mixture was centrifuged with fresh portions of THF (4 × 5 mL) and Et_2O (2 × 5 mL). The resulting silica-supported pre-catalyst **Si-9** was finally dried (0.1 mbar, 40 °C, 6 h) and submitted to elemental and FT-IR analyses FT-IR (KBr): ν = 3440 (N–H), 2997 (C–H) cm^{-1}. Elemental analysis (%) found N 1.98 (loading = 0.47 mmol g^{-1}). Similar loading was obtained by argentometric titration; 0.2 g of **Si-9** was suspended in 1 mL of water. Then, 0.2 g of $NaNO_3$ was added and the suspension was kept stirring for 5 hours. Then, the mixture was titrated by 0.005 M of $AgNO_3$ solution with potassium chromate as indicator (loading = 0.45 mmol g^{-1}).

(Si-12). Cyclopropenimine supported-catalyst **Si-12** was obtained by suspending the corresponding hydrochloride salt **Si-9** (80 mg, *loading* = 0.47 mmol g^{-1}) in 0.05 M LiOH solution in MeOH (2.0 mL). The mixture was stirred at room temperature for 30 minutes. Then the solution was centrifugated and the catalyst was suspended in a fresh portion of 0.05 M LiOH solution in MeOH (2.0 mL). The mixture was stirred at room temperature for other 30 minutes. After centrifugation and removal of the basic solution, the resin was sequentially washed with MeOH (2 × 9.0 mL), THF (3 × 9.0 mL) and EtOAc (1 × 9.0 mL). Later, after drying, activated silica supported cyclopropenimine superbase **Si-12** was directly used as catalyst. Elemental analysis (%) found N 1.96 C 27.38 H 3.43 S 2.56 (*loading* = 0.47 mmol g^{-1}). FT-IR (KBr) ν 2937 (C–H), 2856 (C–H) cm^{-1}. Argentometric titration was performed on **Si-12** as described for **Si-9** observing no chloride anion left after basic treatment.

General procedure for the synthesis of racemic 15. Derivative **13** (40 mg, 0.14 mmol) and CsOH (20 mg, 0.14 mmol) were dissolved in anhydrous toluene (1.0 mL). Michael acceptor (0.20 mmol, 1.5 equiv.) **14** was then added to the vial and the reaction solution was stirred at room temperature. Upon complete consumption of starting material (^{1}H NMR analysis), the reaction solution was concentrated, and the crude material was purified by flash silica column chromatography.

General procedure for the synthesis of 15 under batch conditions. Si-12 (32 mg, loading = 0.47 mmol g^{-1}, 15 mol%) or **PS-12** (55 mg, loading = 0.45 mmol g^{-1}, 25 mol%) were suspended in anhydrous EtOAc (0.5 mL for **Si-12**; 1.5 mL for

PS-12). Then, **13** (20 mg, 0.10 mmol) and the Michael acceptor **14** (0.30 mmol) were added to the vial and the reaction was degassed under vacuum and saturated with argon (by an Ar-filled balloon) three times. The mixture was stirred at room temperature for 24 h. Then, the mixture was centrifuged with fresh portions of THF (4×7.0 mL) and Et_2O (2×7.0 mL). The collected supernatants were concentrated under vacuum and elution of the resulting residue from a column of silica with the suitable elution system afforded **15**.

(*R*)-1-*tert*-Butyl-5-methyl 2-(diphenylmethyleneamino) pentanedioate (15a). Column chromatography on silica gel (9:1 cyclohexane:EtOAc) afforded **15a** (35 mg, 92%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D$ = 73.2 (*c* 0.8 $CHCl_3$); CSP HPLC analysis Lux-Amylose-2 (92:8 hexane:IPA, flow rate 1 mL min^{-1}, 254 nm, 20 °C) t_R (*R*): 9.1 min, t_R (*S*): 10.5 min, 98.75:1.25 er; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.59 (m, 2H, ArH), 7.48–7.37 (m, 3H, ArH), 7.42–7.30 (m, 1H, ArH), 7.35–7.25 (m, 2H, ArH), 7.21–7.10 (m, 2H, ArH), 3.96 (dd, *J* = 6.8, 5.7 Hz, 1H, $HCCO_2tBu$), 3.59 (s, 3H, $–CH_2CH_2CO_2CH_3$) 2.42–2.32 (m, 2H, $–CH_2–$), 2.27–2.15 (m, 2H, $–CH_2–$), 1.44 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 173.7, 170.9, 170.8, 139.6, 136.6, 130.4, 128.9, 128.7, 128.6, 128.1, 127.9, 81.3, 64.9, 51.6, 30.6, 28.8, 28.2 (3 C); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{28}NO_4$ 382.4800; found: 382.4821. *Gram-scale experiment*: **13a** (1.00 g, 3.39 mmol), **Si-12** (1.08 g, loading = 0.47 mmol g^{-1}, 15 mol%), EtOAc (15 mL): **15a** (1.20 g, 93%; 98% *ee*).

(*R*)-1-*tert*-Butyl-5-ethyl 2-(diphenylmethyleneamino) pentanedioate (15b). Column chromatography on silica gel (9:1 cyclohexane:EtOAc) afforded **15b** (36 mg, 91%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D$ = 74.9 (*c* 1.2 $CHCl_3$); Chiral stationary phase HPLC analysis Lux-Amylose-2 (92:8 hexane:IPA, flow rate 1 mL min^{-1}, 270 nm, 20 °C) t_R (*R*): 8.7 min, t_R (*S*): 10.3 min, 98.32:1.68 er; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.71–7.62 (m, 2H, ArH), 7.49–7.42 (m, 3H, ArH), 7.42–7.37 (m, 1H, ArH), 7.37–7.30 (m, 2H, ArH), 7.23–7.14 (m, 2H, ArH), 4.06 (q, *J* = 7.1 Hz, 2H, $CO_2CH_2CH_3$), 3.98 (dd, *J* = 6.9, 5.7 Hz, 1H, $HCCO_2tBu$), 2.42–2.31 (m, 2H, $–CH_2–$), 2.30–2.15 (m, 2H, $–CH_2–$), 1.46 (s, 9H, $C(CH_3)_3$), 1.21 (t, *J* = 7.1 Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 170.2 (2 C), 170.0, 135.9 (2 C), 129.7, 128.2 (2 C), 128.0, 127.8 (2 C), 127.4 (2 C), 127.2 (2 C), 80.6, 64.3, 59.7, 30.2, 28.1, 27.5 (3 C), 13.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{24}H_{29}NO_4$ 396.2175; found: 396.2147.

(*R*)-1-*tert*-Butyl-5- butyl 2-(diphenylmethyleneamino) pentanedioate (15c). Column chromatography on silica gel (9:1 cyclohexane: EtOAc) afforded **15c** (38 mg, 90% yield) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D$ = 78.2 (*c* 1.4 $CHCl_3$); Chiral stationary phase HPLC analysis Lux-Amylose-2 (92:8 hexane:IPA, flow rate 1 mL min^{-1}, 254 nm, 20 °C) t_R (*R*): 8.3 min, t_R (*S*): 9.8 min, 84.72:15.28 er; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.64 (dd, *J* = 8.2, 1.4 Hz, 2H, ArH), 7.50–7.28 (m, 6H, ArH), 7.17 (dd, *J* = 6.7, 2.9 Hz, 2H, ArH), 4.09–3.87 (m, 3H, $HCCO_2tBu$, CO_2CH_2), 2.42–2.27 (m, 2H, $–CH_2–$), 2.27–2.15 (m, 2H, $–CH_2–$), 1.61–1.48 (m, 2H, $–CH_2–$), 1.44 (s, 9H, $C(CH_3)_3$), 1.39–1.20 (m, 2H, $–CH_2–$), 0.90 (t, *J* = 7.3 Hz, 3H, $–CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 173.2, 170.8, 170.6, 139.4, 136.5, 130.3, 128.8 (2 C), 128.5, 128.4 (2 C), 128.0 (2 C), 127.8 (2 C), 81.1, 64.9, 64.2, 30.8, 30.6, 28.7, 28.0 (3 C), 19.1, 13.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}NO_4$ 424.2488; found: 424.2450.

(*R*)-di-*tert*-Butyl 2-(diphenylmethyleneamino)pentanedioate (15d). Reaction time: 48 h. Column chromatography on silica gel (9:1 cyclohexane:EtOAc) afforded **15d** (33 mg, 78%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D$ = 79.3 (*c* 0.9 $CHCl_3$); Chiral stationary phase HPLC analysis Lux-Amylose-2 (92:8 hexane:IPA, flow rate 1 mL min^{-1}, 254 nm, 20 °C) t_R (*R*): 7.2 min, t_R (*S*): 8.6 min, 99.16:1.84 er; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.70–7.59 (m, 2H, ArH), 7.45–7.28 (m, 6H, ArH), 7.22–7.09 (m, 2H, ArH), 3.93 (dd, *J* = 14.0, 8.2 Hz, 1H, $HCCO_2tBu$), 2.34–2.22 (m, 2H, $–CH_2–$), 2.21–2.12 (m, 2H, $–CH_2–$), 1.43 (s, 9H, $C(CH_3)_3$), 1.38 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 172.4, 170.9, 170.5, 139.5, 136.5, 130.2, 128.8 (2 C), 128.5, 128.4 (2 C), 128.0 (2 C), 127.8 (2 C), 81.0, 80.1, 65.0, 32.0, 28.9, 28.0 (6 C); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{29}H_{32}NO_4$ 458.2331; found: 458.2322.

(*R*)-5-Benzyl-1-tert-butyl 2-(diphenylmethyleneamino) pentanedioate (15e). Column chromatography on silica gel (92:8 cyclohexane:EtOAc) afforded **15e** (32 mg, 70%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D$ = 57.3 (*c* 1.1 $CHCl_3$); Chiral stationary phase HPLC analysis Lux-Amylose-2 (92:8 hexane:IPA, flow rate 1 mL min^{-1}, 254 nm, 20 °C) t_R (*R*): 10.6 min, t_R (*S*): 13.5 min, 98.13:1.87 er; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.71–7.56 (m, 2H, ArH), 7.46–7.27 (m, 10H, ArH), 7.20–7.07 (m, 2H, ArH), 5.03 (s, 2H, CO_2CH_2Ph), 3.97 (dd, *J* = 7.0, 5.5 Hz, 1H, $HCCO_2tBu$), 2.47–2.36 (m, 2H, $–CH_2–$), 2.30–2.18 (m, 2H, $–CH_2–$), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 172.9, 170.7 (2 C), 139.4, 136.4, 135.9, 130.3, 128.8 (2 C), 128.5 (2 C), 128.5 (2 C), 128.4 (2 C), 128.1 (2 C), 128.0 (2 C), 127.7 (2 C), 81.2, 66.2, 64.8, 30.7, 28.6, 28.0 (3 C); HRMS(ESI$^+$): *m/z* $[M+H]^+$ calcd for $C_{26}H_{34}NO_4$ 424.2488; found: 424.2449.

(*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-5-oxohexanoate (15f). Column chromatography on silica gel (9:1 cyclohexane: EtOAc) afforded **15f** (33 mg, 90%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D$ = 64.3 (*c* 1.3 $CHCl_3$); Chiral stationary phase HPLC analysis Lux-Amylose-2 (92:8 hexane:IPA, flow rate 1 mL min^{-1}, 270 nm, 20 °C) t_R (*R*): 10.6 min, t_R (*S*): 12.5 min, 97.80:2.20 er; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.68–7.58 (m, 2H, ArH), 7.50–7.27 (m, 6H, ArH), 7.20–7.12 (m, 2H, ArH), 3.95 (t, *J* = 6.1 Hz, 1H, $HCCO_2tBu$), 2.61–2.41 (m, 2H, $–CH_2–$), 2.21–2.13 (m, 2H, $–CH_2–$), 2.12 (s, 3H, $–COCH_3$), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 208.3, 171.0, 170.5, 139.5, 136.5, 130.4, 128.8 (2 C), 128.7, 128.5 (2 C), 128.1 (2 C), 127.8 (2 C), 81.2, 64.8, 39.9, 30.0, 28.1 (3 C), 27.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{23}H_{28}NO_3$ 366.2069; found: 366.20780.

(*R*)-*tert*-Butyl 4-cyano-2-(diphenylmethyleneamino) butanoate (15g). Reaction time: 48 h. **Si-12**: 53 mg (25 mol%). Column chromatography on silica gel (9:1 cyclohexane:EtOAc) afforded **15g** (17 mg, 48%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D$ = 29.1 (*c* 1.2 $CHCl_3$); Chiral stationary phase HPLC analysis Lux-Amylose-2 (92:8 hexane:IPA, flow rate 1 mL min^{-1}, 254 nm, 20 °C) t_R (*R*): 9.8 min, t_R (*S*): 11.1 min, 82.82:17.18 er; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.71–7.59 (m, 2H, ArH), 7.53–7.29 (m, 6H, ArH),

7.24–7.13 (m, 2H, ArH), 4.05 (dd, $J=7.7$, 4.6 Hz, 1H, $HCCO_2{}^tBu$), 2.62–2.38 (m, 2H, $-CH_2-$), 2.38–2.10 (m, 2H, $-CH_2-$), 1.43 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 170.2, 139.5, 136.4, 131.0 (2 C), 129.2 (2 C), 129.0 (2 C), 128.4 (2 C), 128.0 (2 C), 119.8, 82.1, 64.1, 29.8, 28.3 (3 C), 14.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_2O_2^+$ 349.1916; found: 349.1929.

(*R*)-*tert*-Butyl 2-(diphenylmethyleneamino)-4-(phenylsulfonyl)butanoate (15h). Reaction time: 48 h. **Si-12**: 53 mg (25 mol%). Column chromatography on silica gel (45:55 cyclohexane:EtOAc) afforded **15h** (28 mg, 61%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] Chiral stationary phase HPLC analysis Lux-Amylose-2 (85:15 hexane:IPA, flow rate 1 mL min^{-1}, 240 nm, 20 °C) t_R (*R*): 9.6 min, t_R (*S*): 18.5 min, 80.02:19.98 er; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96–7.83 (m, 2H, ArH), 7.70–7.61 (m, 1H, ArH), 7.61–7.49 (m, 4H, ArH), 7.49–7.35 (m, 4H, ArH), 7.36–7.27 (m, 2H, ArH), 7.18–7.05 (m, 2H, ArH), 4.00 (dd, $J=6.6$, 5.0 Hz, 1H, $HCCO_2{}^tBu$), 3.38–3.12 (m, 2H, CH_2SO_2Ph), 2.31–2.04 (m, 2H, $CH_2CH_2SO_2Ph$), 1.39–1.36 (m, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 170.0, 139.1, 139.0, 136.2, 133.7, 130.7 (2 C), 129.4 (2 C), 128.9 (2 C), 128.7 (2 C), 128.2 (2 C), 128.1 (2 C), 127.7 (2 C), 81.80, 63.6, 52.9, 28.0 (3 C), 27.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{27}H_{30}NO_4S$ 464.1896; found: 464.1867.

***tert*-Butyl-2-(diphenylmethyleneamino)-5-oxo-3,5-diphenylpentanoate (15i)**. Column chromatography on silica gel (45:55 cyclohexane:EtOAc) afforded **15i** (35 mg, 70%) as a colorless oil with spectroscopic data in accordance with the literature.[6e] $[\alpha]_D=57.8$ (*c* 0.8 $CHCl_3$); Chiral stationary phase HPLC analysis Lux-Amylose-2 (85:15 Hexane:IPA, flow rate 1 mL min^{-1}, 240 nm, 20 °C) t_R major: 9.6 min, t_R minor: 18.5 min, 98.75:1.25 er; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02–7.89 (m, 2H, ArH), 7.74–7.61 (m, 2H, ArH), 7.57–7.49 (m, 1H, ArH), 7.49–7.27 (m, 8H, ArH), 7.21–7.05 (m, 5H, ArH), 6.77–6.61 (m, 2H, ArH), 4.26–4.10 (m, 2H, $NCHCO_2{}^tBu$, CHPh), 3.74 (dd, $J=16.9$, 9.5 Hz, 1H, CH_2COPh), 3.60 (dd, $J=16.9$, 3.6 Hz, 1H, CH_2COPh), 1.31 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 171.2, 170.1, 141.4, 139.4, 137.3, 136.4, 132.9 (2 C), 130.4, 128.9 (2 C), 128.6 (2 C), 128.5 (2 C), 128.4, 128.3 (2 C), 128.2 (2 C), 128.1 (2 C), 127.6 (2 C), 126.6, 81.4, 71.0, 44.8, 40.1, 27.9 (3 C); HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{34}H_{34}NO_3$ 504.2539; found: 504.2510.

Recycle of Si-12. The solid supported catalyst of Table 2 entries 12 and 13 (32 mg) was collected via centrifugation from the reaction mixture after each run, washed with EtOAc (3 × 9.0 mL), dried, and suspended in 0.05 M LiOH solution in MeOH (2.0 mL). The mixture was stirred at room temperature for 30 minutes. Then the mixture was centrifugated and the reactivation protocol was repeated. After centrifugation and removal of the basic solution, the silica was sequentially washed with MeOH (2 × 9.0 mL), THF (3 × 9.0 mL) and EtOAc (1 × 9.0 mL). Later, before being used in the next cycle, the restored solid supported cyclopropenimine superbase was weighed to exclude any loss of mass and the integrity of organic moiety was confirmed by elemental analysis (Elemental analysis (%) found N 1.91 C 25.83 H 3.29 S 2.62).

Fabrication of mesoreactor R. A slurry solution was prepared suspending an excess of catalyst **Si-12** in anhydrous EtOAc. A stainless-steel column (10 × 0.46 cm) was filled with the slurry solution under constant pressure (300 bars, 30 min, EtOAc as solvent) by using an air driven liquid pump. Microreactor void volume (V_0) was determined by pycnometry, filling and weighting accurately the mesoreactor with two different solvents (solvent 1: chloroform; solvent 2: n-hexane). V_0 was calculated according to the following formula where w_1 and w_2 are the weights of the microreactor filled respectively with solvents 1 and 2 and δ_1 and δ_2 are the solvent densities: $V_0=(w_1-w_2)/(\delta_1-\delta_2)$.

Experimental set-up for flow experiments. The system used for the flow reaction was made of one pump (Agilent 1100 micro series) connected to the reactor by a feeding channel. The channel was used to deliver a continuously degassed solution of **13** (0.04 M) and **14a** (0.12 M) in anhydrous EtOAc. The feed solution was pumped with a flow rate of 5 μL min^{-1} into **R** for 24 h. The collected solution was analyzed hour by hour. Conversion of **13** and enantiomeric excess of the product **15a** were evaluated by ^1H-NMR analysis of the crude reaction mixture and by chiral stationary phase HPLC.

Long-term stability experiment. The long-term stability investigation was performed restoring the catalytic activity of the packing material **Si-12** after 24 h of usage. Mesoreactor **R** packed with **Si-12** was washed with EtOAc for 1 h with a flow rate of 10 μL min^{-1}. Then a 0.05 M solution of LiOH in anhydrous MeOH was fluxed inside **R** for 2 h (10 μL min^{-1} flow rate), which was subsequently washed with anhydrous MeOH (1 h, 10 μL min^{-1} flow rate) and anhydrous EtOAc (1 h; 10 μL min^{-1} flow rate). The restored activity of the catalyst **Si-12** was determined on the benchmark reaction.

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