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Immobilization of catalysts derived from *Cinchona* alkaloids on modified poly(ethylene glycol)

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Abstract—The straightforward immobilization of some derivatives of *Cinchona* alkaloids on modified poly(ethylene glycol)s is reported. The compounds, obtained by simple reactions exploiting different sites for the attachment of the alkaloids to the polymer, were tested as catalysts in the enantioselective benzylation of the benzophenone imine of glycine *t*-butyl ester (ee up to 64%) and in the conjugate addition of thiophenol to cyclohexenone (ee 22%). The observed stereoselectivities were compared to those obtained either with the unsupported catalysts or with the catalysts immobilized on different polymeric matrixes. The influence of the poly(ethylene glycol) moieties on the catalytic activity is discussed.

1. Introduction

Over the last 25 years chiral ligands and catalysts derived from *Cinchona* alkaloids have been used to perform a variety of fundamental organic reactions in an enantioselective fashion.[1] With the aim of improving the efficiency of these catalytic processes by making the ligands and catalysts readily recoverable and recyclable,[2] considerable efforts have been devoted to the immobilization of *Cinchona* alkaloids on polymer supports. In this context, two main strategies have been followed, exploiting either insoluble organic polymers,[3] or inorganic matrixes (mostly silica gel).[4] Soluble supports have been used much less frequently.[5] In particular, Bolm[6] and Janda[7] reported the immobilization of modified quinine and quinidine on poly(ethylene glycol) (PEG) to afford very efficient and recoverable ligands for the Sharpless' asymmetric dihydroxylation reaction. To the best of our knowledge, however, no examples of *Cinchona* catalysts supported on soluble polymers have been described. As part of a project[8–11] devoted to the immobilization of organic (i.e. metal free) catalysts[12] on soluble polymers, we report herein the synthesis of PEG-supported *Cinchona* alkaloids, and their use in asymmetric catalytic processes.

2. Results and discussion

The monomethyl ether of PEG of M_W 5000 Daltons (MeOPEG) was selected as the support.[5,13] This inexpensive, readily functionalized, and commercially available polymer offers distinctive advantages over other supports because it is readily soluble in many organic solvents and insoluble in a few other solvents. Exploiting this property, one can run a reaction under homogeneous catalysis conditions (where the chiral catalyst is expected to perform at its best) and recover the catalyst as if it were bound to an insoluble matrix. In addition, PEG has been shown to be a relatively inert support, interfering minimally or not-at-all with the chemical and stereochemical course of stereoselective processes promoted by PEG-supported catalysts.[5] Moreover, catalyst recovery and recycling is possible for at least a few reaction cycles,[8–11] with the metal-free nature of the catalysts greatly facilitating this procedure since metal re-loading, often required in metal-catalyzed reactions,[6,7,14] is not necessary.

On the basis of our previous experience in this field, two activated derivatives of MeOPEG, namely mesylate **1** and bromide **2** (Scheme 1) were employed to support the catalysts. They were easily obtained in $\geq 95\%$ yield

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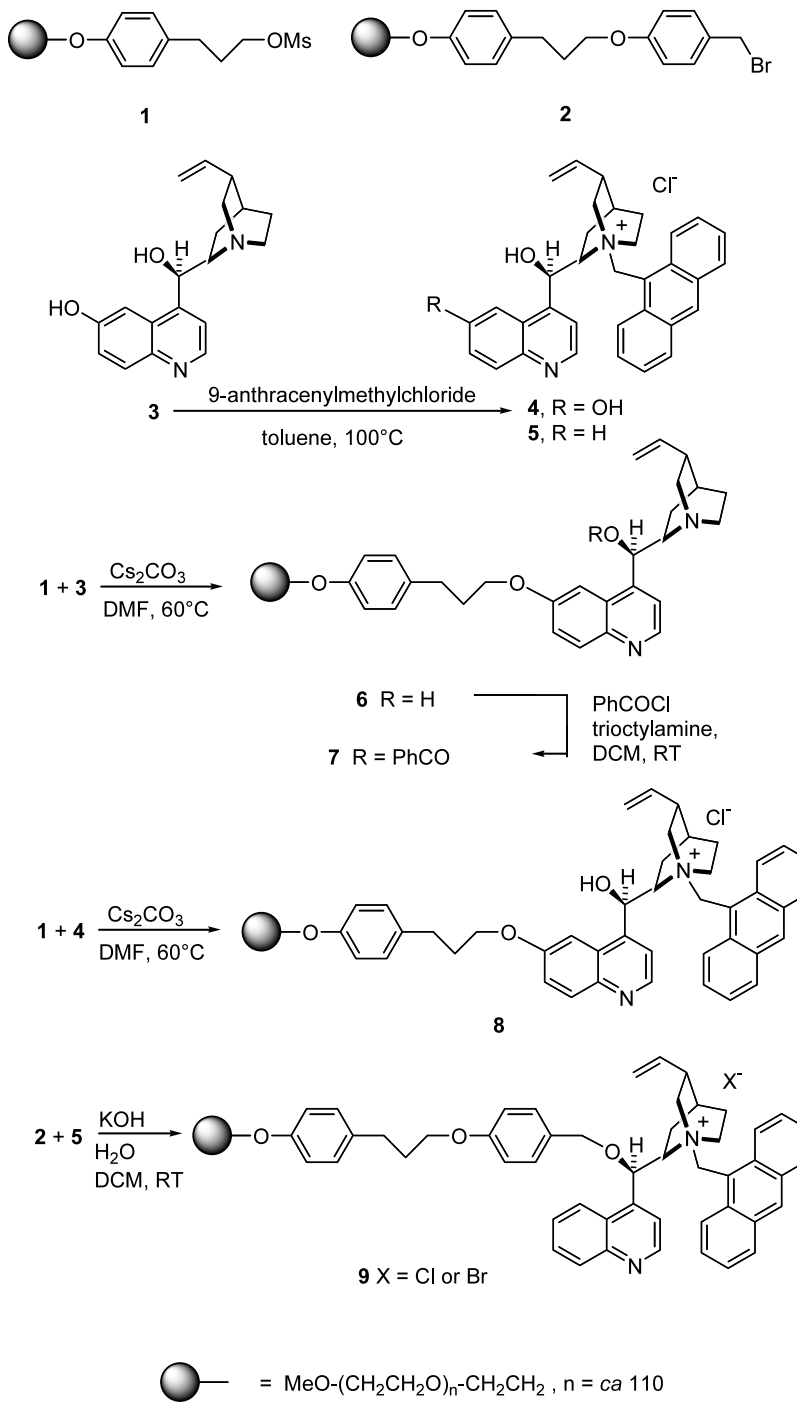


Scheme 1. Synthesis of supported catalysts **6**–**9**.

from MeOPEG as previously described[8,15] and featured good leaving groups to facilitate alkaloid attachment via nucleophilic displacement.

So far, *Cinchona* alkaloids have been immobilized exploiting three different sites of attachment,[1] namely the most commonly used vinyl residue (employed for instance in combination with MeOPEG),[6,7] the benzyl-type oxygen at C-9 (*Cinchona* alkaloids' numbering), and the less frequently employed bridgehead nitrogen of the quinuclidine residue. We reasoned that demethylation of the methoxy group at C-6′ of quinine and quinidine could provide another reactive site for selective attachment. Accordingly, 6′-hydroxycinchonine (6′-*nor*quinine) **3**[16] was synthesized following a known procedure and, from this, quaternary ammonium salt **4** was obtained in 81% yield by alkylation[17] with 9-(chloromethyl)anthracene in toluene (Scheme 1).

Reaction of the caesium salt of compound **3** with mesylate **1** (DMF, 50–60°C, 40 h) afforded adduct **6** in 90% isolated yield.[†] Since relevant enantioselective pro-

[†] For a detailed description of yield and purity determination for PEG-supported compounds, see Section 4.

cesses involve *Cinchona* alkaloid catalysts featuring an ester residue at C-9,[18,19] compound **6** was transformed into the benzoate **7** by reaction with benzoyl chloride and trioctylamine‡ in DCM (83% yield). This compound was also involved in the preparation of catalysts for enantioselective fluorination reactions.[20,21] Reaction of ammonium salt **4** with mesylate **1** under the same conditions employed for the synthesis of **6** afforded adduct **8** in 75% yield.

Finally, a DCM solution of the commercially available *N*-(9-anthracenylmethyl)cinchonidinium chloride **5** (1.2 mol equiv.) and bromide **2** in the presence of a 50% w/w aqueous solution of KOH (rt, 72 h) gave the supported ammonium salt **9** in 70% yield.

It must be noted that the synthesis of **8** and **9** released a mesylate and a bromide ion, respectively. These can compete with the pre-existing chloride ion in neutralizing the positive charge at the bridgehead nitrogen. While ^{1}H NMR analysis allowed to rule out a chloride/mesylate exchange in compound **8**, no evidence was collected about the counterion nature in adduct **9**, that might either be chloride or bromide.

The supported catalysts **8** and **9** were then tested under different conditions in the enantioselective benzylation of the *N*-benzophenone imine derived from glycine *t*-butyl ester (Fig. 1) to afford the corresponding (*S*)-phenylalanine precursor **10**. This reaction has been shown to occur with excellent levels of enantiomeric excess (ee) by Corey[17] (94% ee under solid/liquid conditions with solid CsOH as the base, –78°C, 23 h) and Lygo[22] (91% ee under liquid/liquid conditions with 50% aqueous KOH as the base, rt, 18 h). The results obtained with the same loading of catalysts **8** and **9** (10% mol) are collected in Table 1. The yields were determined by ^{1}H NMR analysis of the crude product and confirmed by HPLC on a chiral stationary phase while assessing the ee; the absolute configuration of the product was assigned by comparison of HPLC profiles with that of a sample of (*S*)-**10** of known absolute configuration.

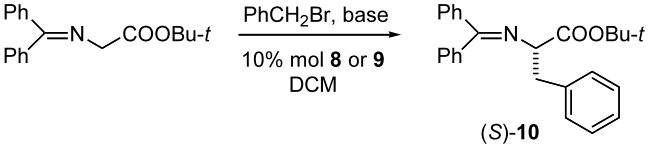


Figure 1. Synthesis of adduct (*S*)-**10**.

As can be seen from the reported data, the supported catalysts **8** and **9** promoted the formation of compound **10** in ee lower than those observed when the reaction was carried out with catalyst **5**. In particular, the quininium catalyst **8** performed less well than the cinchonidinium analog **9** (entry 1 versus 8 and 5 versus 9, Table 1). The latter, therefore, was used for most of the experiments. The difference in behavior of the two catalysts, expected on the basis of previous observations[23] although not to the dramatic extent observed here, suggested that the introduction of the polymer chain affected **8** more strongly than **9**.

When the same base was used, solid/liquid conditions gave higher ee than liquid/liquid conditions (entry 3 versus 1). The use of solid CsOH instead of solid KOH improved the ee (entry 7 versus 4). Low reaction temperatures were beneficial for the ee but not for the chemical yield (entry 7 versus 6 versus 5). Under the best conditions (entry 7), a maximum ee of 64% was observed for the product obtained in 75% yield.

Among the factors that can explain why the enantioselectivities observed here were lower than those obtained with the unsupported catalysts,[17,22] the involvement of the PEG portion of catalysts **8** and **9** seems the most likely. We believe that PEG can influence the steric course of the reaction essentially exerting two effects: Firstly, by increasing the polarity of the organic phase, PEG in part prevents the formation of a tight ion pair

Table 1. Enantioselective benzylation of the benzophenone imine of glycine *t*-butyl ester catalyzed by compounds **8** and **9** under different conditions

Entry	Catalyst	Base	*T* (°C); time (h)	Yield (%)[a]	Ee (%)[b]
1	**9**	50% aq. KOH	23; 20	93	30
2	**9**	10% aq. KOH	23; 20	65	18
3	**9**	Solid KOH	23; 20	85	40
4	**9**	Solid KOH	−78; 60	80	58
5	**9**	Solid CsOH	−78 to 23; 22	92	30
6	**9**	Solid CsOH	−78 to −5; 22	86	46
7	**9**	Solid CsOH	−78; 60	75	64
8	**8**	50% aq. KOH	23; 20	90	8
9	**8**	Solid CsOH	−78 to 23; 22	94	12

[a] Determined by ^{1}H NMR and HPLC on the crude product. The only contaminant was the starting material.
[b] Determined by HPLC on a chiral stationary phase.

‡ The use of trioctylamine instead of other bases (e.g. TEA, DIPEA) as HCl scavenger in this reaction greatly simplified the isolation of pure PEG-supported compounds (see Ref. 15).

between the enolate and the chiral ammonium salt (a factor regarded as crucial for achieving high stereocontrol).[17] Secondly, PEG enhances the solubility of the inorganic cation in the organic phase leading to competing nonstereoselective alkylation occurring on an achiral caesium or potassium enolate rather than the chiral ammonium enolate of the substrate.

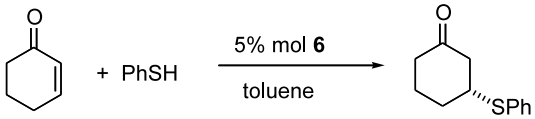
To establish the influence of PEG, control experiments were performed by running the reaction with unsupported catalyst **5** in the presence of the bismethyl ether of PEG having M_W 2000 Daltons. Under the conditions of entries 1 and 7 compound **10** was obtained in 76 and 65% ee, respectively. The almost perfect coincidence of the ee obtained under solid/liquid conditions with catalyst **5** in the presence of PEG (65%) and with catalyst **9** (64%) seems to indicate that the above-mentioned solubilizing effect of the inorganic cation in organic solution can indeed be a negative factor in the reaction promoted by the supported catalyst. In this respect, it is also worth mentioning that the PEG-portion of achiral PEG-supported phase transfer catalysts[8,10] was shown to have very limited catalytic ability itself, but strongly enhanced that of a PEG-supported catalyst in base-promoted alkylations.[8,10]

Recycling of the supported catalyst **9** was then studied: The catalyst was recovered from the reaction (entry 7) by evaporation of the solvent and addition of diethyl ether. In this solvent the unsupported materials were readily soluble while the insoluble catalyst was isolated by filtration. However, ^{1}H NMR analysis showed that the recovered material was largely decomposed. A liberal estimate indicated that **9** represented no more than 50% of the recovered mixture. It was not surprising, therefore, that when this material was used to catalyze a second reaction run described in Fig. 1 (carried out under the conditions of entry 7) product **10** was isolated in only 11% yield and 30% ee. Repetition of this experiment after addition of fresh CsOH improved the yield of **10** to 70% but the ee was lowered to 25%.

In order to establish if the instability of the catalyst was due to the presence of PEG, the reaction (Fig. 1 was repeated at −78°C for 20 h with catalyst **5** and with **5**/PEG (see above). ^{1}H NMR analysis of the catalyst recovered from both these reactions showed that extensive catalyst decomposition occurred, independently of the presence of PEG, as shown by the appearance, inter alia, of peaks at δ 9.80, 9.05, 8.60, 8.25, 6.15, 5.20 ppm. These experiments suggested that the unsupported catalyst was intrinsically unstable and such remained when supported on PEG.

The results obtained in the synthesis of **10** with catalyst **9** can be compared to those observed under very similar conditions (entry 7) with the catalyst prepared by Plaquevent and Cahard[24] by immobilization of **5** on insoluble Merrifield resin by means of an ether bond, also involving the benzyl-type oxygen. With this insoluble catalyst product **10** was isolated in 67% yield and 94% ee. Unfortunately, no mention of the stability, recovery, and recycling of the catalyst was reported. This high ee value has not been surpassed by the use of other insoluble-polymer supported catalysts related to **5**, where the bridgehead nitrogen was employed for polymer attachment.[25,26] Since some of these catalysts could be recycled, they appear to be stable.[25]

The conjugate addition of thiophenol to cyclohexenone to afford adduct (*R*)-**11** (Fig. 2) carried out in the presence of **6** (5% mol) was studied to test the behavior of a neutral supported catalyst. After 24 h reaction in toluene (a solvent in which the PEG-derivative is soluble at rt) the product was obtained in 75% yield and 22% ee, as determined by comparison of its specific rotation value. The obtained ee was lower than that observed by Wynberg and Hiemstra in the same reaction catalyzed by 1% molar of non supported quinine (ee = 41%).[27] The possibility that the PEG backbone can, at least in part, prevent the formation of the hydrogen bonding between the catalyst and cyclohexenone (a mechanistic factor regarded as relevant to secure a stereoselective addition reaction[27]) can tentatively rationalize the decrease in the ee of adduct **11**. It is interesting to note, however, that the ee obtained with the PEG-supported catalyst **6** was slightly higher than that observed in a very similar reaction (addition of 4-methylthiophenol to cyclohexenone) with quinine immobilized on insoluble polystyrene as the catalyst (ee = 18% under the same reaction conditions).[28]



(*R*)-**11**

Figure 2. Synthesis of adduct (*R*)-**11**.

3. Conclusions

In conclusion, some derivatives of *Cinchona* alkaloids were supported on modified poly(ethylene glycol)s by simple reactions and exploiting different sites of attachment for the polymer. The resulting species were employed as catalysts in the enantioselective benzylation of the benzophenone imine of glycine *t*-butyl ester (ee up to 64%) and in the conjugate addition of thiophenol to cyclohexenone (ee 22%). Tentative explanations for the fact that the observed stereoselectivities were lower than those obtained with the unsupported catalysts have been proposed.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded at 300 MHz and were referenced to tetramethylsilane (TMS) at 0.00 ppm. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in chloroform-*d* ($CDCl_3$). Optical rotations were measured at the Na-D line in a 1 dm

cell at 22°C. IR spectra were recorded on thin film or as solution in CH_2Cl_2. **1**, **2**, **3**, the benzophenone imine of *t*-butyl glycinate,[29] and **10**[17] are known compounds; **5** is commercially available.

All PEG samples were melted at 80°C in vacuum for 30 min before use to remove traces of moisture. After reaction PEG-supported product purification involved evaporation of the reaction solvent in vacuum and addition of the residue dissolved in a few mL of CH_2Cl_2 to diethylether (50 mL g^{-1} of polymer), which was stirred and cooled at 0°C. After 20–30 min stirring at 0°C, the obtained suspension was filtered through a sintered glass filter, and the solid repeatedly washed on the filter with diethylether (up to 100 mL per gram of polymer, overall).

4.2. Yield and purity determination of PEG-supported compounds

The yields of the PEG-supported compounds were determined by weight with the assumption that M_w is 5000 Da for the PEG fragment. The M_w actually ranged from 4500 to 5500. The indicated yields were for pure compounds. The purity of these compounds was determined by ^{1}H NMR analysis in $CDCl_3$ at 300 MHz with pre-saturation of the methylene signals of the polymer at $\delta = 3.63$. In recording the NMR spectra, a relaxation time of 6 s and an acquisition time of 4 s were used to ensure complete relaxation and accuracy of the integration. The relaxation delay was selected after T_1 measurements. The integration of the signals of the PEG CH_2OCH_3 fragment at $\delta = 3.30$ and 3.36 were used as internal standard. The estimated integration error was +5%.

4.3. *N*-(9-Anthracenylmethyl)-6′-hydroxycinchoninium chloride, 4

To a suspension of compound **3** (0.310 g, 1 mmol) in dry toluene (5 mL) stirred at 100°C, 9-anthracenylmethyl chloride (0.238 g, 1.05 mmol) was added in one portion. After 20 h stirring at 100°C, the mixture was cooled at rt and poured into diethylether (10 mL). The precipitate was filtered and washed with diethylether to afford a pale yellow solid (0.434 g, 81% yield). Mp 160°C (dec.); $[\alpha] = -320.7$ (*c* 0.3, chloroform). ^{1}H NMR: δ 9.25 (bs, 1H, ArOH), 9.08 (d, 1H, $J = 9.0$ Hz, H-C1 of anthracenyl), 8.75 (d, 1H, $J = 4.5$ Hz, H-C2 of quinoline), 8.46 (d, 1H, $J = 9.2$ Hz, H-C7 of anthracenyl), 8.15 (d, 1H, $J = 2.1$ Hz, H-C5 of quinoline), 7.97 (s, 1H, H-C10 of anthracenyl), 7.88 (d, 1H, $J = 4.5$ Hz, H-C3 of quinoline), 7.64 (d, 1H, $J = 8.2$ Hz, H-C4 of anthracenyl), 7.58 (m, 2H, H-C8 of quinoline and H-C5 of anthracenyl), 7.47 (bd, 1H, $J = 3.8$ Hz, quinoline-CH-*OH*), 7.40 (t, 1H, $J = 7.8$ Hz, H-C2 of anthracenyl), 7.26 (m, 2H, H-C7 and H-C3 of anthracenyl), 7.08 (t, 1H, $J = 7.4$ Hz, H-C6 of anthracenyl), 6,78 (m, 2H, quinoline–*CH*-OH and H-C7 of quinoline), 6.49 (B part of AB system, 1H, $J = 15.7$ Hz, one H of anthracene-CH_2), 6.39 (A part of AB system, 1H, $J = 15.7$ Hz, one H of anthracene-CH_2), 5.34 (m, 2H, C*H*=C*H*H), 4.99 (d, 1H, CH*H*=), 4.62 (m, 2H, *H*C-COH and one H of N-CH_2CH$_2$), 4.00 (d, 1H, $J = 13.0$ Hz, one H of N-CH_2–CH-vinyl), 2.68 (t, 1H, $J = 12.0$ Hz, one H of N-CH_2–CH-vinyl), 2.27 (m, 1H, N-CH_2CH$_2$), 2.18 (m, 1H, *H*-C-vinyl), 1.73 (m, 3H, bridgehead CH and one H of both CH_2 bound to this C), 1.07 (m, 2H, one H of both CH_2 bound to the bridgehead C). $C_{34}H_{33}ClN_2O_2$ requires: C, 76.03; H, 6.19; N, 5.22. Found: C, 75.88; H, 6.02; N, 5.08%.

4.4. General procedure for the synthesis of adducts 6 and 8 from mesylate, 1

The synthesis of adduct **8** is illustrative of the procedure. To a solution of mesylate **1** (0.940 g, 0.181 mmol) in dry DMF (3 mL), cesium carbonate (0.140 g, 0.398 mmol) and compound **4** (0.100 g, 0.186 mmol) were added in this order. The resulting mixture was stirred at 50–60°C for 40 h. DCM (2 mL) was then added to the cooled mixture and cesium carbonate was filtered off. The filtrate concentrated under vacuum and diethylether was added to the residue. The resulting solid was filtered off, washed with diethylether, and dried to afford the product as a pale brown solid (0.770 g, 75% yield). $[\alpha] = -7.75$ (*c* 0.3, chloroform). ^{1}H NMR: δ 8.74 (d, 1H, $J = 4.5$ Hz, H-C2 of quinoline), 8.49 (d, 2H, $J = 9.0$ Hz, H-C1 and H-C8 of anthracenyl), 8.42 (s, 1H, H-C10 of anthracenyl), 8.06 (d, 1H, $J = 9.2$ Hz, H-C8 of quinoline), 8.00 (d, 2H, $J =$ H-C3 of anthracenyl), 7.50 (m, 5H, H-C2, H-C3, H-C6, and H-C7 of anthracenyl, and H-C7 of quinoline), 7.28 (d, 1H, $J =$ 4.5 Hz, H-C3 of quinoline), 7.23 (s, 1H, H-C5 of quinoline), 7.13 (B part of AB system, 2H, $J = 8.4$ Hz, H *meta* to O in PEG-O-*Ph*), 6.84 (A part of AB system, 2H, $J = 8.4$ Hz, H *ortho* to O in PEG-O-*Ph*), 6.10 (m, 1H, C*H*=CH$_2$), 5.01 (m, 2H, CH=CH_2), 4.39 (s, 2H, anthracenyl-CH_2), 4.10 (m, 5H, PEGCH_2OPh, CH_2O-quinoline, and C*H*-OH), 3.87 (t, 2H, $J = 6.7$ Hz, PEGOCH_2CH$_2$OPh), 3.36 (s, 3H, *Me*OPEG), 3.00–2.50 (m, 4H, H close to N in quinuclidine), 2.80 (t, 2H, $J = 7.8$ Hz, PhCH_2), 2.46 (m, 1H, *CH*-vinyl), 2.33 (m, 1H, other H close to N in quinuclidine), 2.17 (m, 2H, CH$_2$$CH_2CH_2$), 1.90–1.50 (m, 5H, remaining H of quinuclidine).

4.4.1. Compound 6. Compound **6** was obtained in 90% yield by a similar procedure to that shown above. $[\alpha] = -3.7$ (*c* 0.15, chloroform). ^{1}H NMR: δ 8.75 (d, 1H, $J = 4.5$ Hz, H-C2 of quinoline), 8.03 (d, 1H, $J = 9.0$ Hz, H-C8 of quinoline), 7.53 (d, 1H, $J = 4.5$ Hz, H-C3 of quinoline), 7.38 (d, 1H, $J = 9.0$ Hz, H-C8 of quinoline), 7.28 (s, 1H, H-C5 of quinoline), 7.13 (B part of AB system, 2H, $J = 8.4$ Hz, H *meta* to O in PEG-O-*Ph*), 6.84 (A part of AB system, 2H, $J = 8.4$ Hz, H *ortho* to O in PEG-O-*Ph*), 5.83 (m, 1H, C*H*=CH$_2$), 5.45 (d, 1H, $J = 5.0$ Hz, C*H*-OH), 4.92 (m, 2H, CH=CH_2), 4.10 (m, 4H, PEGCH_2OPh and CH_2O-quinoline), 3.87 (t, 2H, $J = 6.7$ Hz, PEGOCH_2CH$_2$OPh), 3.36 (s, 3H, *Me*OPEG), 3.30 (m, 2H, MeO CH_2), 3.10–2.50 (m, 5H, H close to N in quinuclidine), 2.80 (t, 2H, $J = 7.8$ Hz, PhCH_2), 2.26 (m, 1H, *CH*-vinyl), 2.10 (m, 2H, CH$_2$$CH_2CH_2$), 1.90–1.50 (m, 5H, remaining H of quinuclidine).

4.5. Benzoylation of compound 6 to give ester, 7

To a stirred solution of compound **6** (0.525 g, 0.093 mmol) and trioctylamine (0.082 mL, 0.186 mmol) in DCM (3 mL), freshly distilled benzoyl chloride (0.017 mL, 0.140 mmol) in DCM (0.5 mL) was added. After 15 h stirring at rt, the reaction was quenched by the addition of water (2 mL). The organic phase was separated, the aqueous phase was extracted with DCM (2×5 mL), and the combined organic phases were dried over sodium sulfate. Evaporation of the solvent under vacuum gave a residue to which diethylether (10 mL) was added. The suspension was stirred for 30 min and then filtered to afford the product as a pale yellow solid (0.443 g, 83%). $[\alpha]=+6.6$ (*c* 0.3, chloroform). ^{1}H NMR: δ 8.68 (d, 1H, $J=4.5$ Hz, H-C2 of quinoline), 8.10 (d, 1H, $J=9.0$ Hz, H-C8 of quinoline), 8.00 (d, 2H, $J=9.0$ Hz, H *ortho* to C=O), 7.54 (d, 1H, $J=4.5$ Hz, H-C3 of quinoline), 7.40 (m, 4H, H-C8 of quinoline and remaining 3 H of *Ph*CO), 7.28 (s, 1H, H-C5 of quinoline), 7.13 (B part of AB system, 2H, $J=8.4$ Hz, H *meta* to O in PEG-O-*Ph*), 6.84 (A part of AB system, 2H, $J=8.4$ Hz, H *ortho* to O in PEG-O-*Ph*), 6.70 (d, 1H, $J=6.0$ Hz, *CH*-OCOPh), 5.85 (m, 1H, C*H*=CH$_2$), 5.00 (m, 2H, CH=C*H*$_2$), 4.10 (m, 4H, PEG*CH*$_2$OPh and *CH*$_2$O-quinoline), 3.86 (t, 2H, $J=$ 6.7 Hz, PEGO*CH*$_2$CH$_2$OPh), 3.36 (s, 3H, *Me*OPEG), 3.30 (m, 2H, MeO *CH*$_2$), 2.80 (t, 2H, $J=7.8$ Hz, Ph*CH*$_2$), 2.70–2.50 (m, 5H, H close to N in quinuclidine), 2.32 (m, 1H, *CH*-vinyl), 2.17 (m, 2H, CH$_2$*CH*$_2$CH$_2$), 2.05–1.50 (m, 5H, remaining H of quinuclidine).

4.6. Synthesis of catalyst 9 from bromide, 2

To a stirred solution of bromide **2** (2.0 g, 0.376 mmol) in DCM (10 mL), compound **5** (0.235 g, 0.451 mmol) and a 50% w/w aqueous solution of KOH (0.7 mL) were added in this order. The reaction was vigorously stirred at rt for 72 h (longer reaction times led to the formation of by-products) and water (5 mL) was then added. The mixture was then filtered on a Celite cake and the filtrate was allowed to stand for a couple of hours to obtain a satisfactory phase separation (the time necessary for phase separation was found to directly depend on the amount of **2** used). The organic phase was then separated and the aqueous phase was extracted with DCM (3×10 mL). The combined organic phases were dried over sodium sulfate, filtered and concentrated under vacuum to give a residue (ca. 2 mL) from which the product was precipitated by addition of diethylether. The product was then isolated by filtration as a pale brown solid (1.485 g, 70% yield). $[\alpha]=+3.3$ (*c* 0.8, chloroform). ^{1}H NMR: δ 8.88 (d, 1H, $J=4.6$ Hz, H-C2 of quinoline), 8.59 (d, 2H, $J=8.4$ Hz, H-C1 and H-C8 of anthracenyl), 8.41 (s, 1H, H-C10 of anthracenyl), 8.27 (d, 1H, $J=8.7$ Hz, H-C8 of quinoline), 8.13 (d, 2H, $J=8.4$, H-C5 of quinoline), 8.00 (d, 2H, $J=7.6$ Hz, H-C4 and H-C5 of anthracenyl), 7.73 (t, 1H, $J=7.6$ Hz, H-C6 of quinoline), 7.50 (m, 5H, H-C2, H-C3, H-C6, and H-C7 of anthracenyl, and H-C7 of quinoline), 7.30 (d, 1H, $J=$ 4.3 Hz, H-C3 of quinoline), 7.08 (m, 4H, H *meta* to O in the phenyl rings of the spacer), 6.82 (m, 4H, H *ortho* to O in the phenyl rings of the spacer), 6.10 (m, 1H, C*H*=CH$_2$), 5.14 (t, 1H, $J=4.0$ Hz, *H*-C-N$^+$), 5.01 (m, 2H, CH=C*H*$_2$), 4.39 (s, 2H, Ph-*CH*$_2$-O-CH), 4.36 (s, 2H, anthracenyl-C*H*$_2$), 4.10 (m, 3H, PEG*CH*$_2$OPh and C*H*-O), 3.90 (m, 4H, PEGO*CH*$_2$CH$_2$OPh and PhCH$_2$CH$_2$*CH*$_2$OPh), 3.36 (s, 3H, *Me*OPEG), 2.95–2.50 (m, 5H, Ph*CH*$_2$CH$_2$CH$_2$OPh and 3H close to N$^+$), 2.36–1.40 (m, 9H, PhCH$_2$*CH*$_2$CH$_2$OPh and remaining H in quinuclidine).

4.7. General procedures for the synthesis of 10

4.7.1. Liquid/liquid procedure. To a stirred solution of the imine (0.060 g, 0.2 mmol), benzyl bromide (0.031 mL, 0.26 mmol), and catalyst **9** (0.112 g, 0.02 mmol) in dry DCM (5 mL), a 50% w/w aqueous solution of KOH (0.5 mL) was added. The solution was vigorously stirred at rt for 20 h, whereupon 2 mL of water were added. The organic phase was separated, the aqueous phase was washed with DCM (2×5 mL), and the combined organic phases were dried over sodium sulfate and concentrated under vacuum. To the residue, diethylether (10 mL) was added to precipitate the catalyst. This was filtered off and the filtrate was concentrated under vacuum to give the product (93% yield by NMR) contaminated only by the starting imine. The ee was determined by HPLC on a Chiralcel OD column, 99:1 hexane: 2-propanol mixture as eluent, flow rate 1 mL/min, 23°C, $\lambda=254$ nm: retention time of the minor (*R*) isomer: 7.3 min; of the major (*S*) isomer: 10 min.

4.7.2. Solid/liquid procedure. To a stirred solution of the imine (0.060 g, 0.2 mmol), benzylbromide (0.120 mL, 1 mmol), and catalyst **9** (0.112 g, 0.02 mmol) in dry DCM (5 mL) cooled at −78°C, CsOH monohydrate (0.336 g, 2 mmol) was added. The solution was vigorously stirred at −78°C for 60 h. The mixture was the warmed up to rt and CsOH was filtered off. The filtrate was concentrated under vacuum. To the residue, diethylether (10 mL) was added to precipitate the catalyst. This was filtered off and the filtrate was concentrated under vacuum to give the product (75% yield by NMR) contaminated only by the starting imine. The ee was determined by HPLC as above.

4.8. Synthesis of adduct 11

To a stirred solution of freshly distilled thiophenol (0.118 mL, 1.15 mmol) in dry toluene (5 mL) kept under nitrogen, catalyst **6** (0.275 g, 0.05 mmol) was added. After 5 min stirring at rt, cyclohexenone (0.097 mL, 1.0 mmol) in toluene (1 mL) was added and stirring was continued for 24 h at rt. The solvent was then evaporated under vacuum and diethylether (10 mL) was added to the residue. The precipitated catalyst was removed and recovered by filtration, whereas the filtrate was concentrated under vacuum to afford the crude product, that was purified by flash chromatography with a 9:1 hexanes:EtOAc mixture as eluent. Adduct (*R*)-**11**, $[\alpha]_{578}=+21.5$ (*c* 1.0, CCl_4) was obtained in 75% yield (0.206 g).

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