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Solid Supported 9-Amino-9-deoxy-*epi*-quinine as Efficient Organocatalyst for Stereoselective Reactions in Batch and Under Continuous Flow Conditions

Riccardo Porta,[a] Maurizio Benaglia,[a,*] Francesca Coccia,[a] Franco Cozzi,[a] and Alessandra Puglisi[a,*]

[a] Dipartimento di Chimica, Universitá degli Studi di Milano, via Golgi 19, 20133 Milano, Italy
Fax: (+39)-02-5031-4159: phone: (+39)-02-5031-4171; e-mail: maurizio.benaglia@unimi.it or alessandra.puglisi@unimi.it

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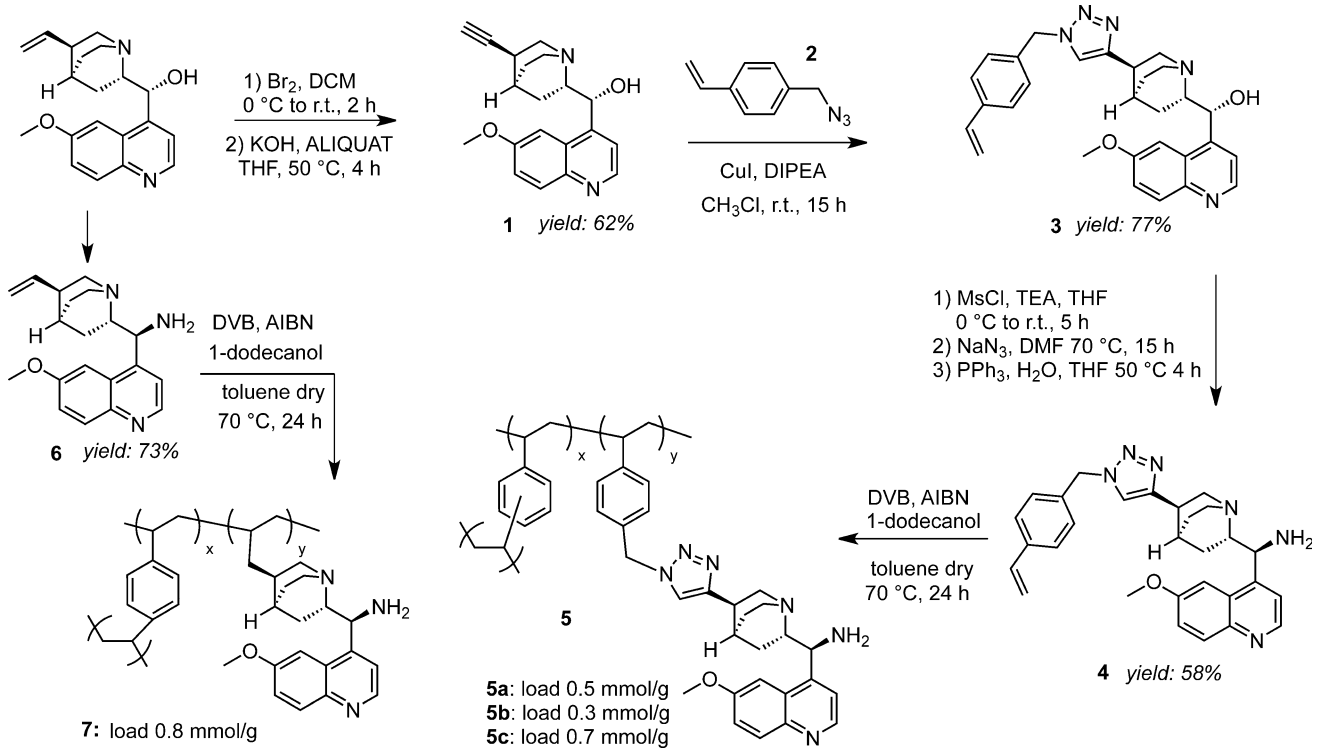
Abstract: Polystyrene-supported 9-amino-9-deoxy-*epi*-quinine was synthesized through co-polymerization of an *ad hoc*-designed chiral monomer with divinylbenzene, in the presence of azobis(isobutyronitile) (AIBN) as radical initiator and toluene and 1-dodecanol as porogenic solvents. The heterogenized catalyst efficiently promoted the reaction of isobutyric aldehyde with β-nitrostyrene, in very high yield and enantioselectivity, comparable or even higher than that of the homogeneous counterpart (up to 95% *ee*). The recyclability of the catalyst, its general applicability and its successful application to other reactions was also demonstrated. Finally, for the first time, a 9-amino-*epi*-quinine derivative was employed to perform an enantioselective Michael reaction under continuous-flow conditions; by using a home-made, packed-bed catalytic reactor, the aldehyde addition to nitrostyrene was successfully realized in flow mode, leading to the product in up to 93% *ee*.

Keywords: aminocatalysis; catalytic reactor; organocatalysis; stereoselective synthesis; supported catalysts

Organocatalysis is a widely recognized powerful tool for the development of sustainable processes and eco-friendly technologies.[1] In this field, aminocatalysis, with its ability to promote numerous transformations by different mechanisms, plays a major role; it has opened the way to new enantioselective reactions and to the discovery of unprecedented patterns of reactivity.[2] Since the behavior of secondary amines is greatly influenced by steric factors, primary amines, less sensitive to the structural features of the carbonyl compounds, have recently found widespread use in the activation of sterically hindered aldehydes and ketones.[3] In particular 9-amino-9-deoxy-*epi*-*Cinchona* derivatives,[4] by either enamine or iminium ion formation, have catalyzed several transformations, including organocascade reactions proceeding either through an iminium ion/enamine sequence or enamine/iminium ion formation.[5] *Cinchona*-based primary amines have been successfully applied also in the preparation, *via* dienamine catalysis,[6] of highly functionalized cyclic compounds, especially cyclohexanone derivatives.[7]

The great versatility and the excellent levels of enantioselectivity showed by 9-amino-*Cinchona* derivatives in different organocatalyzed reactions, make the immobilization of this class of catalysts extremely attractive in view of possible industrial applications; easy work-up, possibility to simplify scale up and to develop reactions in flow mode, are all key features of extreme interest for a modern approach to the synthesis of APIs, fine chemicals and chiral intermediates. The use of chiral supported organocatalysts under continuous flow conditions[8] offers a great opportunity to combine a powerful methodology, like organocatalysis, with other *enabling technologies*,[9] opening new avenues towards the automated synthesis of complex molecules.[10] Recent contributions from the Fulop,[11] Wennemers,[12] Bortolini and Massi,[13] our group[14] and Pericas[15] groups have clearly demonstrated the potentiality of the organocatalyzed reactions performed in continuo with supported catalysts. However, almost all the works focused on secondary amines-catalyzed reactions; surprisingly, the immobilization of amino-*Cinchona* catalysts is almost unexplored.[16]

Here we wish to report the preparation of polystyrene supported 9-amino-9-deoxy-*epi*-quinine and its successful application in the addition of isobutyric al-



Scheme 1. Synthesis of supported catalysts **5a–c** and **7**.

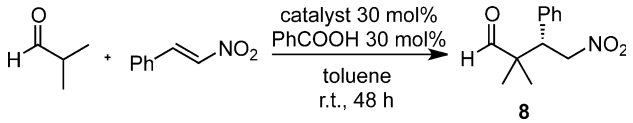
dehyde to β-nitrostyrene (up to 95% *ee*). Furthermore, for the first time, a 9-amino-*epi*-quinine derivative was employed to perform an enantioselective reaction under continuous-flow conditions; by using a home-made, packed-bed catalytic reactor in a Michael reaction whereby good chemical yields and remarkable stereoselectivity (93% *ee*) were obtained.

The general strategy to prepare polystyrene supported 9-amino *Cinchona* derivatives involves the introduction of a linker on the quinuclidine ring suitable for radical polymerization. The synthesis of supported catalysts **5** is illustrated in Scheme 1. The double bond of commercially available quinine was converted into a triple bond[17] to afford compound **1**, that was subjected to a CuAAC click reaction with azide **2** in order to establish a styrene moiety ready for polymerization. Alcohol **3** was then converted into amine **4**, isolated in 58% overall yield after one chromatographic purification only,[18] and employed in a radical co-polymerization under Fréchet-type conditions, with divinylbenzene in the presence of azobis-(isobutyronitile) (AIBN) as radical initiator and toluene and 1-dodecanol as porogenic solvents.[19] Catalysts **5a–c** with different catalyst loadings were prepared, based on the DVB/**4** ratio (see the Supporting Information for further details). In order to study the influence of the linker on the catalytic activity, 9-amino-*epi*-quinine **6**, without the styrene moiety, was also synthesized and co-polymerized with divinylbenzene under the same conditions to afford catalyst **7**.

The reaction of isobutyric aldehyde with β-nitrostyrene, originally reported by Connon,[20] in the presence of heterogeneous catalysts **5a–c** and **7** and benzoic acid as an additive, was chosen as a model reaction (Scheme 2). The reaction is known to proceed *via* the formation of the enamine between the primary amino group of the alkaloid and the aldehyde, followed by the addition to the nitroolefin, coordinated to the catalyst. Results are reported in Table 1.

All supported catalysts proved to be very active in the reaction, affording the desired product in very high yields and enantioselectivities, comparable to or even higher than those of the homogeneous counterpart (95% *ee vs.* 88% *ee* with 9-amino-*epi*-dihydroquinidine).[20] Catalyst **5c**, with higher catalyst loading, proved to be the most efficient (entry 3), could also be used with lower loading (entry 4), without affecting yield or *ee*, so it was chosen for further studies.[21]

One of the main goals of supporting a catalyst is to facilitate its recovery and recycle. After 16 h of reaction, the polymer was separated by centrifugation, removed from the crude mixture and completely recov-



Scheme 2. Model reaction: addition of isobutyric aldehyde to β-nitrostyrene.

Table 1. Preliminary studies with supported organocatalysts **5a–c** and **7**.

Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**5a**	75	90
2	**5b**	81	94
3	**5c**	>99	94
4	**5c**[c]	>99	95
5	**7**	67	95

[a] Isolated yield; aldehyde/nitrostyrene ratio 5/1.
[b] Determined by HPLC on a chiral stationary phase.
[c] 20 mol% of catalyst was used.

Table 2. Recycling experiments of catalyst **5c**.[a]

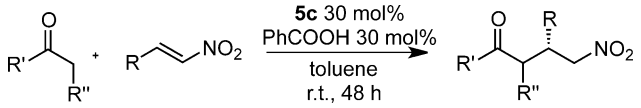
Entry	Cycle	Reaction Time [h]	Yield [%][b]	*ee* [%][c]
1	1st	16	>99	94
2	2nd	16	>99	97
3	3rd	16	78	98
4	4th	16	30	98
		new sample		
5	1st	48	>99	95
6	2nd	48	>99	95
7	3rd	48	88	96
8	4th	48	53	96
9	5th	48	41	97
10	6th	48	31	95

[a] 20 mol% of catalyst was used; aldehyde/nitrostyrene 5/1.
[b] Isolated yield.
[c] Determined by HPLC on a chiral stationary phase.

ered. The solid was washed twice with methanol, dried under high vacuum for 1 hour at room temperature and recycled under the same reaction conditions.[22] Its activity was tested in a second reaction between isobutyric aldehyde and β-nitrostyrene, for 16 h in the presence of benzoic acid; the results are summarized in Table 2.

Catalyst **5c** showed to maintain high *ee* (up to 98%), while a drop in the yields from the 1st cycle to the 4th was observed (entries 1–4);[23] by performing the recycling experiments for longer reaction times (48 h, entries 5–10, Table 2), it was possible to reuse the catalyst 5 times, recovering the product always with an enantioselectivity higher than 95%, although with decreasing yields.[24] By employing the conditions of entries 1–3 of Table 2, a large-scale preparation was performed: by using 0.7 g of functionalized resin (0.5 mmol of chiral catalyst), in 72 operation hours (3 cycles of 16 h of reaction time each) more than 1 g of product was obtained in 95% enantioselectivity.

Once the best reaction conditions were settled and the possibility of recycling the catalyst was demonstrated, the scope of the reaction was investigated. Variations both on the α-branched aldehyde and the nitroolefin (Scheme 3) were studied. The results are summarized in Table 3.

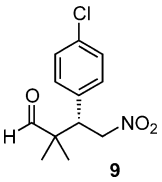
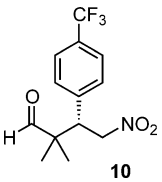
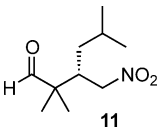
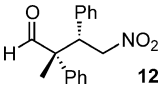
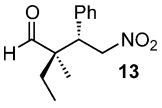
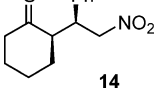
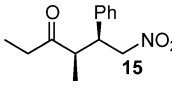


Scheme 3. Addition of carbonyl compounds to nitroolefins promoted by **5c**.

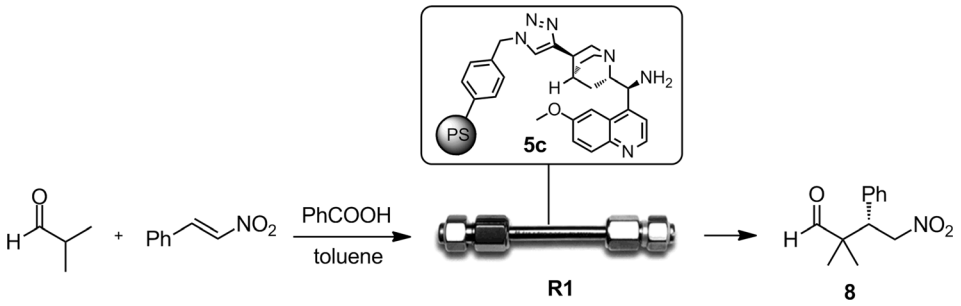
The reaction worked very well not only with substituted β-nitrostyrenes, affording the products in high yields and excellent enantioselectivity (entries 1 and 2), but also with nitroalkenes bearing an alkyl group (product **11**, entry 3).

Differently α,α-disubstituted aldehydes such as 2-phenylacetaldehyde could be used, leading to product **12** in good yield, excellent diastereoselctivity (*syn*/*anti* >20/1) and high *ee* for the major product (82%,

Table 3. Scope of reaction between carbonyl compounds and nitroolefins promoted by **5c**.

Entry	Product	Yield [%][a]	*syn*:*anti*[b]	*ee* [%][c]
1	 **9**	>99	–	90
2	 **10**	78	–	97
3	 **11**	64	–	97
4	 **12**	77	>20:1	82
5	 **13**	78	70:30	94
6	 **14**	65	87:13	83
7	 **15**	17[d]	95:5	98

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.
[c] Determined by HPLC on a chiral stationary phase.
[d] Reaction time = 120 h.



Scheme 4. Michael reaction promoted by **5c** under continuous-flow conditions.

entry 4); as expected,[20] 2-methylbutanal, carrying two similar substituents on the α-carbon, maintained the high levels of yield and enantioselectivity with a lower diastereoselectivity (entry 5).

Ketones, both cyclic and acyclic, could also be employed: the reaction of cyclohexanone with β-nitrostyrene afforded product **14** in 65% yield, 87/13 diastereoisomeric ratio and 83% *ee* (entry 6), while 3-pentanone led to product **15** in low yield but excellent diastereo- and enantioselectivity (*syn/anti* 95/5, 98% *ee*, entry 7). It is noteworthy that polystyrene-supported catalyst **5c** proved to be comparable with, and in some cases superior to, the homogeneous catalyst (9-*epi*-aminodihydroquinidine)[20] in promoting the enantioselective addition of carbonyl compounds to nitroolefins.[25] Moreover, the easy reaction work-up for catalyst separation makes this methodology particularly attractive for the preparation of enantioenriched functionalized molecules.

Finally, a stainless steel column (*i.d.* 0.4 cm, *L* 6 cm) was packed with 0.215 g of catalyst **5c** in order to perform the reaction under continuous-flow conditions (Scheme 4). A solution of β-nitrostyrene, isobutyric aldehyde and benzoic acid in toluene was flushed into the reactor **R1** (for experimental details, see the Supporting Information).

Preliminary results are reported in Table 4. Every run was performed by flowing 2 mL of reaction mixture, collecting the products and washing the reactor with 1 mL of toluene before running the following run.

The first run afforded the desired product **8** in good yield and 80% *ee*, significantly lower than that obtained in the batch reaction; in the second run, performed without additional amount of acid, enantioselectivity increased to 88%, and further grew up to 93% in the next runs 3–4, although with a decrease in yield. It could be possible to restore the catalytic activity of the reactor by washing the column with a benzoic acid solution in toluene before running the reaction: this allowed us to obtain, after 100 h of operation, a good yield (61%) maintaining 90% *ee*, thus highlighting the fact that the catalytic column could be used for at least 120 h continuously.[26]

Table 4. Preliminary studies for **5c**-catalyzed Michael reaction under continuous-flow conditions.

Entry[a]	Run	Operation Time [h]	Yield [%][b]	*ee* [%][c]
1[d]	1	0–20	73	80
2	2	20–40	73	88
3	3	40–60	18	93
4	4	60–80	20	93
		80–100[e]		
5	5	100-120	61	90

[a] *Conditions:* 1 equiv. β-nitrostyrene, 5 equiv. isobutyric aldehyde, flow rate: 0.1 mL h^{-1}, residence time 4 h.
[b] Isolated yield.
[c] Determined by HPLC.
[d] PhCOOH (1 equiv.) was flushed together with the reagents.
[e] A solution of PhCOOH was flushed through the reactor before run 5.

In the attempt to improve the efficiency of the reactor, additional studies were performed; in order to obtain a more homogeneous material, the functionalized resin was triturated and decanted (for details see the Supporting Information). Additionally, since concentration and mode of addition of benzoic acid play a role in determining the enantioselectivity of the reaction, after several experiments, we selected, as procedure of choice, to feed the reactor a toluene solution of all reagents (0.4 M *trans*-β-nitrostyrene, 2 M isobutyrric aldehyde, 0.4 M benzoic acid). Under these conditions reactor **R2**, prepared by filling a stainless steel HPLC column (*i.d.* 0.4 cm, *L* 6 cm, *V* 0.75 mL) with catalyst **5c** (311 mg, 0.22 mmol, 0.29 M), was able to operate continuously for almost 200 h, producing more than 1 g of the expected product with enantioselectivity constantly higher than 90% (Table 5).

Further studies are needed in order to optimize the reaction under continuous flow conditions; however the improved protocol already offers the possibility to prolong the life of the catalyst, longer than in batch mode, further suggesting interesting future applications for the catalytic reactors, compare to the batch reactors.

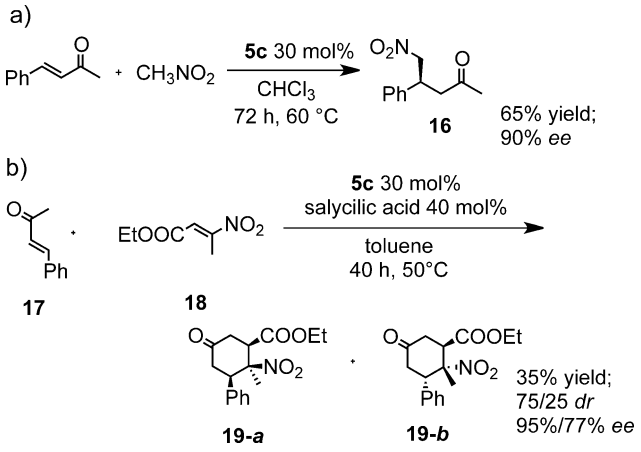
Table 5. Optimized Michael reaction catalyzed by **5c** under continuous-flow conditions.

Entry[a]	Operation Time [h]	Yield [%][b]	*ee* [%][c]
1	0–20	99	85
2	20–40	99	88
3	40–60	95	90
4	60–80	86	91
5	80–157 157–160[d]	77	93
6	160–178 170–182[d]	81	90
7	182–196	70	85

[a] *Conditions:* 1 equiv. β-nitrostyrene, 5 equiv. isobutyric aldehyde, 1 equiv. benzoic acid, room temperature, flow rate: 0.1 mL h^{-1}.
[b] Isolated yield.
[c] Determined by HPLC.
[d] A solution of PhCOOH was flushed through the reactor at 0.5 mL h^{-1} before run 6 and run 7.

With the aim of demonstrating the general applicability of the supported catalyst, we tested it in another two reactions, working with a different activation pathway. In 2013 Wang and co-workers reported the enantioselective conjugate addition of nitroalkanes to enones catalyzed by *Cinchona* alkaloid derived primary amines,[27] that is known to proceed *via* iminium ion. The reaction between nitromethane and benzalacetone promoted by **5c** was investigated [Eq. (a), Scheme 5]. It was found that in chloroform product **16** could be obtained in 72 h at 60 °C in 65% yield, 90% *ee*.

A third activation mode of the 9-amino *Cinchona*, that is dienamine activation of α,β-unsaturated carbonyl compounds, was also explored.[7] The addition of *E*-nitroacrylates to α,β-unsaturated ketones promoted by amino-*Cinchona* alkaloid derivatives in the presence of acidic additives, was recently developed



Scheme 5. Stereoselective reactions promoted by supported catalyst **5c**.

in our laboratories.[28] The reaction allowed us to obtain highly functionalized cyclohexanones bearing three stereogenic centers in excellent diastereo- and enantioselctivity. As a model reaction the addition of ethyl *E*-3-methyl-3-nitroethylacrylate **18** to benzalacetone **17** in toluene was selected and performed in the presence of 30 mol% of **5c** and 40 mol% of salicylic acid as additive [Eq. (b), Scheme 5]. We were pleased to find that polystyrene-supported catalyst **5c** was able to promote the reaction with 75:25 isomeric ratio in favor of diastereosiomer **19-*a*** and excellent enantiocontrol (95% *ee*, 77% *ee*), totally comparable with catalysis under homogeneous conditions, although in 35% yield only.

In conclusion, a polystyrene supported 9-amino-9-deoxy-*epi*-quinine was prepared and successfully applied to the addition of isobutyric aldehyde to β-nitrostyrene, in up to 95% *ee*. Its recyclability and general applicability to a variety of substrates were also demonstrated. For the first time a 9-amino-*epi*-quinine derivative was employed to perform an enantioselective Michael reaction under continuous-flow conditions, with excellent enantioselectivity (up to 93%). Furthermore, the supported catalyst was employed to efficiently promote two different reactions, including an organocascade transformation (in up to 95% *ee*), thus demonstrating the versatility of the novel heterogeneous catalyst, and opening new avenues to the use of immobilized metal-free catalysts in the stereoselective synthesis of complex chiral molecules, possibly also under continuous flow conditions.[29]

Experimental Section

General Procedure for Batch Reaction and Catalyst Recycle

Into a vial, the solid-supported catalyst (80 mg, 0.056 mmol, loading 0.7 mmol g^{-1}) was suspended in dry toluene (0.5 mL) under a nitrogen atmosphere and benzoic acid (0.056 mmol) and trans-β-nitrostyrene (0.28 mmol) were added. After 10 min freshly distilled isobutyric aldehyde (1.4 mmol) was added, the vial was sealed and the mixture was stirred at room temperature for the indicated reaction time. The mixture was then diluted with methanol (8 mL) and the heterogeneous catalyst was precipitated by centrifugation. The solid was washed twice with methanol (8 mL), then it was transferred into a round-bottom flask and dried under high vacuum at room temperature for 3 h. The combined organic layers were concentrated under vacuum. The crude product was purified by flash column chromatography (eluent: hexane/AcOEt = 9/1). The enantiomeric excess of the final product was determined by HPLC (see the Supporting Information).

The recovered heterogeneous catalyst was used in another reaction cycle under the same conditions. After each recycle, the whole amount of solid catalyst was recovered (>97% by weight).

General Procedure for Continuous Flow Reaction

Reactor **R1** was prepared by filling a stainless steel HPLC column (*i.d.* 0.4 cm, *L* 6 cm, *V* 0.75 mL) with catalyst **5c** (215 mg, 0.3 mmol, 0.4 M) and it was wettened through a syringe pump with 4 mL of toluene at a flow rate of 1 mL h^{-1}.

Void volume V_{R1} of **R1** was measured experimentally by picnometry to be $V_{R1} = 0.40$ mL.

A syringe pump was charged with 2 mL of a toluene solution of reagents (**R1**: 0.4 M *trans*-β-nitro-styrene, 2 M isobutyric aldehyde, 0.4 M benzoic acid), and was fed to the reactor at the indicated flow rate (mL h^{-1}) at room temperature. Subsequently the flow reactor was washed with 2 mL of toluene at the same flow rate. The product at the way-out of the reactor was collected at room temperature. The conversion of *trans*-β-nitro-styrene into the desired product was determined by ^{1}H NMR of the crude mixture. Subsequently the pure product was isolated after flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 9/1). The enantiomeric excess of the final was determined by HPLC on chiral stationary phase.

Supporting Information

Synthesis of monomers **4** and **6**, synthesis of supported catalysts **5–7**, detailed experimental procedures for catalytic reactions, ^{1}H and ^{13}C NMR spectra of compounds **1–4** and **6**, ^{1}H NMR spectra of known reaction products **8–19**, and HPLC traces of reaction products **8–19** are given in the Supporting Information.

Acknowledgements

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[22] For detailed descriptions on the recycling experiments see the Supporting Information.

[23] Different recycle procedures were attempted in order to overcome catalyst deactivation. The recovered solid supported catalyst was heated at 70 °C under high vacuum for 2 h and then subjected to the reaction; alternatively, basic washing with NH_4OH (aqueous solution, 33 wt%) and methanol was attempted; any appreciable improvement in the efficiency of the recycling procedure was observed (see Table S2 in the Supporting Information).

[24] No leaching of the catalyst from the solid support could be observed; preliminary CP-MAS NMR experiments on the supported catalysts before and after the reaction did not show any significant difference. Probably, for long reaction times, a chemical degradation, or deactivation, occurs to the catalyst, confirmed by the fact that any attempt to regenerate the catalyst through basic washings or heating (see ref.[24]) was unsuccessful, thus suggesting that a sort of irreversible modification of the catalyst happened. Further studies are due on this aspect and are currently underway in our laboratories.

[25] Further studies are underway in our group, by exploiting different materials, with modified morphological properties; preliminary experiments showed that enantioselectivity may be heavily influenced not only by the nature of the support, but by other factors like molarity and type of the acid additive.

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