Poly(ethylene glycol) Supported Chiral Quaternary Ammonium Salts as Phase-Transfer Catalysts for Catalytic Enantioselective Synthesis of α-Amino Acids

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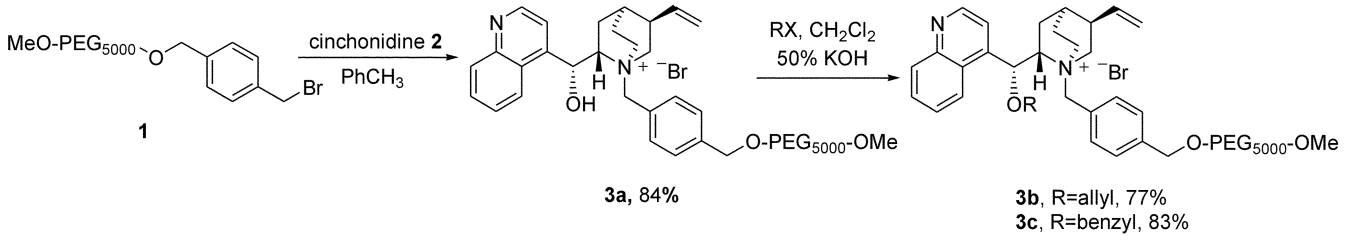
The enantioselective synthesis of α-amino acids using chiral phase transfer catalysts derived from cinchona alkaloids has been widely studied over the last decade.[1] The immobilization of chiral catalysts on polymer supports is a current subject of intense research because of some advantages: simple catalyst recovery, recycle, and good stability.[2] While the use of insoluble supports has been widespread,[3] immobilization on soluble supports has been used much less frequently.[4] In particular, the monomethyl ether of poly(ethylene glycol) (PEG) has successfully being used for supporting chiral ligand to be transformed in catalysts for the Sharpless' asymmetric dihydroxylation reaction.[5] Recently, Cahard and Benaglia groups reported enantioselective synthesis of α-amino acids using poly(ethylene glycol) supported cinchona alkaloids as phase transfer catalysts independently.[6] These reports prompt us to disclose our results with chiral new PEG supported cinchonidinium salts for the enantioselective synthesis of α-amino acids.

As part of our research program toward the development of a more effective cinchona alkaloid derived phase transfer catalysts, we report the catalytic enantioselective reactions promoted by quaternary ammonium salts from cinchona alkaloids as phase transfer catalysts.[7] In this paper, we wish to report the catalytic enantioseletive alkylation of *N*-diphenylmethylene glycine *t*-butyl ester **6a** using PEG-supported cinchona alkaloids. PEGs are inexpensive, readily functionalized, and commercially available in different molecular weights and broad solubility profile. PEG monomethyl ether (MeO-PEG-OH, *Mw* 5000) was easily alkylated with α,α′-dibromo-*p*-xylene to afford bromide **1** in 91% yield as previously described.[8]

Reactions of cinchonidine **2** with bromide **1** (toluene, reflux, 48 h) afforded compound **3a** (84% yield). Compounds **3a** was transformed into ethers **3b**-**3c** by reaction of alkyl bromide in CH_2Cl_2 (Scheme 1). To determine suitable reaction conditions for the catalytic enantioselective alkylation of glycine derivatives, we initially investigated the reaction system using 10 mol% catalyst for the reaction between *N*-dipenylmethylene glycine ester **4a** and benzyl bromide (Table 1). We first examined benzylation of **4a** in the presence of 50% aq. KOH and phase transfer catalyst (10 mol%) in toluene at room temperature. Catalyst **3b** was more effective than other catalysts (entries 1-3). Also, we investigated the effect of ester alkyl group, and the results are illustrated in Table 1. When the *t*-butyl, *i*-propyl, or ethyl ester derivatives **4a**, **4b**, or **4c** were employed as starting materials in the presence of 50% aq. KOH and catalyst **3b**, alkylated products were obtained in 73, 57, or 41% ee, respectively (entries 2 and 4-5). 50% aq. KOH was the effective base in their reaction (entries 2 and 6-9). Toluene gave better enantioselectivity than H_2O and CH_2Cl_2 (entries 10-11). Lowering the reaction temperature to 0 °C and -20 °C leads to longer reaction times, however, enantioselectivity was not improved (entries 12-13).

Under the optimized reaction conditions described above (10 mol% catalyst **3b**, 50% aq. KOH, toluene, rt), we investigated catalytic enantioselective alkylation of benzophenone imine of glycine *t*-butyl ester **4a** with other alkyl halides (Table 2). The reaction smoothly proceeded to afford the corresponding alkylated product **5** with high yields and enantioselectivities.[9] Catalyst **3b** was recovered quantitatively, at the end of the reaction, by precipitation from ethyl ether. The catalyst was used in a second run to achieve 69% yield and 70% ee of the product **5a**.



Scheme 1

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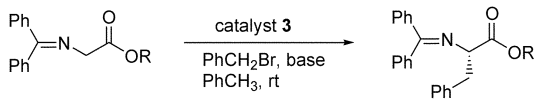
Table 1. Optimization of condition on the alkylation of *N*-diphenylmethylene glycine **4**

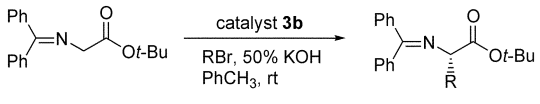


4 **5**

entry	R	catalyst	base	time (h)	yield[a]	ee[b] (%)
1	**4a**, *t*-Bu	**3a**	50% aq KOH	20	67	56
2	**4a**, *t*-Bu	**3b**	50% aq KOH	20	83	73
3	**4a**, *t*-Bu	**3c**	50% aq KOH	20	78	57
4	**4b**, *i*-Pr	**3b**	50% aq KOH	20	71	57
5	**4c**, Et	**3b**	50% aq KOH	20	76	41
6	**4a**, *t*-Bu	**3b**	KOH	20	82	31
7	**4a**, *t*-Bu	**3b**	*t*-BuOK	14	83	47
8	**4a**, *t*-Bu	**3b**	CsOH	16	70	41
9	**4a**, *t*-Bu	**3b**	50% aq NaOH	16	75	52
10[c]	**4a**, *t*-Bu	**3b**	50% aq KOH	21	68	35
11[d]	**4a**, *t*-Bu	**3b**	50% aq KOH	18	72	5
12[e]	**4a**, *t*-Bu	**3b**	50% aq KOH	30	53	58
13[f]	**4a**, *t*-Bu	**3b**	50% aq KOH	48	25	57

[a]Isolated yields are based on *N*-(dipenylmethylene)glycine *t*-butyl ester. [b]Enantiopurity was determined by HPLC analysis with chiralcel OD-H and AS (entries 4 and 5) columns, 2-propanol/hexane (2.5 : 500), 1.0 mL/min^{-1}, λ_{max} = 254 nm. The absolute configuration was assigned by comparison with literature data.[1] [c]Carried out in H_2O solvent. [d]Carried out in CH_2Cl_2 solvent. [e]This reaction was carried out at 0 °C. [f]This reaction was carried out at -20 °C.

Table 2. Enantioselective alkylation of benzophenone imine of glycine *t*-butyl ester **4a**



4a **5**

entry	R	yield[a] (%)	ee[b] (%)
1	benzyl	**5a**, 83	73
2	cinnamyl	**5d**, 87	71
3	allyl	**5e**, 77	47
4	ethyl	**5f**, 62	35

[a]Isolated yields are based on *N*-(dipenylmethylene)glycine *t*-butyl ester. [b]Enantiopurity was determined by HPLC analysis with a chiralcel OD-H column, 2-propanol/hexane (2.5 : 500), 1.0 mL/min^{-1}, λ_{max} = 254 nm.

In conclusion, we have synthesized new chiral PEG_{5000}-bound cinchona alkaloids with ether linkage. These catalysts were employed in the enantioselective alkylation of benzophenone imine of glycine *t*-butyl ester.

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9. *General procedure for benzylation of N-diphenylmethylene glycine t-butyl ester*: To a mixture of *N*-diphenylmethylene glycine *t*-butyl ester **4a** (29.5 mg, 0.1 mmol) and catalyst **3b** (55.7 mg, 0.01 mmol) in toluene (5 mL) was added benzyl bromide (25.7 mg, 0.15 mmol) and a 50% KOH aqueous solution (0.2 mL) at room temperature. The mixture was stirred for 20 h, whereupon water (2 mL) was added. The organic layer was separated, the aqueous layer was washed with CH_2Cl_2 (5 × 5 mL), and the combined organic layers were dried over $MgSO_4$ and poured onto diethyl ether to precipitate the catalyst. The filtrate was then concentrated under vacuum and the residue was purified by flash chromatography (EtOAc : hexane = 1 : 15) to afford the desired product **5a** as a colorless oil in 83% yield. The enantiomeric excess was determined by chiral HPLC (Chiralcel OD-H column, 0.5% *iso*-propanol, heptane, 1 mL min^{-1}, λ = 254 nm, retention times: (*R*) enantiomer: 12.5 min, (*S*) enantiomer: 20.6 min. Spectral data were in agreement with literature values.[1]