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Comparison of Different Polymer- and Silica-Supported 9-Amino-9-deoxy-*epi*-quinines as Recyclable Organocatalysts

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9-Amino-9-deoxy-*epi*-quinine, properly modified by suitable linkers, was anchored on highly cross-linked polystyrene, poly(ethylene glycol), and silica. The resulting species were characterized by NMR spectroscopy and tested as supported organocatalysts in the reaction between isobutyric aldehyde and *trans*-β-nitrostyrene. Polystyrene- and poly(ethylene glycol)-supported catalysts outperformed their nonsupported counterpart affording the desired product in high yield and *ee* (>90% *ee*). Silica-supported catalysts proved to be less efficient in terms of both chemical yield and enantioselectivity. Polystyrene- and poly(ethylene glycol)-supported 9-amino-9-deoxy-*epi*-quinine were then used in the same reaction with different substrates, leading to the desired products in high yield and *ee*, as well as in three other reactions operating with different mechanism. An investigation of the recyclability of the polystyrene- and poly(ethylene glycol)-supported systems showed that these could be recovered and recycled with no loss of stereochemical activity but with a marked erosion of chemical efficiency occurring at the fifth reaction cycle. This was ascribed to chemical degradation of the alkaloid occurring during the reaction.

Introduction

The immobilization[1] of organic catalysts onto solid supports[2] has been an intense research area soon after the recent renaissance of organocatalysis.[3] Owing to the absence of coordinated metal species, organocatalysts are particularly prone to immobilization onto a solid support, since the risk of metal leaching is intrinsically avoided. The immobilization of a chiral catalyst onto a support has the main goal to facilitate the recovery and recycle of the precious species. Two different approaches are possible for the immobilization depending on the soluble or insoluble nature of the support. Both approaches are valuable and display advantages and drawbacks. In principle, a heterogeneous catalyst derived from immobilization on an insoluble support suffers from slower reaction rates but could be more easily recovered and recycled (generally by simple filtration). On the other hand a soluble polymer-supported catalyst works under homogeneous conditions and thus generally offers faster reaction rates, but it needs a heterogenization step to be recovered (for example, addition of a solvent that favors catalyst precipitation followed by filtration). In this work we explored both possibilities with the goal of assessing their pros and cons. Among organic catalysts that have been used in recent years, 9-amino-9-deoxy-*epi*-cinchona derivatives[4] have shown to be able to catalyze several transformations, including organocascade reactions proceeding either through iminium ion/enamine sequence or enamine/iminium ion formation.[5] Cinchona-based primary amines have been successfully applied also in the preparation, through 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, simplified scale-up and development of flow-mode reactions are all key features of extreme interest for a modern approach to the synthesis of active pharmaceutical ingredients, fine chemicals, and chiral intermediates.

Despite these enormous potentialities, the anchoring of 9-amino-cinchona derivatives onto solid supports remains scarcely investigated. In 2012 Ma and co-workers reported the use of 9-amino-9-deoxy-*epi*-cinchonine and cinchonidine supported on polyacrylonitrile[8] and on porous zirconium phosphonate[9] to promote aldol reaction in aqueous media. Recently we have realized the immobilization on polystyrene of 9-amino-9-deoxy-*epi*-cinchona derivative that was successfully employed under continuous-flow conditions by using a home-made, packed-bed catalytic reactor.[10] Herein we describe the synthesis of 9-amino-*epi*-quinine derivatives supported onto soluble poly(ethylene glycol) and on insoluble silica gel and provide a comparison of the efficiency of these catalysts with that of the previously reported polystyrene-supported one in some organocatalyzed reactions which differ in activation mode mechanism. The characterization as well as recovery and recycle experiments of the catalysts are also described.

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Results and Discussion

Synthesis of supported catalysts

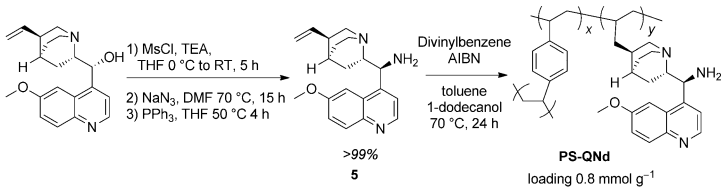
In this study three different supports with well-marked different properties were chosen: an insoluble organic polymer (cross-linked polystyrene, PS), a soluble organic polymer (poly(ethylene glycol), PEG, M_w 5000 Da) and an insoluble inorganic matrix (silica).

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 **PS–QN** is illustrated in Scheme 1. The double bond of commercially available quinine was converted in a triple bond[11] to afford compound **1**, which was subjected to copper-catalyzed azide–alkyne cycloaddition with azide **2** in order to establish a styrene moiety ready for polymerization. Alcohol **3** was then converted into amine **4**, isolated in 62% overall yield after one chromatographic purification step only,[12] and employed in a radical copolymerization under Fréchet-type conditions, with divinylbenzene in the presence of azobisisobutyronitrile (AIBN) as radical initiator and toluene and 1-dodecanol as porogenic solvents.[13] Catalysts **PS–QNa–c** with different catalyst loadings were prepared, taking advantage on different divinylbenzene/**4** ratio in the preparation of the materials (see Supporting Information for further details). To study the influence of the linker on the catalytic activity, 9-amino-*epi*-quinine **5**, without the styrene moiety, was also synthesized and copolymerized with divinylbenzene under the same conditions to afford catalyst **PS–QNd** (Scheme 2).

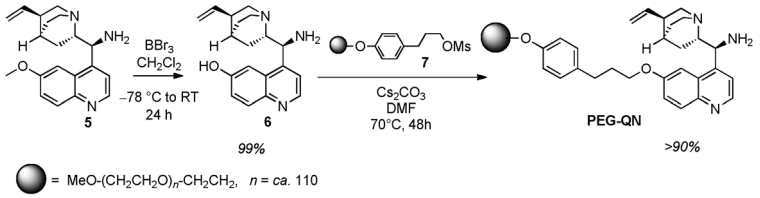
By using the same strategy as described above, quinine was converted into 9-amino-*epi*-quinine **5**[12] and then demethylated by BBr_3 to afford compound **6**, that was supported onto poly(ethylene glycol) derivative **7** (M_w 5000 Da) in DMF at 70 °C in the presence of Cs_2CO_3, according to a well-established procedure.[14] Catalyst **PEG–QN** was isolated and purified by precipitation with diethyl ether in >90% yield (Scheme 3).

Finally, the synthesis of 9-amino-*epi*-quinine on silica nanoparticles was attempted (Scheme 4). Amine **5** was protected as trifluoroacetamide **8** and subjected to hydrosilylation with trimethoxysilane and $Ptdcp_2Cl_2$ as catalyst (dcp = dicyclopentadienyl) to afford derivative **9**; this was grafted onto commercially available silica to afford material **10**, which was subjected to hydrolysis under mild conditions ($MeNH_2$ in EtOH) to restore the free amine functionality and obtain catalyst **SIL–QNa**.[15] The amide hydrolysis was monitored by ^{13}C direct-polarization magic-angle-spinning (DP MAS) NMR (see below).

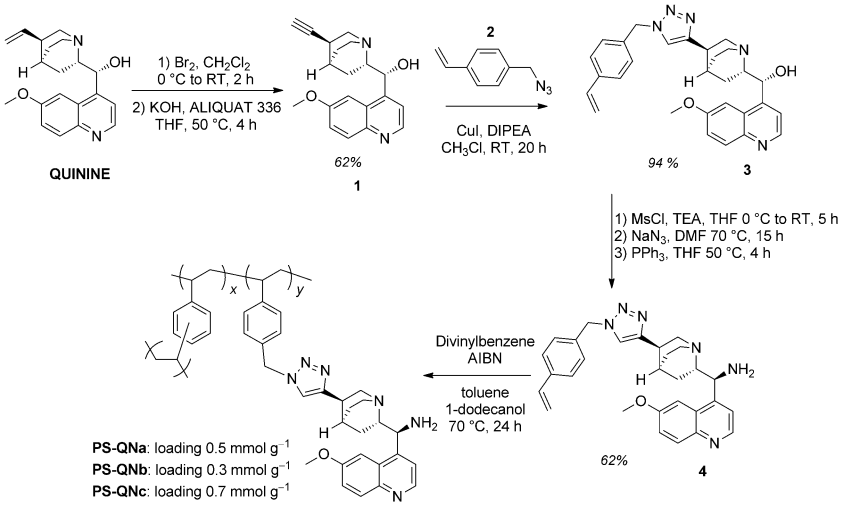
The catalyst was also anchored to silica by a different method: commercially available silica was modified by grafting with 3-mercaptopropyl-triethoxysilane **11** and subjected to radical thiol–ene coupling with compound **5** in the presence of AIBN, and in toluene and $CHCl_3$ as solvents, at 80 °C for 24 h. The obtained material, **SIL–QNb**, was isolated by filtration and washed several times before use (Scheme 5).



Scheme 2. Synthesis of polystyrene-supported 9-amino-*epi*-quinine **PS–QNd**.



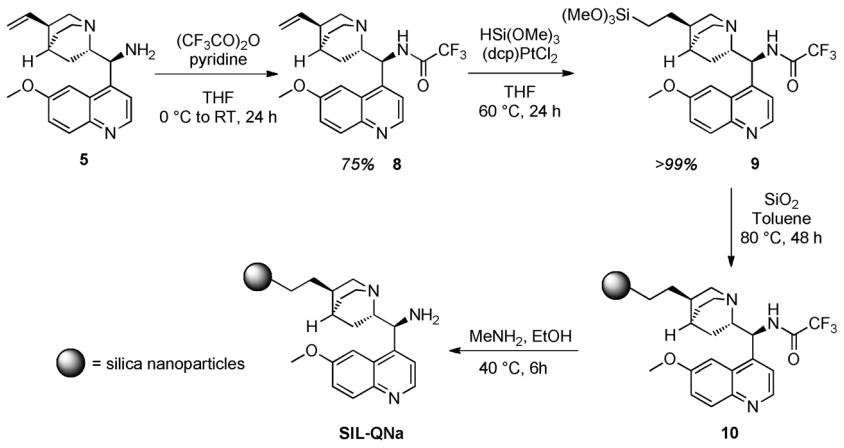
Scheme 3. Synthesis of poly(ethylene glycol)-supported 9-amino-*epi*-quinine **PEG–QN**.



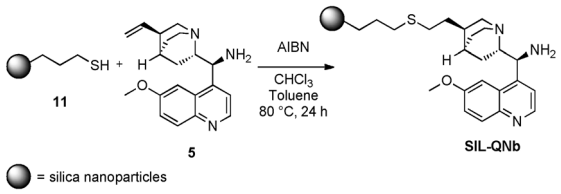
Scheme 1. Synthesis of polystyrene-supported 9-amino-*epi*-quinine **PS–QNa–c**. ALIQUAT 336 = trioctylmethylammonium chloride, DIPEA = *N*,*N*-diisopropylethylamine, MsCl = methanesulfonyl chloride, TEA = triethylamine.

Catalyst characterization by NMR spectroscopy

Soluble catalyst **PEG–QN** was characterized by ^1H and ^{13}C NMR in $CDCl_3$ as the solvent by comparing the obtained spectra with those of nonsupported catalyst **5** (see Supporting Information). The structures of insoluble cata-



Scheme 4. Synthesis of silica-supported 9-amino-*epi*-quinine **SIL–QNa**.



Scheme 5. Synthesis of silica-supported 9-amino-*epi*-quinine **SIL–QNb**.

lysts **PS–QN** and **SIL–QN** were elucidated by CP (cross-polarization) and DP MAS NMR techniques.

Catalyst PS–QN

PS–QNc was studied by ^{13}C CP and DP MAS NMR. (see Supporting Information for further details). As a consequence of the high cross-linking degree, both techniques gave spectra with broad signals, as expected on the basis of literature[16] data showing that in the polymer the line width is proportional to the degree of cross-linking. Moreover, the presence of several aromatic rings could give rise to a tight packing of the polymer chains, favored by Ar–Ar interactions, leading to a very rigid system with difficult relaxation modes.[17] The ^{13}C DP MAS NMR experiments afforded spectra resolved enough, with sharper signals, but unfortunately it was impossible to eliminate the side bands, although both rotation rate and temperature were varied.[18] On the contrary, the ^{13}C CP MAS NMR spectra showed broader signals but no side bands; nevertheless, by comparing the results arising from both techniques and by comparison with the solution spectra of the monomer, it was possible to elucidate the structure and confirm the incorporation of the quinine moiety into the polystyrene backbone (see Supporting Information).

Catalyst SIL–QNa

Solid state ^{13}C and ^{29}Si DP MAS NMR spectra were used for structural elucidation of amide **10**. Then, the same technique allowed us to monitor hydrolysis of amide **10** to catalyst **SIL–QNa**. ^{13}C CP MAS NMR experiments confirmed that the trifluoroacetyl moiety was lost upon hydrolysis of the material. The ^{13}C spectra of amide **10** and the corresponding amine **SIL–QNa** are reported in Figure 1 a and b, respectively; the comparison of the two spectra revealed the disappearance of the ***C***F_3 quartet at 114, 116, 118, 120 ppm in the amine spectrum, and the decreased intensity, nearly to a half, of the signal at 160 ppm (ascribed to the aromatic carbon ***C***–OCH_3 and the ***C***=O amidic carbon).

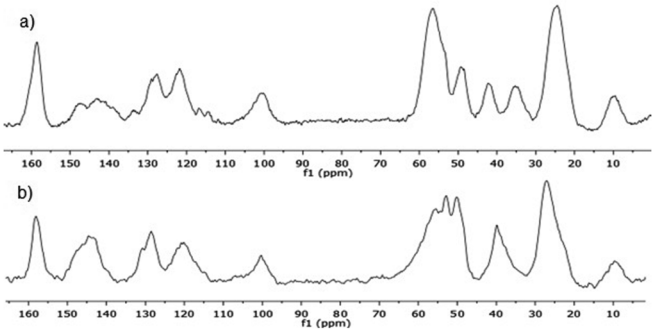


Figure 1. ^{13}C DP MAS NMR of compound a) **10** and b) **SIL–QNa**.

^{29}Si DP MAS NMR spectra, reported in Figure 2, showed significant changes passing from amide **10** to amine **SIL–QNa**. After deconvolution of the silicon signals it was possible to calculate the values of Q_n (silicon atoms that do not bear organic functionality), T_n (silicon atoms carrying organic residues), SC (surface coverage, determined as $(T_1+T_2+T_3)/(Q_2+Q_3+T_1+T_2+T_3)$, and MC (molecular concentration, mmol g^{-1}).[19] In particular, the silicon signals of T_1 species decreased significantly passing from 14.7% to 2.6%. Moreover, the surface coverage and the loading of the molecule decreased from 46.4% to 34.4% and from 2.14 to 1.88 mmol g^{-1}, respectively (Table 1). These results revealed that an evident partial loss of the organic moiety from the material is occurring upon hydrolysis. This may account for the results in the catalytic tests (see below).

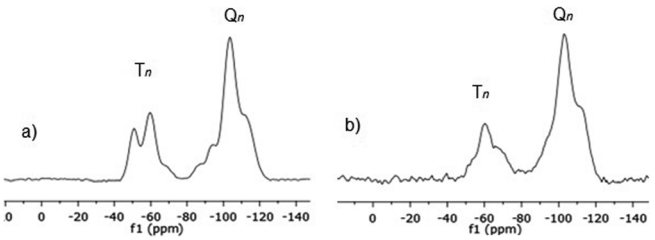


Figure 2. ^{29}Si DP MAS NMR of compound a) **10** and b) **SIL–QNa**.

Table 1. T_n, Q_n, surface coverage, and molecular concentration values of compounds **10**, **SIL–QNa**, and **SIL–QNb** obtained by ^{29}Si DP MAS NMR analysis after spectra deconvolution.

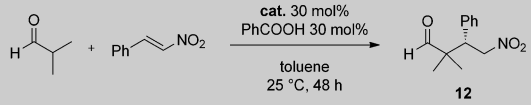
	T_1 [%] −53 ppm	T_2 [%] −60 ppm	T_3 [%] −68 ppm	Q_2 [%] −96 ppm	Q_3 [%] −103 ppm	Q_4 [%] −113 ppm	SC [%]	MC [mmol g^{-1}]
10	14.7	19.7	3.6	9.1	34.8	18.1	46.4	2.14
SIL–QNa	2.6	18.7	7.3	4.4	50.2	16.8	34.4	1.88
SIL–QNb	5.5	25.1	9.6	4.6	34.7	20.5	50.6	1.87

Catalyst SIL–QNb

Solid-state ^{13}C and ^{29}Si MAS NMR allowed us to confirm the structure of the catalyst **SIL–QNb**. This showed a ^{13}C spectrum very similar to that of **SIL–QNa;** also in this case it was possible to confirm the incorporation of the quinine moiety into the silica network by comparison of the **SIL–QNb** ^{13}C spectrum with the solution spectrum of compound **5**. Moreover, the linking of the quinuclidine ring with the $SiOCH_2CH_2SCH_2CH_2$ group was revealed by the ^{13}C resonances at 50.2, 26.6, and 11.2 ppm ascribed to the methylene carbons of this chain.

The ^{29}Si DP MAS NMR spectrum displayed, after deconvolution, a 3:2 ratio between Q_n and T_n species with the percentage for each species reported in Table 1. With respect to **SIL–QNa**, **SIL–QNb** has a greater surface coverage (50.6% vs. 34.4%) and a very similar molecular concentration (1.87 mmol g^{-1}).

Table 2. Addition of isobutyric aldehyde to *trans*-β-nitrostyrene promoted by supported catalysts **PS–QN**, **PEG–QN**, and **SIL–QN**.



Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**PS–QNa**	81	94
2	**PS–QNb**	59	90
3	**PS–QNc**	99	95
4	**PS–QNd**	67	95
5[c]	**PS–QNc**	99	95
6	**PEG–QN**	87	94
7	**SIL–QNa**	81	78
8	**SIL–QNb**	77	73

[a] Isolated yield; aldehyde/nitrostyrene ratio 5:1; [b] determined by HPLC on chiral stationary phase; [c] 20 mol% catalyst was used, reaction time 16 h.

Catalytic activity determination

The catalysts were tested in the Michael addition of isobutyric aldehyde to *trans*-β-nitrostyrene, originally reported by Connon and McCooey.[5c] This reaction is known to proceed in the presence of benzoic acid as an additive through the formation of the enamine between the primary amino group of the alkaloid and the aldehyde, followed by the addition to the nitroolefin, coordinated through hydrogen bonding to the protonated quiniclidine ring of the catalyst.

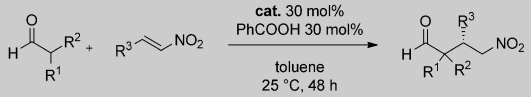
To assess the influence of the supports, we first conducted the model reaction using nonsupported 9-amino-*epi*-quinine **5** in the presence of the supports: nonfunctionalized polystyrene, poly(ethylene glycol) dimethyl ether, and nonfunctionalized silica. In all cases the product was obtained in high yields and 90% *ee* as reported in the literature,[5c] thus showing the inertness of the support towards the reaction.

The results obtained with the supported catalysts are summarized in Table 2. All solid-supported catalysts proved to be very active, affording the desired product **12** in high yield and enantioselectivity, comparable to or even higher than those obtained with the nonsupported counterpart (95% *ee* vs. 88% *ee* with 9-amino-*epi*-dihydroquinidine).[5c] Polystyrene-supported catalyst **PS–QNc**, with higher catalyst loading, proved to be the most efficient (entry 3), and could also be used in a lower concentration (20 vs. 30 mol%) and with shorter reaction time (entry 5), without affecting yield or *ee*. These results are interesting, considering that the reaction with polystyrene-supported 9-amino-*epi*-quinine proceeds under heterogeneous conditions, whereas that of its poly(ethylene glycol)-supported counterpart **PEG–QN** works under homogeneous conditions (entry 6). Silica-supported quinine **SIL–QNa** afforded the product in lower yield and *ee* (81% and 77%, respectively). On the basis of this result and of the above described MAS NMR experiments we hypothesized that the hydrolysis step somehow degraded the quinine moiety of **SIL–QNa**. However, the observation that the analogous silica-supported catalyst **SIL–QNb** afforded the product in only 77% yield and 73% *ee* supported the hypothesis that silica is the less suitable support for the amino catalyst. Further studies are ongoing in our laboratories to investigate the influence of the free silanols of the silica surface on the course of the reaction.

On the basis of these results, we decided to continue our studies using only **PEG–QN** and **PS–QNc** catalysts.

The scope of the reaction was expanded by introducing structural variations both on the α-branched aldehyde and the nitroolefin. The results are summarized in Table 3. The reaction worked very well not only with substituted β-nitrostyrenes, affording the products in high yield and excellent enantioselectivity (entry 1 and 2) but also with nitroolefin bearing an alkyl group (entry 3). Differently α,α-disubstituted aldehydes such as 2-Ph-propanal could also be used, leading to product **16** in good yield, excellent diastereoselectivity (*syn*/*anti* > 20:1) and high *ee* for the major product (82%, entry 4). The reaction of 2-methylbutanal, carrying two similar substituents on the α-carbon, occurred in high yield and enantioselectivity but, as expected, with a lower diastereoselectivity, (entry 5, Ref. [5c]). Notably, polystyrene-supported catalyst **PS–QNc** proved to be comparable, and in some cases superior, to the homogeneous catalyst (9-*epi*-amino-dihydroquinidine) in promoting the enantioselective addition of carbonyl compounds to nitroolefins.[5c]

Table 3. Scope of the reaction, variation of aldehydes and nitroalkenes.



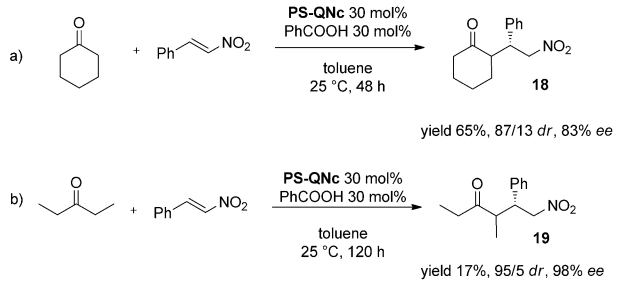
Entry	$R_1/R_2/R_3$	PS–QNc		PEG–QN	
		Yield [%][a]	*ee* [%][b]	Yield [%][a]	*ee* [%][b]
1	Me/Me/*p*-ClPh **13**	99	90	64	95
2	Me/Me/*p*-CF_3Ph **14**	78	97	50	95
3	Me/Me/isobutyl **15**	64	97	–	–
4	Me/Ph/Ph **16**	77 (>20:1)	82	70 (50:50)	60
5	Me/Et/Ph **17**	78 (2:1)	94, 92	40 (2:1)	99, 97

[a] Isolated yield; carbonyl compound/nitrostyrene ratio 5:1, *syn/anti* ratio given in brackets; [b] determined by HPLC on chiral stationary phase.

Moreover, the easy reaction work-up for catalyst separation makes this methodology particularly attractive. **PEG–QN** afforded products with *ee* comparable (and in some cases superior) to those obtained with **PS–QNc**, but in lower yields. The fact that the PEG-supported catalyst, although catalyzing the reaction under homogeneous conditions, affords somehow slower reaction rates than the heterogeneous polystyrene-supported analogue is surprising and remains, at this stage, unexplained.

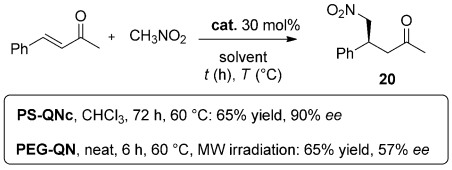
Cyclic and acyclic ketones were also tested in the reaction with *trans*-β-nitrostyrene. Surprisingly, only polystyrene-supported catalyst **PS–QNc** afforded the desired products although in low yields, whereas catalyst **PEG–QN** did not lead to the formation of the products. Reaction of cyclohexanone with *trans*-β-nitrostyrene in the presence of 30 mol% of **PS–QNc** afforded product **18** in 65% yield, 87:13 diastereomeric ratio (*dr*) and 83% *ee* of the major product; the use of pentan-3-one led to product **19** in only 17% yield, but with very high *dr* (95:5) and *ee* (98%), after 120 h reaction time (Scheme 6).

With the aim of demonstrating the general applicability of the supported catalysts, their use was extended to reactions proceeding by different activation pathways. The enantioselective conjugate addition of nitroalkanes to enones catalyzed by



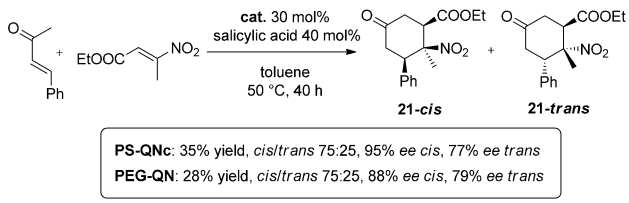
Scheme 6. Addition of a) cyclohexanone and b) pentan-3-one to *trans*-β-nitrostyrene.

cinchona-alkaloid-derived primary amine, which is known to proceed through iminium ion activation, was reported in 2013 by Wang and co-workers.[21] Choosing as a model the reaction between nitromethane and benzalacetone with **PS–QNc** and **PEG–QN** as the catalysts (Scheme 7), a careful screening of reaction conditions was performed (see Supporting Information). Catalyst **PS–QNc** (30 mol%) was able to promote the reaction between nitromethane and benzalacetone after 72 h reaction time in chloroform at 60 °C in 65% yield and 90% *ee*, which were both slightly lower than those reported by Wang et al. (67% yield, 99% *ee*).[20] Catalyst **PEG–QN** was able to promote the same reaction in neat nitromethane after only 6 h reaction time at 60 °C under microwave irradiation in 65% yield, but in lower enantioselectivity (57% *ee*).



Scheme 7. QN-promoted addition of nitromethane to benzalacetone.

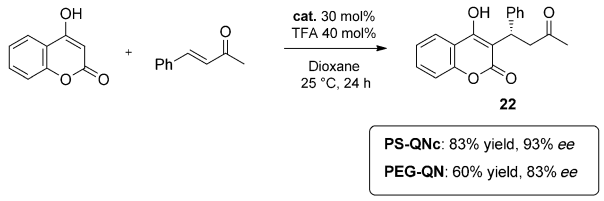
The dienamine activation of α,β-unsaturated carbonyl compounds was also explored as a third activation mode available using the 9-amino cinchona catalyst.[10] The addition of (*E*)-nitroacrylates to α,β-unsaturated ketones promoted by aminocinchona alkaloid derivatives in the presence of acidic additives was recently developed in our laboratories.[7g] The reaction allowed us to obtain highly functionalized cyclohexanones bearing three stereogenic centers in excellent diastereo- and enantioselectivity. As a model reaction, the addition of (*E*)-ethyl 3-methyl-3-nitroacrylate to benzalacetone in toluene was selected and performed in the presence of 30 mol% of heterogenized catalyst and 40 mol% of salicylic acid as an additive (Scheme 8). We were pleased to find that the polystyrene-supported catalyst **PS–QNc** was able to promote the reaction with diastereoselectivity (75:25) and enantioselectivity (95% and 77% *ee* for the two isomers, respectively) fully comparable with the results obtained with the nonsupported catalyst, although in 35% yield only. **PEG–QN** behaved similarly, affording the desired products **21** in 28% yield, 75:25 isomeric ratio, and good enantiomeric excess (88% *ee*, 79% *ee*) after 48 h reaction time at 40 °C in toluene. This result is particularly interesting



Scheme 8. Quinine-promoted addition of (*E*)-ethyl 3-methyl-3-nitroacrylate to benzalacetone.

considering the highly challenging reaction and the fact that high-molecular-weight PEG derivatives are scarcely soluble in toluene.

Finally, we attempted the preparation of a widely prescribed anticoagulant, the chiral drug warfarin. This was prepared by enantioselective Michael addition of 4-hydroxycoumarin to benzalacetone catalyzed by 9-amino-*epi*-quinine as reported by Chen et al.[21] (Scheme 9). After screening the reaction conditions, it was found that **PEG–QN** led to the desired compound **22** in 60% yield and 83% *ee*. Better results were obtained with the polystyrene-supported catalyst **PS–QNc**: the reaction proceeded very well in dioxane in the presence of trifluoroacetic acid (TFA) as a co-catalyst, affording product **22** in 83% yield and 93% *ee* after 24 h reaction time at room temperature; these results reproduced very well those reported by Chen et al. with nonsupported 9-amino-9-deoxy-*epi*-quinine as a catalyst (20 mol% catalyst, 30 mol% TFA, CH_2Cl_2, room temperature, 12 h, 90% yield, 92% *ee*).



Scheme 9. Quinine-promoted addition of 4-hydroxycoumarin to benzalacetone.

Catalyst recycling

As mentioned above, one of the major goals of supporting a catalyst onto a solid support is to facilitate its recovery and recycle. In the present study, **PS–QNc** was isolated by centrifugation, removed from the crude mixture, washed, and quantitatively recovered. **PEG–QN** was precipitated by addition of diethyl ether to the crude reaction mixture, filtered, and recovered with yields ranging from 90 to 95%. The catalyst was dried under vacuum at 80 °C before every subsequent run. Both catalysts were subjected to more reaction cycles. The results reported in Table 4 showed that the catalysts performed similarly in the recovery–recycle process. If catalyst **PS–QNc** was recycled, a slight decrease in chemical yield was observed in the third run (down from 99 to 88%). The decrease became more significant in the following cycle (fourth run, 53%) to reach 28% in the sixth cycle. Remarkably however, no erosion in the enantiomeric excess was observed up to the sixth run. **PEG–QN** performed comparably, with high yield up to the third run (95%), a decreased yield at the sixth run (37%), and slight decrease in *ee* from the fourth run on (down to 86%).

In an attempt to circumvent the problem of the diminished chemical yields, catalyst **PS–QNc** was dried under vacuum at 80 °C before use, to eliminate possible impurities trapped in the porous structure.[22] However, no improvements were obtained (Table 4).

Table 4. Recycling of catalysts **PS–QNc** and **PEG–QN**.

Cycle	PS–QNc		PEG–QN	
	Yield [%][a]	*ee* [%][b]	Yield [%][a]	*ee* [%][b]
1	99	95	87	94
2	99	94	95	97
3	88	96	95	98
4	53	96	60	86
5	37	97	60	86
6	28	95	37	85
Recycling of catalyst **PS–QNc** (drying under vacuum at 80 °C)				
1	99	95		
2	99	96		
3	68	96		
4	31	95		

[a] Isolated yield; aldehyde/nitrostyrene ratio 5:1; [b] determined by HPLC on chiral stationary phase.

Based on these results and suspecting an intrinsic instability of the catalyst under the reaction conditions, we decided to investigate the recovery and recycle of nonsupported catalyst **5**. After the reaction between isobutyric aldehyde and *trans*-β-nitrostyrene, the crude reaction mixture was concentrated and purified by silica-gel chromatography using dichloromethane/MeOH as eluent. The recovered catalyst **5** (94%) was used in a second run with almost identical results. However, after this second reaction catalyst recovery became difficult and was not possible altogether after a third reaction because of extensive catalyst degradation (Table 5).

Table 5. Recovery of homogeneous catalyst **5**.

Cycle	Yield [%][a]	*ee* [%][b]	Recovered catalyst **5** [%][c]
1	85	90	94
2	84	90	32
3	15	85	0

[a] Isolated yield; aldehyde/nitrostyrene ratio 5:1; [b] determined by HPLC on chiral stationary phase; [c] after silica-gel chromatography.

The degradation of the catalytic species and its mechanism is still not clear and will be the subject of further investigation. Preliminary NMR results seem to suggest that catalyst degradation occurs in particular after several hours use. On the other hand, notably, the immobilization onto a support such as highly cross-linked polystyrene or poly(ethylene glycol) extends catalyst's lifetime affording a more robust and performing species. Further studies are necessary to elucidate the mechanism of the aminocinchona derivative degradation; these will help in designing more stable and more usefully recyclable catalysts.

Conclusions

We reported the synthesis of modified 9-amino-*epi*-quinine onto three different solid supports: highly cross-linked polystyrene, poly(ethylene glycol) (M_w 5000 Da) and silica. The supported catalysts were fully characterized by NMR spectroscopy and tested in the addition reaction of isobutyric aldehyde to β-nitrostyrene. Polystyrene-supported and poly(ethylene glycol)-supported catalysts performed better than the nonsupported catalyst, affording the desired product in higher *ee*. They were also superior to silica-supported derivatives and were chosen for further studies in the same reaction with different substrates, in three other reactions with different activation modes and in the efficient synthesis of warfarin. The full recyclability of the polystyrene- and poly(ethylene glycol)-supported systems for at least three reaction cycles was demonstrated, after which the catalyst showed some chemical degradation affecting its chemical efficiency much more than its stereoselectivity. The fact that the same problem occurred also for the nonsupported catalyst pointed out to some degradation occurring during the reaction, which is, however, slowed down by catalyst immobilization. Further studies are ongoing to elucidate the possible degradation mechanism, in order to design a more robust supported catalyst.

Experimental Section

General Methods

Reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F 254 precoated glass plates (0.25 mm thickness) and visualized using UV light. Flash chromatography was performed on silica gel (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on spectrometer Bruker Avance 500 operating at 500 and 125.6 MHz, respectively, in $CDCl_3$ as solvent and tetramethylsilane (TMS) as external reference. ^{13}C and ^{29}Si solid-state NMR spectra were recorded on a Bruker Avance 500 spectrometer, operating at 125.62 and 99.36 MHz, respectively, equipped with a 4 mm MAS broad-band probe (spinning rate ν_R up to 13 kHz). The MAS spectra were performed on solid samples (typically 0.12 g); each sample was packed into a 4 mm MAS rotor (50 μL sample volume), the rate spinning from 8000 to 13 kHz and the temperature values from 300 up to 325 K, depending on the products. DP- and variable-amplitude CP method (contact time τ_c 1 ms) were used for recording the ^{29}Si spectra with 400 scans and a delay of 300.0 s and 25 000 scans and a delay of 3.0 s, respectively; the chemical shifts were externally referenced to TMS. The ^{13}C experiments were performed with DP and/or CP method with 70 000 scans and 3.0 s of delay, the contact time τ_c used with CP was in the range of 1–1.5 ms. The ^{29}Si resonances were assigned following previous reports in the literature and those of ^{13}C were referred to the chemical shifts of the corresponding unbound compounds. High-resolution mass spectrometry was performed at CIGA (Centro Interdipartimentale Grandi Apparecchiature, Milano), with mass spectrometer APEX II & Xmass software (Bruker Daltonics). Electrospray ionization mass spectra were recorded as methanol solutions by using a AB Sciex Instruments triple quadrupole LC/MS/MS API 365 mass spectrometer. Scanning electron micrographs were obtained by a field-emission SEM instrument operating at 0.2–30 kV. The powder samples were coated with gold before analysis. Optical rotations were obtained on a polarimeter at 589 nm using 5 mL cell with a length of 1 dm. Enantiomeric excess determinations were performed under below reported conditions with Agilent 1200 series HPLC. Solid-supported catalysts were isolated by centrifugation using MPW Med. Instruments, Laboratory Centrifuge MPW-260. Reagents mixtures were fed to continuous-flow reactors using Syringe Pump KF Technology, New Era Pump system, model NE4000 and Syringe Pump Chemix Fusion 100.

Materials

Dry solvents were purchased and stored under nitrogen over molecular sieves (bottles with crown caps). Commercial-grade reagents and solvents were used without further purifications. Quinine (anhydrous, technical grade 98%), *trans*-β-nitrostyrene (technical grade 97%), *trans*-4-Cl-β-nitrostyrene (technical grade 97%), 4-chloromethylstyrene (technical grade 97%), 1-dodecanol (technical grade 98%), styrene (99%), divinylbenzene (55%), mercaptopropyltrimethoxysilane (95%), trifluoroacetic anhydride (99%), dichloro(dicyclopentadienyl)platinum(II) (97%), trifluoroacetic acid (99%), benzalacetone (98%), trimethoxysilane (95%) were purchased from Sigma–Aldrich. *trans*-4-CF_3-β-nitrostyrene,[23] *trans*-4-methyl-1-nitropent-1-ene[24] and *trans*-ethyl-3-nitrobut-2-enoate[25] were prepared according to published procedures. Isobutyraldehyde, 2-methyl-butanal, 2-pentanone, nitromethane were purified by distillation under nitrogen atmosphere before use. Cyclohexanone and 2-phenylacetaldehyde were purified by distillation under reduced pressure before use. Silica (Apex Prepsil Silica Media 8 μm) was purchased from Grace Davison–Discovery Science. 4-Hydroxycoumarin was recrystallized from AcOEt and AIBN was recrystallized from Et_2O.

General procedure for the synthesis of catalysts PS–QN

Polymer-supported catalysts were prepared according to literature[10,17] by radical copolymerization in a closed vessel. The feed mixture for the polymerization reaction was composed of monomer (**4** or **5**), divinylbenzene, toluene, and 1-dodecanol as porogens and AIBN as radical initiator. The mixture was prepared under inert atmposhpere, placed into a sealed vial, and heated with an oil bath at 70 °C for 24 h. After reaction time the polymer was removed from the vessel, crushed, suspended in methanol (15 mL), and stirred for 10 min at RT. Then the solid was isolated by centrifugation (4000 rpm, 10 min) and washed three times with methanol (15 mL). The solid was recovered and dried under high vacuum at 40 °C for 3 h. Catalysts loadings (mmol g^{-1}) were determined by the stoichiometry of reagents in the polymerization mixture. In the case of catalysts **PS–QNa–c** no monomer **4** was recovered from the organic phase used to wash the polymer. The organic phase recovered from the washing process of catalyst **PS–QNd** contained some monomer **5**, which did not polymerize.

Polymerization feed mixtures

Catalyst **PS–QNa** was prepared from monomer **4** (0.4 mmol, 11 wt%), divinylbenzene (4.47 mmol, 32 wt%), toluene (2.77 mmol, 14 wt%), 1-dodecanol (4.16 mmol, 42 wt%), and AIBN (0.11 mmol, 1 wt%); loading = 0.5 mmol g^{-1}.

Catalyst **PS–QNb** was prepared from monomer **4** (0.08 mmol, 6 wt%), styrene (0.56 mmol, 9 wt%, as comonomer), divinylbenzene (1.35 mmol, 27 wt%), toluene (2.23 mmol, 32 wt%), 1-dodeca-

nol (0.88 mmol, 25 wt%), and AIBN (0.04 mmol, 1 wt%); loading = 0.3 mmol g^{-1}

Catalyst **PS–QNc** was prepared from monomer **4** (0.68 mmol, 11 wt%), divinylbenzene (5.00 mmol, 22 wt%), toluene (10.28 mmol, 32 wt%), 1-dodecanol (5.38 mmol, 34 wt%), and AIBN (0.17 mmol, 1 wt%); loading = 0.7 mmol g^{-1}.

Catalyst **PS–QNd** was prepared from monomer **5** (0.78 mmol, 11 wt%), divinylbenzene (3.88 mmol, 22 wt%), toluene (7.97 mmol, 32 wt%), 1-dodecanol (4.19 mmol, 34 wt%), and AIBN (0.14 mmol, 1 wt%); 0.26 mmol of monomer **5** recovered from the organic phase, loading = 0.8 mmol g^{-1}.

Synthesis of catalyst PEG–QN

To a DMF solution (10 mL) of compound **7** (1 mmol), previously dried under vacuum at 80 °C for 1 h, a solution of **6** (4 mmol) in dry DMF (30 mL) and Cs_2CO_3 (8 mmol) were added. After 48 h stirring at 70 °C, the mixture was cooled at RT, the solvent was evaporated under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and the solution was filtered on a short pad of celite. The mixture was concentrated under vacuum until few ml solution which was poured dropwise in cold Et_2O (250 mL). The precipitated was filtered, washed with Et_2O (5 mL), and dried under vacuum to give 5.5 g of **PEG–QN** as a brown solid; quantitative yield, loading 0.19 mmol g^{-1}. To recover the excess of **6**, the ether solution was treated with TFA (4 mmol), concentrated under vacuum and purified by flash column chromatography on silica-gel (AcOEt/MeOH = 1:1, with 1% Et_3N).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.74 (d, $J_{2',3'}$ = 4.5 Hz, 1H) (H-2′), 8.02 (d, $J_{8',7'}$ = 9.2 Hz, 1H) (H-8′), 7.63 (bs, 1H) (H-5′), 7.45 (d, 1H) (H-3′), 7.39 (dd, 1H) (H-7′), 7.13 (d, $J_{13,12}$ = 8 Hz, 2H) (H-13), 6.85 (d, 2H) (H-12), 5.80 (ddd, $J_{10,11}$ = 7.4 Hz, 1H) (H-10), 5.00 (d, 1H) (H-11 A), 4.96 (d, 1H)(H-11B), 4.56 (d, $J_{9,8}$ = 10.7 Hz, 1H) (H-9), 3.40 (dd, 2H) (H-16),3.38 (s, 3H) (PEG–OCH_3), 3.27 (dd, $J_{2,3}$ = 9.9 Hz, 1H)(H-2 A), 3.19 (m, 3H) (H-2B), 3.05 (m, 1H) (H-8), 2.82 (m, 1H) (H-14), 2.75 (m, 2H) (H-6), 2.3 (bs, 2H) (NH_2), 2.16 (m,2H) (H-15), 1.61 (bs,1H) (H-4), 1.52 (m, 2H) (H-5), 1.40 (m, 1H) (H-7A), 0.75 ppm (dd, $J_{7,8}$ = 7.8 Hz, 1H)(H-7B). (See Supporting Information).

Synthesis of catalyst SIL–QNa

Compound **9** (1.3 mmol) was dissolved in dry toluene (13 mL) under nitrogen atmosphere, then unfunctionalized silica was added (1.00 g, Apex Prepsil Silica Media 8 μm). The mixture was stirred at 80 °C for 48 h and then it was filtered. The solid was washed with dichloromethane (10 mL) and methanol (10 mL), and then it was recovered and dried under high vacuum for 3 h. The organic phase was concentrated under vacuum and unreacted compound **9** was recovered. Loading of **10** was determined by weight difference of silica before and after the reaction. Compound **10** was obtained as a yellowish solid (1.26 g, 0.5 mmol g^{-1}). Compound **10** (300 mg) was suspended in EtOH (3 mL) under nitrogen atmosphere and then methylamine was added (3 mL, 33% wt ethanol solution). The mixture was stirred at 40 °C for 6 h, then the solid was filtered and washed with methanol (10 mL) and dichloromethane (10 mL). Finally it was dried under high vacuum for 3 h; catalyst **SIL–QNa** was obtained as a yellowish solid (280 mg).

Synthesis of catalyst SIL–QNb

Mercaptopropyl silica **11** was prepared according to a published procedure.[26] Before the reaction, unfunctionalized silica (1.9 g, Apex Prepsil Silica Media 8 μm) was dried under high vacuum at 100 °C for 1 h. Then, under hydrogen atmosphere dry toluene (19 mL) and dry triethylamine (0.57 mmol) were added. After 5 min, mercaptopropyltrimethoxysilane (MPTMS) (5.7 mmol) was added dropwise. The mixture was stirred at 80 °C for 24 h. After the reaction time, the solid was filtered and washed with methanol (10 mL) and dichloromethane (10 mL) and then dried under high vacuum for 3 h. The organic layer was concentrated under vacuum and unreacted MPTMS was recovered (3.8 mmol). **11** was obtained as a white solid (1.85 g, 1.0 mmol g^{-1}). Loading of **11** was determined by the amount of MPTMS recovered after the reaction.

Silica compound **11** (620 mg) was suspended in dry toluene (10 mL) under nitrogen atmosphere and then a solution of **5** (0.56 mmol, g) and AIBN (0.56 mmol) in dry chloroform (3 mL) was added slowly. The mixture was stirred at 80 °C for 24 h under inert atmosphere. After reaction time, the solid was filtered and washed with CH_2Cl_2 (10 mL) and methanol (10 mL) and then it was dried under high vacuum for 3 h. The organic layer was concentrated under vacuum and unreacted compound **5** was recovered (0.26 mmol). Catalyst **SIL–QNb** was obtained as a yellowish solid (600 mg, 0.5 mmol g^{-1}). Loading of **SIL–QNb** was determined by the amount of unreacted compound **5** recovered from the organic layer.

General procedure for the addition of isobutyric aldehyde to *trans*-β-nitrostyrene with PS–QNc.

Into a vial, the solid-supported catalyst **PS–QNc** (60 mg, 0.042 mmol) was suspended in dry toluene (0.5 mL) under nitrogen atmosphere and benzoic acid (5 mg, 0.042 mmol) and nitroalkene (21 mg, 0.14 mmol) were added. After 10 min the carbonyl compound (50 mg, 0.7 mmol) was added, the vial was sealed and the mixture was allowed to stir at 25 °C 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 vacuum for 1 h. The combined organic layers were concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel. The enantiomeric excess of the final product was determined by HPLC on chiral stationary phase.

General procedure for the addition of isobutyric aldehyde to *trans*-β-nitrostyrene with PEG–QN

Into a two-necks flask the catalyst **PEG–QN** (0.036 mmol, 200 mg) was dried under vacuum at 80 °C for 1 h, then dry toluene (1 mL) was added and after the total solubilization of **PEG–QN** under nitrogen atmosphere, benzoic acid was added (4 mg, 0.036 mmol) under stirring; after 5 min the nitroalkene (18 mg, 0.12 mmol) and the carbonyl compound (43 mg, 0.6 mmol) were added. The mixture was left to react at 25 °C for the indicated reaction time. Then the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 (0.5 mL) and this solution was poured dropwise in Et_2O (50 mL). The filtered solution was concentrated under vacuum and purified by flash column chromatography on silica gel. The enantiomeric excess of the final product was determined by HPLC on chiral stationary phase.

General procedure for the addition of isobutyric aldehyde to *trans*-β-nitrostyrene with SIL–QN

Into a vial, the solid-supported catalyst **SIL–QN** (0.04 mmol) was suspended in dry toluene (0.5 mL) under nitrogen atmosphere and benzoic acid (5 mg, 0.04 mmol) and *trans*-β-nitrostyrene (19 mg, 0.13 mmol) were added. After 10 min freshly distilled isobutyraldehyde (47 mg, 0.65 mmol) was added, the vial was sealed and the mixture was allowed to stir at 25 °C for 48 h. The mixture was then diluted with methanol (8 mL) and the heterogeneous catalyst was isolated by filtration. The solid was washed with methanol (8 mL), then it was transferred into a round bottom flask and dried under vacuum for 1 h. The organic layer was concentrated under vacuum and the crude product was purified by flash column chromatography on silica gel. The enantiomeric excess of the final product was determined by HPLC on chiral stationary phase.

Compound **12** is known;[5c] it was purified by flash column chromatography on silica gel (eluent: hexane/AcOEt = 9:1) to afford a colorless oil. TLC $R_f = 0.27$ (hexane/AcOEt = 9:1, stained blue with phosphomolibdic acid). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.55$ (s, 1H), 7.33 (m, 3H), 7.22 (d, 2H), 4.83–4.92 (dd, 1H), 4.68–4.74 (dd, 1H), 3.81 (dd, 1H), 1.15 (s, 3H), 1.03 ppm (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 204.2$, 135.1, 128.9, 128.5, 127.9, 76.1, 48.1, 21.4, 18.5 ppm. The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralcel OD-H column: eluent hexane/iPrOH = 8/2, flow rate 0.8 mL min^{-1}, $\lambda = 210$ nm, $\tau_{minor} = 16.1$ min, $\tau_{major} = 22.1$ min.

General procedure for the synthesis of (*S*)-warfarin with PS–QNc

Into a vial, the solid-supported catalyst **PS–QNc** (80 mg, 0.056 mmol) was suspended in dry dioxane (1 mL) under nitrogen atmosphere then TFA (9 mg, 0.076 mmol), benzalacetone (54 mg, 0.37 mmol), and 4-hydroxycoumarin (31 mg, 0.19 mmol) were added; the vial was sealed and the mixture was stirred at 25 °C for 24 h. 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 25 °C for 3 h. The combined organic layers were concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel. The enantiomeric excess of the final product was determined by HPLC on chiral stationary phase.

General procedure for batch reaction with catalyst PEG–QN

Into a two-necked round bottom flask, the solid-supported catalyst **PEG–QN** (0.13 g, 0.024 mmol) was dried under high vacuum at 80 °C for 1 h and then it was dissolved in dry dioxane (4 mL) under nitrogen atmosphere; TFA (5 mg, 0.048 mmol), benzalacetone (28 mg, 0.24 mmol), and 4-hydroxycoumarin (20 mg, 0.12 mmol) were then added. The flask was sealed and the mixture was stirred at 25 °C for 24 h. After reaction time the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 (0.5 mL) and this solution was poured dropwise in Et_2O (50 mL). The filtered solution was concentrated under vacuum and purified by flash column chromatography on silica gel. The enantiomeric excess of the final product was determined by HPLC on chiral stationary phase.

Compound **22** is known,[21] it was purified by flash column chromatography on silica gel (eluent: Hexane/AcOEt = 7/3) to afford a white-off solid. TLC $R_f = 0.28$ (Hexane/AcOEt = 7/3, stained yellow with $KMnO_4$). Compound **22** was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. However, the equilibrium is very rapid and therefore no pseudo-diastereomers were observed during HPLC analysis using the mixture of hexane/2-propanol containing 0.1% TFA as the eluent. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.98$ (dd, 1H), 7.93 (dd, 2.38H), 7.85 (dd, 3.15H), 7.58–7.50 (m, 7.83H), 7.22–7.4 (m, 54.13H), 4.73 (dd, 1.24H), 4.32 (dd, $J = 3.6$, 2.87H), 4.12–4.18 (m, 5.53H), 3.9 (dd, 1.55H), 3.35 (dd, 1.8H), 3.2 (bs, 2.76H), 2.6–2.4 (m, 10.6H), 2.09–2.00 (dd, 5H), 1.76 (s, 12H), 1.71 ppm (s, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 212.4$, 161.6, 159.8, 152.8, 152.7, 143.3, 141.6, 131.9, 131.4, 129.0, 128.5, 128.1, 127.9, 127.0, 126.6, 126.3, 123.9, 123.8, 123.5, 123.0, 122.7, 116.5, 116.3, 116.1, 115.8, 103.9, 101.2, 100.6, 99.1, 45.1, 42.6, 40.1, 35.2, 34.8, 34.4, 30.0, 29.6, 27.8, 27.3 ppm. The enantiomeric excess was determined by HPLC on chiral stationary phase with Daicel Chiralpack AD column: eluent Hexane/*i*PrOH = 8/2 + 0.1% TFA, flow rate 0.8 mL min^{-1}, $\lambda = 280$ nm, $\tau_{minor} = 7.8$, $\tau_{major} = 19.5$ min.

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