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Poly(ethylene glycol) supported *cinchona* alkaloids as phase transfer catalysts: application to the enantioselective synthesis of α-amino acids

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Abstract—We have demonstrated that quaternary ammonium salts of *cinchona* alkaloids grafted to a poly(ethylene glycol) matrix are efficient homogeneous catalysts in the enantioselective alkylation of glycine Schiff base derivatives. The role of the solvent, the molecular weight of the polymer and the anchorage site on the alkaloid were investigated, leading to ee's up to 81%. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The asymmetric synthesis of α-amino acids under phase-transfer conditions has been widely studied over the last 15 years, leading to very high enantioselectivity being achieved.[1] This attractive method which was first introduced by O'Donnell in 1989[2] used liquid/liquid phase-transfer catalysed asymmetric alkylation of *N*-diphenylmethylene glycine *t*-butyl ester with the aid of *N*-benzyl *cinchona* alkaloids as catalysts. Further development of this reaction was due to the same group in 1994,[3] introducing *N*-benzyl-*O*-alkyl *cinchona* alkaloids as improved catalysts. Finally, a third generation of catalysts was reported in 1997 independently by Lygo[4] and Corey,[5] incorporating a *N*-methyl anthracenyl moiety as a powerful unit for masking the nitrogen face and leading to substantially improved ee's. Recently, dimeric[6] or trimeric[7] *cinchona* alkaloid salts, other ammonium salts,[8] guanidinium salts[9] and metal catalysts[10] have emerged as powerful variants.

During the last 2 years, our contribution to this field has consisted of the anchorage of *cinchona* alkaloids on polymeric supports to produce polymer-bound phase-transfer catalysts.[11–14] Such catalysts present several advantages: simplified work-up for product purification, easy recovery, good stability, reduced toxicity and potential recycling. We introduced new polymer bound chiral phase-transfer catalysts possessing a spacer between the polystyrene Merrifield matrix and the quaternary nitrogen atom of the *cinchona* alkaloid (Scheme 1, type I). The enantioselective alkylation of *N*-diphenylmethylene glycine *t*-butyl ester was achieved in up to 81% ee.[11,12] It is noteworthy that the pseudoenantiomeric effect was not observed with these catalysts. Other laboratories reported a similar approach using *cinchona* alkaloids grafted on Merrifield resins at the nitrogen atom of the quinuclidine moiety without any spacer ($27<ee<90\%$).[15,16] In a second approach, we thought that the enantioselectivity could possibly be improved by anchoring the alkaloid elsewhere. The hydroxyl function was selected for this purpose, leaving the nitrogen of the quinuclidine moiety free to be quaternarized with the aid of 9-(chloromethyl)-anthracene (Scheme 1, type II). With this Merrifield-type bound catalyst, we improved ee's by up to 94%.[13]

The catalyst could possibly be improved further by changing the nature of the polymeric backbone to a soluble non-cross linked polymer. Indeed, linear polymers are soluble in a range of organic solvents and are easily recovered by precipitation in another appropriate solvent, thus rendering recycling of the catalyst possible. Such homogeneous catalysts should provide higher levels of enantioselectivity owing to their ability to mimic the activity and stereoselectivity of the corresponding unsupported catalysts. Moreover, it is easy to characterise the catalyst using standard NMR techniques.

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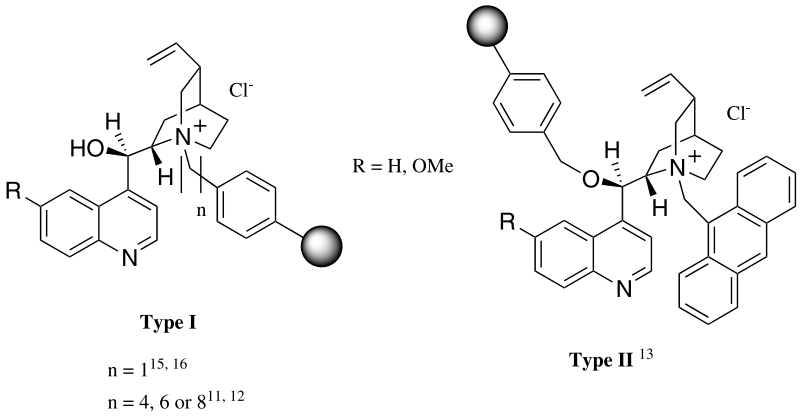


Scheme 1. Merrifield bound *cinchona* alkaloid phase-transfer catalysts.

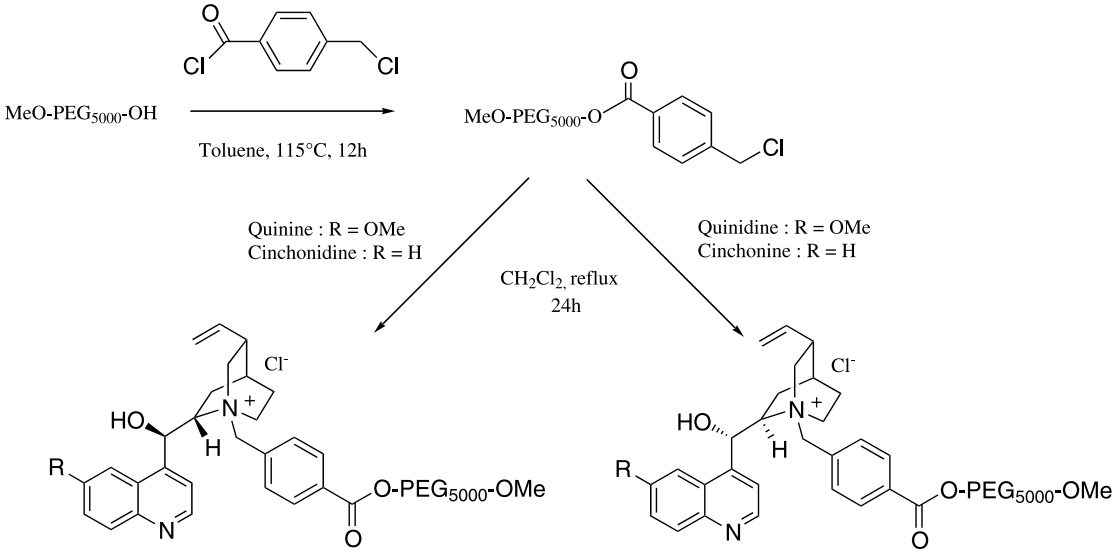
We selected poly(ethylene glycol) (PEG) to explore a new non-cross linked matrix type on which to support phase-transfer catalysts. PEGs are inexpensive, commercially available in different molecular weights and have high solubilising and reprecipitating properties.[17] Benaglia et al. reported the synthesis of an efficient recoverable and recyclable PEG-supported phase-transfer catalyst derived from achiral ammonium salts.[18,19] Recently, the same group described two cinchonidinium salts supported on modified poly(ethylene glycol) applied to enantioselective benzylation of *N*-diphenylmethylene glycine *t*-butyl ester (ee up to 64%) and conjugate addition of thiophenol to cyclohexenone (22% ee).[20]

We herein report our contribution to the synthesis of poly(ethylene glycol) bound *cinchona* alkaloid salts and the evaluation of their catalytic asymmetric behaviour in the phase-transfer alkylation of glycine Schiff base derivatives.

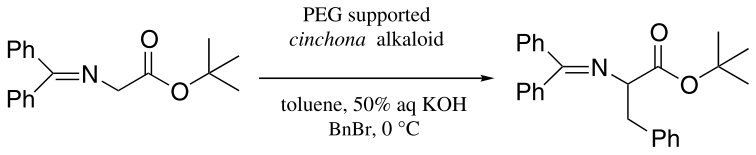
2. Results and discussion

On polyethylene glycol monomethyl ether MeO-PEG-OH Mw 5000 was condensed 4-(chloromethyl)benzoyl chloride in refluxing toluene. Conventional ^{1}H NMR (300 MHz) was used to monitor the progress of the electrophilic linker loading.[21] Then, the terminal chloromethyl group was reacted in dichloromethane at reflux with the nitrogen of the quinuclidine moiety of the four alkaloids: cinchonine (CN), cinchonidine (CD), quinine (QN) and quinidine (QD) to afford four new catalysts (Scheme 2).

They were first evaluated in the catalytic asymmetric liquid/liquid phase-transfer benzylation of *N*-diphenyl methylene glycine *t*-butyl ester (Scheme 3). For this reaction, toluene at 0°C was used as the solvent and 50% aqueous KOH as the base (Table 1).



Scheme 2. Synthesis of the MeO-PEG$_{5000}$ *N*-bound *cinchona* alkaloids.



Scheme 3. Enantioselective benzylation of *N*-diphenylmethylene glycine *t*-butyl ester.

Table 1. Alkaloid effect on the enantioselectivity

Alkaloid	Time (h)[a]	Yield (%)[b]	Ee (%)[c]
CN	15	81	53 (*R*)
CD	15	84	81 (*S*)
QN	15	78	33 (*S*)
QD	15	82	13 (*R*)

[a] The reaction was followed by TLC and quenched when no further conversion was observed.
[b] Purification by column chromatography over silica gel (eluent: dichloromethane/triethylamine, 99:1).
[c] Determined by HPLC (Chiralcel OD, *iso*-propanol/heptane, 0.5:99.5, 1 mL/min, 23°C, $\lambda = 254$ nm). The absolute configuration was assigned by comparison with literature data.[5]

After screening the four alkaloids, we concluded that diastereomeric CN and CD are superior to the couple QD/QN while CD was preferred to its pseudoenantiomer CN to achieve higher enantioselectivity. The pseudoenantiomeric effect was observed with CN giving the (*R*) enantiomer and CD the (*S*) enantiomer but with significantly different enantioselectivities. Moreover, reaction times were shorter than with type I and II catalysts (see Ref. 12). The best catalyst incorporating cinchonidine was selected for the rest of this study.

A parameter we believed interesting to study was the nature of the solvent which is responsible for the unfolding of the long linear PEG chain, and thus has an impact on asymmetric induction. We evaluated a wide range of solvents commonly used in phase-transfer catalysis (Table 2).

Table 2. Solvent effect on the enantioselectivity[a]

Entry	Solvent	Yield (%)[b]	Ee (%)[b]
1	Toluene	84	81 (*S*)
2	Benzene	76	64 (*S*)
3	CF_3-Ph	82	39 (*S*)
4	Xylene	71	58 (*S*)
5	CCl_4	77	65 (*S*)
6	CH_2Cl_2	86	3 (*S*)
7	$CHCl_3$	75	1 (*S*)
8	*t*-BuOMe	71	40 (*S*)
9	THF	61	6 (*R*)

[a] Reactions were run with MeO-PEG_{5000} *N*-bound cinchonidinium chloride at 0°C for 15 h with 50% aqueous KOH as the base and BnBr as the alkylating agent.
[b] See Table 1.

Whatever the solvent used, the enantioselectivity was not improved and yields for the alkylation remained similar. Nonpolar solvents (Table 2, entry 1–5) gave moderate ee's. Dichloromethane and chloroform which are usually efficient solvents in phase-transfer catalysis produced almost no asymmetric induction. Polar solvents such as methyl *t*-butyl ether or THF which are poor solvents for the PEG thus giving heterogeneous conditions, produced poor results. Unexpected reversal of the enantioselectivity was observed in THF although in a low ee. The unsatisfactory solubility of the catalyst in THF and complexation of the potassium enolate with the PEG chain in this solvent might be responsible of this phenomenon. This study demonstrates the dramatic role of the solvent on the asymmetric behaviour of PEG bound *cinchona* alkaloid catalysts. For solvents leading to low enantioselectivity, we suggest that the PEG chain acts as a host molecule for the potassium cation in the same way as crown ethers and that this explains the poor chiral discrimination.

We next examined other parameters: base, temperature and alkylating agent (Table 3).

The temperature was lowered to –20°C leading to longer reaction times (20 h), however the enantioselectivity was not improved (Table 3, entry 2). Employing 50% aqueous sodium hydroxide as base led to a lower ee of 69% (Table 3, entry 3). The use of $CsOH{\cdot}H_2O$ at low temperatures under liquid/solid conditions gave 73% ee at –60°C in 26 h (Table 3, entry 4).

Other alkylating agents such as hexyl iodide or diphenyl methylene bromide were evaluated. These electrophiles are reported to give higher ee's than benzyl bromide on alkylation of glycine Schiff base,[5] however, no asymmetric induction superior to 34% was observed (Table 3, entries 5 and 6).
Because of the great importance of these last studied parameters, we thought that the polymeric backbone, in particular the length of the poly(ethylene glycol) chain would be important to explore. We therefore selected a PEG with an average molecular weight of 750. Syntheses of the catalysts were done using the same strategy as above, and they were evaluated using the optimum conditions previously established in the alkylation of glycine Schiff base (Table 4). However, none of the four alkaloids gave satisfactory enantioselectivity, clearly showing the great importance of polymer length.

In an attempt to improve enantioselectivity, we explored a second anchorage site on the PEG. Obviously, the benzylic linker so far described is not as sterically hindered as the 9-anthracenylmethyl described

Table 3. Base, temperature and alkylating agent effects

Entry	Base	T (°C)	R–X	Time (h)[a]	Yield (%)[a]	Ee (%)[a]
1	KOH	0	BnBr	15	84	81 (*S*)
2	KOH	−20	BnBr	20	77	76 (*S*)
3	NaOH	0	BnBr	15	76	69 (*S*)
4	$CsOH·H_2O$	−60	BnBr	26	72	73 (*S*)
5	KOH	0	HexI	24	66	20 (*S*)
6	KOH	0	Ph_2CHBr	15	63	34 (*S*)[b]

[a] See Table 1.

[b] Determined by HPLC (Regis Whelk-O1 column, *iso*-propanol/heptane, 2.5:97.5, 1 mL/min, 23°C, $\lambda = 254$ nm). The absolute configuration was assigned by comparison with literature data.[5]

Table 4. Investigation of the catalysts supported on PEG_{750} matrix[a]

Alkaloid	Yield (%)[b]	Ee (%)[b]
CN	74	11 (*R*)
CD	67	25 (*S*)
QN	71	3 (*S*)
QD	77	10 (*R*)

[a] Reactions were run with MeO-PEG_{750} *N*-bound cinchonidinium chloride at 0°C for 15 h with 50% aqueous KOH as the base and BnBr as the alkylating agent.

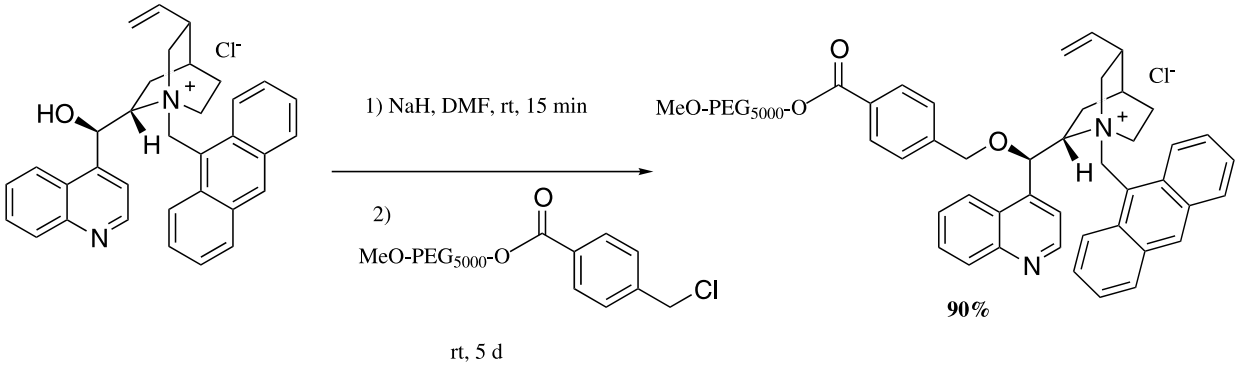
[b] See Table 1.

by Lygo[4] or Corey.[5] Thus, we considered two possible linkages between the PEG and hydroxyl function of the alkaloid (ether or ester linkage), leaving the nitrogen of the quinuclidine moiety free to be quaternarized with the bulky 9-(chloromethyl)-anthracene. The preparation of these catalysts is depicted in Scheme 4 and Scheme 5, and their evaluation is reported in Table 5.

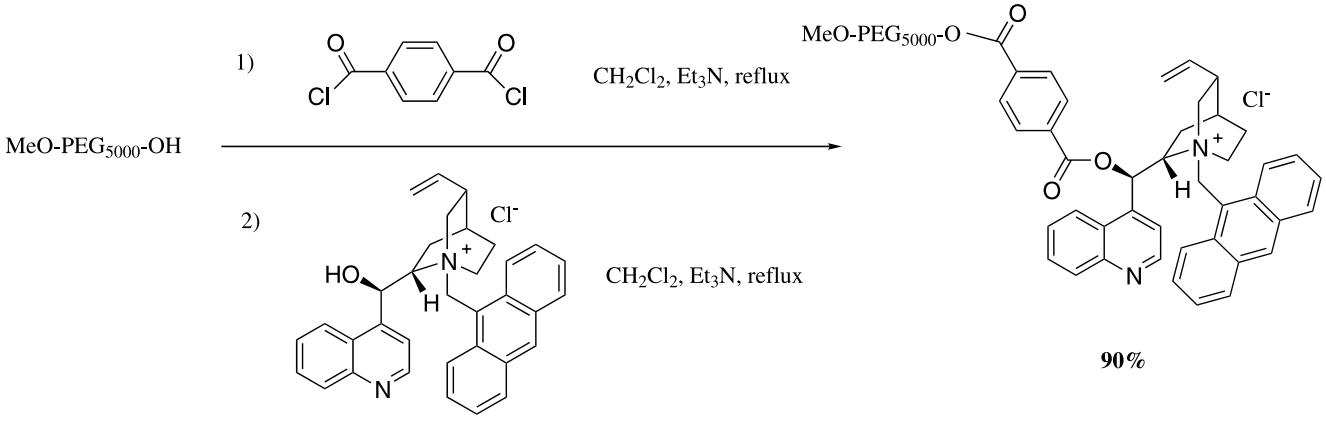
The results obtained did not meet our expectations since a maximum ee of 62% was recorded using the best reaction conditions previously described with the *N*-bound catalyst (Table 5, entry 4). This is surprising considering the high efficiency of *N*-methyl anthracenyl cinchonium salts in phase-transfer catalysis. The ee was slightly improved when the reaction was run at −60°C with cesium hydroxide (Table 5, entry 5).

3. Conclusion

In conclusion, we have synthesised new chiral poly(ethylene glycol) bound *cinchona* alkaloid salts with



Scheme 4. Synthesis of the MeO-PEG_{5000} *O*-bound *cinchona* alkaloid ammonium salts (ether linkage).



Scheme 5. Synthesis of the MeO-PEG_{5000} *O*-bound *cinchona* alkaloid ammonium salts (ester linkage).

Table 5. Evaluation of *O*-bound catalysts

Entry	Linker	Alkaloid	Solvent	Base	*T* (°C)	R–X	Time (h)[a]	Yield (%)[a]	Ee (%)[a]
1	Ether	CN	Toluene	KOH	0	BnBr	19	86	14 (*R*)
2	Ether	CD	Toluene	KOH	0	BnBr	15	74	54 (*S*)
3	Ester	CN	Toluene	KOH	0	BnBr	15	85	29 (*R*)
4	Ester	CD	Toluene	KOH	0	BnBr	15	83	62 (*S*)
5	Ester	CD	Toluene	CsOH	−60	BnBr	72	67	71 (*S*)

[a] See Table 1.

two different anchorage sites, and two different chain lengths. Application to the enantioselective alkylation of glycine Schiff base under phase-transfer conditions has clearly demonstrated high catalyst efficiency in terms of reaction time and yield, ee's are strongly dependent on the nature of the alkaloid, anchorage site, and linear polymer length, giving up to 81% ee. Further development of these PEG supported catalysts toward higher enantioselectivity and efficient recycling is in progress.[22]

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Bruker DPX 300 spectrometer in $CDCl_3$, and δ (ppm) is quoted relative to the residual signal of $CDCl_3$ (^{1}H NMR $\delta_H = 7.27$ ppm). HPLC was carried out using a Waters 600 apparatus equipped with Chiralcel columns. Specific rotation were measured with a Perkin–Elmer M341 polarimeter. IR spectra were recorded on a Perkin–Elmer 16 PC FT-IR. Flash chromatography was performed on silica gel Merck Kieselgel 60 (230–400 Mesh). THF was dried by heating under reflux over Na and benzophenone followed by distillation. CH_2Cl_2 and toluene were freshly distilled from CaH_2 under N_2.

4.2. Synthesis of MeO-PEG$_{5000}$-pClCH$_2$Bz

To a solution of poly(ethylene glycol) monomethyl ether (Mw 5000) (11.02 g, 2.20 mmol) in 200 mL of toluene was added 4-(chloromethyl)benzoyl chloride (500 mg, 2.64 mmol) and the mixture was refluxed for 12 h. The solution was then cooled to room temperature, concentrated to about 10 mL and poured onto 250 mL of diethyl ether. The polymer was filtered, washed several times with diethyl ether and dried under vacuum at 50°C for 12 h (95% yield). IR (Film): 2889, 2741, 1965, 1715, 1469, 1279, 1113, 842. ^{1}H NMR: δ 8.06 (d, 2H, $J = 8.4$ Hz), 7.48 (d, 2H, $J = 8.4$ Hz), 4.63 (s, 2H), 4.49 (m, PEG), 3.65 (m, PEG).

4.3. Synthesis of MeO-PEG$_{750}$-pClCH$_2$Bz

Same procedure as above. ^{1}H NMR: δ 7.98 (d, 2H, $J = 8.2$ Hz), 7.39 (d, 2H, $J = 8.2$ Hz), 4.55 (s, 2H), 4.40 (m, 2H, PEG), 3.57 (m, PEG), 3.31 (s, PEG).

4.4. Synthesis of MeO-PEG$_{5000}$ *N*-bound *cinchona* alkaloids

To a solution of MeO-PEG$_{5000}$-pClCH$_2$Bz (1 g, 0.19 mmol) in dichloromethane (30 mL) was added the alkaloid (0.20 mmol) and the mixture was refluxed for 24 h. The solution was then cooled to room temperature, concentrated to about 5 mL and poured onto 100 mL of diethyl ether. The polymer was collected by filtration, and dried under vacuum at 50°C to afford the catalysts in 80<yield<90%.

MeO-PEG$_{5000}$ *N*-bound cinchoninium chloride: $[\alpha]_D^{25} = +13.3$ (*c* 0.3, $CHCl_3$); ^{1}H NMR: δ 8.84 (d, 1H, $J = 4$ Hz), 8.06 (m, 4H), 7.55 (m, 2H), 7.39 (M, 3H), 5.65 (m, 1H), 5.23 (m, 1H), 4.96 (m, 3H), 4.55 (s, 2H), 4.41 (m, 2H, PEG), 3.58 (m, PEG), 2.84 (m, 2H), 2.54 (m, 3H), 2.17 (m, 1H), 1.74 (m, 3H), 1.49 (m, 2H).

MeO-PEG$_{5000}$ *N*-bound cinchonidinium chloride: $[\alpha]_D^{25} = -4.3$ (*c* 0.3, $CHCl_3$); ^{1}H NMR: δ 8.83 (d, 1H, $J = 4$ Hz), 8.00 (m, 4H), 7.54 (m, 2H), 7.39 (m, 3H), 5.64 (m, 1H), 5.17 (m, 1H), 4.88 (m, 1H), 4.62 (s, 2H), 4.50 (m, 2H, PEG), 3.65 (m, PEG), 3.10 (m, 2H), 2.67 (m, 3H), 2.27 (m, 1H), 1.75 (m, 3H), 1.48 (m, 2H).

MeO-PEG$_{5000}$ *N*-bound quininium chloride: $[\alpha]_D^{25} = -3.7$ (*c* 0.3, $CHCl_3$); ^{1}H NMR: δ 8.69 (d, 1H, $J = 4$ Hz), 7.97 (m, 3H), 7.51 (m, 2H), 7.34 (m, 2H), 7.27 (m, 1H), 5.92 (m, 1H), 5.22 (m, 1H), 5.02 (m, 1H), 4.60 (s, 2H), 4.41 (m, 2H, PEG), 3.64 (PEG), 3.08 (m, 2H), 2.91 (m, 1H), 2.80 (m, 1H), 2.57 (m, 1H), 2.24 (m, 1H), 1.96 (m, 4H), 1.75 (m, 2H), 1.52 (m, 2H), 1.16 (m, 1H).

MeO-PEG$_{5000}$ *N*-bound quinidinium chloride: $[\alpha]_D^{25} = +15.7$ (*c* 0.3, $CHCl_3$); ^{1}H NMR: δ 8.68 (d, 1H, $J = 4$ Hz), 7.97 (m, 3H), 7.53 (m, 2H), 7.38 (m, 2H), 7.31 (m, 1H), 5.95 (m, 1H), 5.21 (m, 1H), 5.02 (m, 1H), 4.56 (s, 2H), 4.39 (m, 2H, PEG), 3.62 (m, PEG), 3.11 (m, 1H), 2.89 (m, 2H), 2.80 (m, 1H), 2.56 (m, 1H), 2.23 (m, 1H), 1.95 (m, 4H), 1.74 (m, 2H), 1.53 (m, 2H), 1.18 (m, 1H).

4.5. Synthesis of MeO-PEG$_{750}$ *N*-bound *cinchona* alkaloids

Same procedure as above.

MeO-PEG$_{750}$ *N*-bound cinchoninium chloride: ^{1}H NMR: δ 8.77 (d, 1H, $J = 4$ Hz), 8.03 (m, 4H), 7.69 m, 2H), 7.38 (m, 3H), 5.96 (m, 1H), 5.17 (m, 1H), 5.03 (m,

1H), 4.54 (s, 2H), 4.38 (m, 2H, PEG), 3.57 (m, PEG), 3.30 (s, PEG), 3.07 (m, 2H), 2.51 (m, 3H), 2.09 (m, 1H), 1.72 (m, 3H), 1.58 (m, 2H).

MeO-PEG_{750} *N*-bound cinchonidinium chloride: ^{1}H NMR: δ 8.77 (d, 1H, $J=4$ Hz), 7.99 (m, 4H), 7.74 (m, 2H), 7.41 (m, 2H), 5.89 (m, 1H), 5.24 (m, 1H), 4.96 (m, 1H), 4.55 (s, 2H), 4.40 (m, 2H, PEG), 3.57 (m, PEG), 3.30 (s, PEG), 2.42 (m, 2H), 2.09 (m, 9H).

MeO-PEG_{750} *N*-bound quininium chloride: ^{1}H NMR: δ 8.60 (d, 1H, $J=4$ Hz), 7.95 (m, 3H), 7.66 (m, 2H), 7.39 (m, 2H), 7.20 (m, 1H), 6.07 (m, 1H), 5.11 (m, 1H), 4.90 (m, 1H), 4.56 (s, 2H), 4.41 (m, 2H, PEG), 3.57 (m, PEG), 3.30 (s, PEG), 2.98 (m, 1H), 2.62 (m, 2H), 2.48 (m, 1H), 2.13 (m, 4H), 1.97 (m, 3H), 1.72 (m, 2H), 1.23 (m, 1H), 1.15 (m, 1H).

MeO-PEG_{750} *N*-bound quinidinium chloride: ^{1}H NMR: δ 8.60 (d, 1H, $J=4$ Hz), 7.80 (m, 4H), 6.92 (m, 4H), 5.83 (m, 1H), 5.13 (m, 1H), 4.96 (m, 1H), 4.54 (s, 2H), 4.38 (m, 2H, PEG), 3.56 (m, PEG), 3.30 (s, PEG), 2.52 (m, 4H), 1.83 (m, 5H).

4.6. Synthesis of MeO-PEG_{5000} *O*-bound *N*-anthracenyl *cinchona* alkaloids

4.6.1. Ether linkage. To a mixture of sodium hydride (4.61 mg, 0.192 mmol) in dry DMF (50 mL) was added the *N*-anthracenyl *cinchona* alkaloid (0.192 mmol) at 22°C. The resulting mixture was stirred for 10 min. MeO-PEG_{5000}-O-p$ClCH_2$Bz (990 mg, 0.192 mmol) was added, and the mixture was stirred under nitrogen at 22°C for 5 days. The mixture was filtered, washed with diethyl ether and dried under vacuum for 1 day to afford the catalyst in 90% yield.

MeO-PEG_{5000} *O*-bound *N*-anthracenyl cinchoninium chloride: $[\alpha]_D^{25}=+4.0$ (*c* 0.3, $CHCl_3$); IR (Film): 2887, 2693, 1959, 1715, 1469, 1100, 844. ^{1}H NMR: δ 8.80 (m, 3H), 8.17 (m, 3H), 7.76 (m, 2H), 7.47 (m, 2H), 7.25 (m, 8H), 7.07 (m, 1H), 5.42 (m, 1H), 5.19 (m, 1H), 4.90 (m, 1H), 4.61 (s, 2H), 4.48 (m, 2H, PEG), 3.63 (PEG), 2.55 (m, 2H), 2.16 (m, 2H), 1.88 (m, 1H), 1.12 (m, 1H).

MeO-PEG_{5000} *O*-bound *N*-anthracenyl cinchonidinium chloride: $[\alpha]_D^{25}=-4.0$ (*c* 0.3, $CHCl_3$); IR (Film): 2893, 2693, 1970, 1720, 1454, 1061, 844. ^{1}H NMR: δ 8.81 (m, 3H), 8.39 (m, 3H), 7.94 (m, 2H), 7.43 (m, 2H), 7.27 (m, 8H), 7.09 (m, 1H), 6.04 (m, 1H), 5.05 (m, 1H), 4.67 (m, 1H), 4.31 (s, 2H), 4.13 (m, 2H, PEG), 3.57 (PEG), 2.83 (m, 2H), 1.97 (m, 2H), 1.35 (m, 1H), 1.12 (m, 1H).

4.6.2. Ester linkage. To a mixture of terephthaloyl chloride (38.8 mg, 0.192 mmol) in dichloromethane (50 mL) was added the MeO-PEG_{5000}-OH (960 mg, 0.192 mmol) and triethylamine (14.1 μL, 0.192 mmol) at 0°C. The mixture was refluxed for 15 h. After cooling to 0°C, *N*-anthracenyl *cinchona* alkaloid (0.192 mmol) and triethylamine (14.1 μL, 0.192 mmol) were added to the solution, which was refluxed for 15 h. The solution was then cooled, concentrated to about 5 mL and poured onto 100 mL of diethyl ether. The polymer was collected by filtration and dried under vacuum at 50°C for 1 day to afford the catalyst in 90% yield.

MeO-PEG_{5000} *O*-bound *N*-anthracenyl cinchoninium chloride: $[\alpha]_D^{25}=+3.7$ (*c* 0.3, $CHCl_3$); IR (Film): 2873, 2693, 1970, 1720, 1469, 1279, 842. ^{1}H NMR: δ 8.06 (m, 3H), 7.96 (m, 2H), 7.93 (m, 1H), 7.54 (m, 2H), 7.35 (m, 2H), 7.19 (m, 8H), 6.84 (m, 1H), 5.95 (m, 1H), 5.41 (m, 1H), 5.18 (m, 1H), 4.41 (m, 2H, PEG), 3.57 (m, PEG), 2.11 (m, 2H), 1.77 (m, 2H), 1.18 (m, 2H).

MeO-PEG_{5000} *O*-bound *N*-anthracenyl cinchonidinium chloride: $[\alpha]_D^{25}=-4.7$ (*c* 0.3, $CHCl_3$); IR (Film): 2889, 2693, 1962, 1715, 1469, 1279, 842. ^{1}H NMR: δ 8.17 (m, 3H), 8.11 (m, 2H), 7.67 (m, 3H), 7.33 (m, 2H), 7.22 (m, 8H), 6.73 (m, 1H), 5.85 (m, 1H), 5.41 (m, 1H), 5.12 (m, 1H), 4.41 (m, 2H, PEG), 3.57 (m, PEG), 2.14 (m, 2H), 1.67 (m, 2H), 1.19 (m, 2H).

4.7. Benzylation of *N*-diphenylmethylene glycine *t*-butyl ester

4.7.1. Liquid/liquid phase-transfer conditions. To a mixture of *t*-butyl glycinate benzophenone imine (50 mg, 0.166 mmol), and catalyst MeO-PEG_{5000} *N*-bound cinchonidinium chloride (87.2 mg, 0.017 mmol) in toluene (5 mL) was added benzyl bromide (0.1 mL, 0.83 mmol) and a 50% KOH aqueous solution (0.1 mL) at 0°C. The mixture was stirred vigorously for 15 h (the reaction was monitored by TLC: eluent CH_2Cl_2). Then, the mixture was quenched with 2 mL of water. Water was extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate, concentrated under vacuum and the residue was taken up with CH_2Cl_2 and poured onto diethyl ether to precipitate the polymer. The filtrate was then concentrated under vacuum and purified by flash chromatography (dichloromethane/triethylamine: 99/1) to afford the desired product (*S*)-α-benzyl *t*-butyglycinate benzophenone imine as a colorless oil in 84% yield. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD-H column, 0.5% *iso*-propanol, heptane, 1 mL min^{-1}, $\lambda=254$ nm, 22°C, retention times: (*R*) enantiomer: 10.4 min, (*S*) enantiomer: 18.1 min. Spectral data are in agreement with literature values.[13]

4.7.2. Liquid/solid phase-transfer conditions. To a mixture of *t*-butyl glycinate benzophenone imine (50 mg, 0.166 mmol), and catalyst MeO-PEG_{5000} *N*-bound cinchonidinium chloride (87.2 mg, 0.017 mmol) in toluene (5 mL) was added benzyl bromide (0.1 mL, 0.83 mmol) and $CsOH\cdot H_2O$ (83.6 mg, 0.458 mmol) at −60°C. The mixture was stirred vigorously for 26 h. The rest of the procedure was then the same as above.

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22. We have studied the recycling of the MeO-PEG_{5000} *N*-bound cinchonidinium chloride. However, the second run gave a dramatic drop in enantioselectivity, indicating deterioration of the catalyst during the first run. Saponification of the ester function due to basic conditions and/or organic transformation of the alkaloid may be responsible for this decreased enantioselectivity.