Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 618–623

Calixarene-based chiral phase-transfer catalysts derived from cinchona alkaloids for enantioselective synthesis of α-amino acids

Selahattin Bozkurt, Mustafa Durmaz, Mustafa Yilmaz and Abdulkadir Sirit*

Department of Chemistry, Selçuk University, 42099 Konya, Turkey

Received 2 January 2008; accepted 5 February 2008

Abstract—The synthesis of the first calixarene-based chiral phase-transfer catalysts derived from cinchona alkaloids has been achieved in two steps from *p-tert*-butylcalix[4]arene. The catalytic efficiency of the chiral calix[4]arenes **3a**–**c** was evaluated by carrying out the phase-transfer alkylation of *N*-(diphenylmethylene)glycine ethyl ester with benzyl bromide. Various factors that affect the chemical yield and enantioselectivity were also examined. Benzylation of glycine imine **4** using calix[4]arene-based dimeric catalyst **3a** as a chiral phase-transfer catalyst in toluene/$CHCl_3$ mixture (7:3 v/v) at 0 °C gave the best enantioselectivities and yields in the presence of aqueous NaOH.

1. Introduction

Amino acids are well known to play a key role in the area of design and preparation of pharmaceuticals, as they are part of the synthesis process in the production of drug intermediates and protein-based drugs. Due to their importance in biological systems and usefulness as a source of chirality in organic synthesis, considerable effort has been devoted to the design and synthesis of optically active amino acids, which can be categorized into four main approaches, using chiral substrates, chiral reagents, chiral auxiliaries, and chiral catalysts.[1] Among them, an asymmetric synthesis using easily available and reusable chiral catalysts presents synthetic advantages for large-scale procedures.[2]

Phase-transfer catalysis (PTC) has been recognized as a convenient and highly useful synthetic method in both research and industry because of its operational simplicity, suitability for large-scale reactions, environmental consciousness, and mild reaction conditions with aqueous media, which meet the current requirement for practical organic synthesis.[3,4] The use of the benzophenone imine of glycine derivatives as substrates in enantioselective alkylation under catalytic phase-transfer conditions has been developed toward an excellent method for the preparation of a wide range of optically active α-amino acids with high chemical yield and enantioselectivity.[5,6] Since O'Donnell et al. published their pioneering studies on the asymmetric alkylation of glycinate esters using the benzylammonium salt of cinchona alkaloid, a variety of phase-transfer catalysts have been synthesized and studied. Lygo et al. and Corey et al. independently developed efficient Cinchona type phase-transfer catalysts by replacing the benzyl group, attached to the quinuclidine nitrogen with the bulkier methylanthracenyl group.[7] Furthermore, dimeric[8] and trimeric[9] cinchona alkaloid derivatives, guanidinium salts,[10] *C*2-symmetric spiral ammonium salts derived from BINOL,[11] phosphonium salts,[12] TADDOL,[13] tartaric derivatives,[14] and other metal catalysts[15] have also been used in asymmetric PTC alkylations.

Calixarenes represent an important class of macrocyclic compound due to their potential for forming host–guest complexes with numerous classes of compounds in supramolecular chemistry. The sites available on these macrocyclic compounds can be easily modified to tailor them for many applications, such as phase-transfer catalysts,[16] ionophores in catalysis, carriers in liquid membrane technology, heavy metal adsorption agents, alkali metal complexation agents, extractants for anions and cations, and chemical sensors.[17] Chirality can be introduced into the calixarene platform either by attaching chiral units at one of the calix rims, or by synthesizing 'inherently' chiral derivatives, in which the non-planarity of the molecule is exploited.[18] Among the most popular chiral building

* Corresponding author. Tel.: +90 332 3238229; fax: +90 332 3238225; e-mail: asirit42@yahoo.com

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.02.006

blocks used, amino acids,[19] peptides,[20] amino alcohols,[21] sugars,[22] tartaric acid esters,[23] binaphthyl,[24] glycidyl,[25] menthone,[26] and guanidinium[27] groups offer a wide range of possibilities for providing calix[4]arenes with asymmetric features. Thus, chiral calix[4]arene derivatives obtained in this way not only provide a controlled means for studying the fundamentals of non-covalent interactions in Nature, but also open up new routes for developing novel enantioselective sensors, asymmetric catalysts,[28] selectors, and other molecular devices.[29]

We had previously reported the synthesis and complexation studies of novel chiral calix[4]arenes[30] toward chiral amines[31] and amino acid derivatives.[32] In order to find novel chiral calixarene derivatives with some specific properties, we herein report the synthesis of calix[4]arene-based chiral phase-transfer catalysts derived from cinchona alkaloids and an evaluation of their catalytic asymmetric behavior in the phase-transfer alkylation of glycine derivatives. To the best of our knowledge, this is the first application of calix[4]arenes as phase-transfer catalysts for the enantioselective α-alkylation of benzophenone glycine imines.

2. Results and discussion

2.1. Synthesis

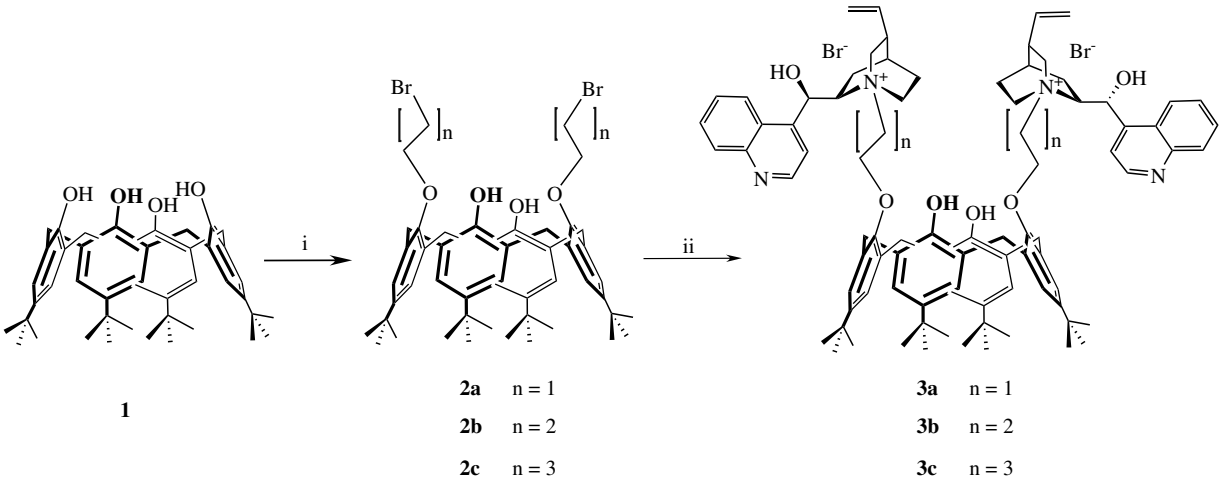
This work is mainly focused on the synthesis and application of catalytically active chiral calix[4]arene derivatives bearing cinchona alkaloids. The syntheses of chiral catalysts are relatively straightforward, requiring only two-step procedures starting from readily available materials. For the preparation of new calix[4]arene-based quaternary ammonium salts, as depicted in Scheme 1, the alkylation of *p-tert*-butylcalix[4]arene **1** with an excess of the respective α,ω-dibromides was carried out in MeCN in the presence of potassium carbonate as a base according to the previously published procedure.[33] Subsequent reactions of **2a**–**c** with an excess of cinchonidine were carried out in toluene at 100 °C for 8 h. The corresponding dicationic compounds **3a**–**c** were isolated as bromide salts, in yields ranging from 86% to 96% after column chromatography.

The products were characterized by a combination of ^{1}H NMR, ^{13}C NMR, FAB MS, IR, and elemental analysis. The conformational characteristics of calix[4]arenes were conveniently estimated by way of the splitting pattern of the $ArCH_2Ar$ methylene protons in the ^{1}H and ^{13}C NMR spectroscopy.[34] ^{1}H and ^{13}C NMR data showed that chiral *p-tert*-butylcalix[4]arene derivatives **3a**–**c** are in a cone conformation. A typical AX pattern was observed for the methylene bridge $ArCH_2Ar$ protons at 3.34 (J = 12.6 Hz) and 4.22 (J = 12.7 Hz) for **3a**, 3.34 (J = 13.0 Hz), and 4.18 (J = 13.0 Hz) for **3b**, and 3.36 (J = 12.7 Hz) and 4.29 (J = 12.7 Hz) for **3c** in ^{1}H NMR.

2.2. Evaluation of the chiral calix[4]arene-based catalysts in the asymmetric alkylation of ethylglycine ester

The catalytic efficiency of the calix[4]arene-based dimeric catalysts was evaluated by carrying out the asymmetric phase-transfer alkylation of *N*-(diphenylmethylene)glycine ethyl ester with benzyl bromide (Scheme 2). An initial attempt was made with 10 mol % of catalyst **3b** in the biphasic system formed by a mixture of toluene/$CHCl_3$ (7:3 v/v) and 50% aqueous KOH solution at room temperature to provide the benzylated product **5** in 93% yield, but these conditions afforded low enantioselectivity as shown in Table 1 (entry 5).

Various factors that affect the chemical yield and enantioselectivity were also examined. In order to investigate the role of a spacer between the quaternary ammonium and the calixarene backbone, the alkylation of glycine imine **4** with benzyl bromide was performed in the presence of chiral catalysts **3a**–**c**, while the other parameters such as solvents, bases, and temperature were kept constant. From the results shown in Table 1, it can be observed that the chiral catalyst **3a** with a two methylene spacer afforded relatively better results than the other catalysts.

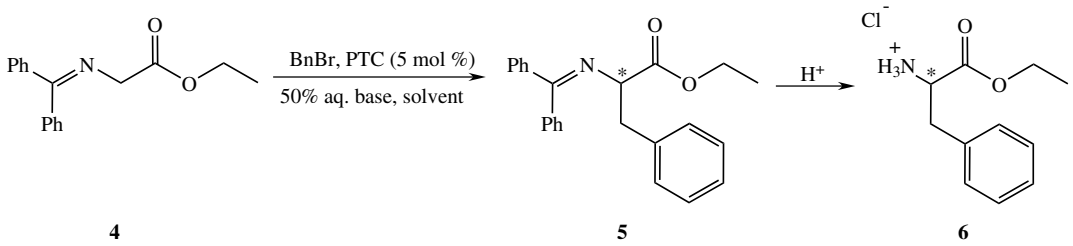


1

2a n = 1
2b n = 2
2c n = 3

3a n = 1
3b n = 2
3c n = 3

Scheme 1. Reagents and conditions: (i) $Br(CH_2)_nBr$, K_2CO_3, MeCN, reflux; (ii) cinchonidine, toluene, 100 °C, 8 h.



4 5 6

Scheme 2. Synthesis of α-alkyl-α-amino acid esters via asymmetric phase-transfer catalytic alkylation of benzophenone imine glycine ester.

Table 1. Results from the screening of the PTCs for the catalytic enantioselective phase-transfer benzylation

Entry	PTC	Solvent	*T* (°C)	Base	Yield[a] (%)	% ee[b] (config[c])
1	**3a**	Toluene/$CHCl_3$ 7:3	−20	KOH	87	25 (*S*)
2	**3a**	Toluene/$CHCl_3$ 7:3	−20	NaOH	89	46 (*S*)
3	**3a**	Toluene/$CHCl_3$ 7:3	0	NaOH	95	57 (*S*)
4	**3a**	Toluene/$CHCl_3$ 7:3	rt	NaOH	92	52 (*S*)
5	**3b**	Toluene/$CHCl_3$ 7:3	rt	KOH	93	15 (*S*)
6	**3b**	Toluene/$CHCl_3$ 7:3	−20	KOH	90	10 (*S*)
7	**3c**	Toluene/$CHCl_3$ 7:3	−20	KOH	91	12 (*S*)
8	**3c**	Toluene/$CHCl_3$ 7:3	−20	NaOH	95	17 (*S*)
9	**3c**	Toluene/$CHCl_3$ 7:3	0	NaOH	96	28 (*S*)
10	**3c**	Toluene/$CHCl_3$ 7:3	0	KOH	97	22 (*S*)
11	**3c**	Toluene/$CHCl_3$ 7:3	rt	KOH	98	18 (*S*)
12	**3c**	Toluene/$CHCl_3$ 7:3	rt	NaOH	97	24 (*S*)
13	**3c**	CH_2Cl_2	−20	KOH	89	9 (*S*)
14	**3c**	CH_2Cl_2	0	KOH	93	15 (*S*)
15	**3c**	CH_2Cl_2	rt	KOH	93	12 (*S*)
16	**3c**	CH_2Cl_2	−20	NaOH	85	7 (*S*)
17	**3c**	CH_2Cl_2	0	NaOH	88	14 (*S*)
18	**3c**	CH_2Cl_2	rt	NaOH	91	13 (*S*)

[a] Isolated yields.
[b] Enantiomeric excess was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H) using hexane/isopropanol (99:1) as an eluent.
[c] The absolute configuration was determined by comparison of the measured specific rotation values of product **6** with that given in the literature.[35]

The nature of the solvent seems to play an important role with regards to the enantioselectivity. On changing the solvent to CH_2Cl_2, a dramatic effect on the enantioselectivity of the reaction was observed, when either aq NaOH or KOH was used as base. In these cases, the ees obtained were lower.

We next examined the effect of the inorganic base on both the enantioselectivity and the catalytic activity. From the results obtained, the best enantioselectivity with good chemical yield was accomplished when 50% aqueous NaOH was used (Table 1, entries 2–4). It was found that the enantioselectivity was sensitive to the cation of the base and that the chelating ability of the calixarene derivative toward the sodium cation presumably plays a key role in making the sodium enolate soluble in organic phase as well as for achieving enantiofacial differentiation in the transition state.[36]

The variation of the reaction temperature also affects the level of the asymmetric induction. By cooling the reaction mixture to 0 °C from room temperature, relatively higher enantioselectivities were obtained for the catalysts used. However, a lower temperature (−20 °C) did not produce an increase in the ee. Thus, when the model benzylation reaction was performed at 0 °C (bath temperature), the enantioselection rose to 57% ee (Table 1, entry 3). Our results show that the enantioselectivity in the phase-transfer catalyzed alkylation of benzophenone glycine imine ethyl ester **4** was relatively low when compared with the previously reported data.[37] The application of other reaction conditions to improve the stereoselectivity by the calix[4]-arene-based catalysts are currently under progress.

For the determination of the absolute configuration (*S*) and the enantiomeric excess, the imine functional group of derivative **5** was hydrolyzed to produce phenylalanine ethyl ester, and the measured specific rotation values were compared with a known one {$[\alpha]_D = +33.7$ (*c* 2, ethanol)}.[35] Since the alkylated imines were found to be unstable to purification by chromatography, these compounds were transformed into the corresponding α-amino acid esters by acidic hydrolysis via the known procedure.[38]

The chiral catalysts were removed from the reaction mixture simply by passing through a short silica gel column with a non-polar solvent and recovered by washing the column with a more polar solvent such as ethyl acetate.

3. Conclusions

We designed three novel *p-tert*-butylcalix[4]arene-based chiral phase-transfer catalysts derived from cinchona alka-

loids, and applied them to the phase-transfer catalytic alkylation of the glycine anion equivalent **4**, which has been recognized as a very powerful way of preparing α-amino acids. Further studies on the applications of these and related calix[4]arene-based catalysts to other asymmetric synthesis are currently under investigation.

4. Experimental

4.1. General

Melting points were determined on an Electrothermal 9100 apparatus in a sealed capillary and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at room temperature on a Varian 400 MHz spectrometer in $CDCl_3$. IR spectra were obtained on a Perkin Elmer 1605 FTIR spectrometer using KBr pellets. Optical rotations were measured on an Atago AP-100 digital polarimeter. Elemental analyses were performed using a Leco CHNS-932 analyzer. FAB-MS spectra were taken on a Varian MAT 312 spectrometer. The HPLC measurements were carried out using an Agilent 1100 apparatus equipped with Chiralcel OD-H column (conditions: *n*-hexane/isopropanol 99:1, flow rate: 1.0 mL, detection: 254 nm). A racemic sample was prepared using *n*-tetrabutylammonium bromide as a phase-transfer catalyst for HPLC analysis.

Analytical TLC was performed using Merck prepared plates (Silica Gel 60 F_{254} on aluminum). Flash chromatography separations were performed on a Merck Silica Gel 60 (230–400 mesh). All reactions, unless otherwise noted, were conducted under a nitrogen atmosphere. All starting materials and reagents used were of standard analytical grade from Fluka, Merck, and Aldrich and used without further purification. Toluene was distilled from CaH_2 and stored over sodium wire. Other commercial grade solvents were distilled, and then stored over molecular sieves. The drying agent employed was anhydrous $MgSO_4$.

4.2. General procedure for the synthesis of phase-transfer catalysts 3a–c

A mixture of cinchonidine (0.32 g, 1.1 mmol) with *p-tert*-butylcalix[4]arene dibromides **2a**–**c** (0.5 mmol) in toluene (7 mL) was stirred at 100 °C for 8 h. After cooling the reaction mixture to room temperature, the suspension was filtered off and the solid dissolved in MeOH (30 mL) after which the turbid solution filtered over a Celite pad. The solvent was then distilled off, and the oily residue was subjected to column chromatography (CH_2Cl_2–MeOH eluent) and recrystallized along with Et_2O–CH_2Cl_2 to afford **3a**–**c** as solids in 86–96% yield.

4.2.1. Compound 3a. Yield 86%; dark brown solid; mp 226 °C (decomp.); $[\alpha]_D^{25} = -25$ (*c* 0.2, MeOH). IR (KBr): 3385, 2960, 1629, 1579, 1468, 1118, 863 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.89 (d, 2H, $J = 4.3$ Hz, NC*H* of quin), 8.12 (d, 2H, $J = 8.4$ Hz, NCC*H* of quin), 8.03 (d, 2H, $J = 8.4$ Hz, NCCHCHCHC*H* of quin), 7.66 (d, 2H, $J = 4.7$ Hz, NCCHC*H* of quin), 7.62–7.5 (m, 2H, NCCHCHC*H* of quin), 7.34 (t, 2H, $J = 7.6$, NCCHC*H* of quin), 7.12 (s, 4H, Ar*H*), 7.04 (s, 2H, ArO*H*), 6.92 (s, 4H, Ar*H*), 6.64–6.52 (m, 2H, C*H*CH$_2$ of eth), 6.18–6.09 (m, 2H, C*H*OH), 5.64–5.60 (m, 2H, CHO*H* of alcohol), 5.09–5.00 (m, 2H, CHCH_2 of eth), 4.97–4.95 (m, 2H, CHCH_2 of eth), 4.61–4.58 (m, 4H, CH_2), 4.35 (t, 2H, $J = 6.6$; CH_2CH$_2$ of met), 4.22 (d, 4H, $J = 12.6$ Hz, ArCH_2Ar), 4.18–4.10 (m, 2H, NC*H*CHOH), 3.92–3.80 (m, 2H, CH_2), 3.53–3.48 (m, 2H, CH_2), 3.47 (m, 2H, CH_2), 3.34 (d, 4H, $J = 12.7$, ArCH_2Ar), 2.86 (br, 4H, CH_2), 2.44–2.23 (m, 6H, CH_2), 2.11–1.98 (m, 6H, CH_2), 1.25 (s, 18H, C(CH_3)$_3$), 0.93 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.9, 149.8, 149.7, 149.4, 146.9, 143.6, 142.6, 137.6, 129.7, 129.5, 128.2, 127.6, 125.8, 125.0, 124.2, 123.8, 120.7, 115.7, 80.3, 65.9, 65.7, 63.9, 61.2, 53.3, 41.3, 38.9, 31.4, 30.5, 26.3, 23.9, 19.8; FAB-MS *m*/*z*: (1474.49) [M+Na]$^+$. Anal. Calcd for $C_{86}H_{106}N_4O_6Br_2$ (1451.59): C, 71.16; H, 7.36; N, 3.86; Br, 11.01. Found: C, 71.39; H, 7.84; N, 3.26; Br, 10.54.

4.2.2. Compound 3b. Yield 90%; dark brown solid; mp 215 °C (decomp.); $[\alpha]_D^{25} = -28$ (*c* 0.2, MeOH). IR (KBr): 3384, 2965, 1627, 1588, 1461, 1124, 867 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.91 (d, 2H, $J = 4.5$ Hz, NC*H* of quin), 8.05 (d, 2H, $J = 8.3$ Hz, NCC*H* of quin), 7.91 (d, 2H, $J = 4.5$ Hz, NCCHCHCHC*H* of quin), 7.82 (d, 2H, $J = 8.3$ Hz, NCCHC*H* of quin), 7.60–7.53 (m, 2H, NCCHCHC*H* of quin), 7.34 (t, 2H, $J = 7.5$ Hz, NCCHC*H* of quin), 7.09 (s, 4H, Ar*H*), 7.00 (s, 2H, ArO*H*), 6.77 (s, 4H, Ar*H*), 6.59–6.55 (m, 2H, C*H*CH$_2$ of eth), 6.37 (d, 2H, $J = 5.4$ Hz, C*H*OH), 5.44 (m, 2H, CHO*H* of alcohol), 5.02 (d, 2H, $J = 17.2$ Hz, CHCH_2 of eth), 4.90 (d, 2H, $J = 10.5$ Hz, CHCH_2 of eth), 4.59–4.48 (m, 4H, CH_2), 4.43–4.36 (m, 2H, CH_2CH$_2$ of met), 4.18 (d, 4H, $J = 13.0$ Hz, ArCH_2Ar), 4.12–3.86 (m, 2H, NC*H*CHOH), 3.78–3.58 (m, 6H, CH_2), 3.56 (t, 2H, $J = 8.6$ Hz, CH_2), 3.43 (m, 2H, CH_2), 3.34 (t, 4H, $J = 13.0$ Hz, ArCH_2Ar), 2.83 (br, 2H, CH_2), 2.70–2.49 (m, 4H, CH_2), 2.20–1.89 (m, 10H, CH_2), 1.29 (s, 18H, C(CH_3)$_3$), 0.92 (s, 18H, C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 150.1, 150.0, 149.8, 149.6, 147.0, 143.9, 142.9, 137.9, 130.1, 129.8, 129.6, 128.3, 127.7, 125.8, 125.3, 124.3, 123.9, 120.9, 115.7, 80.4, 65.9, 65.7, 53.8, 41.4, 39.2, 34.0, 31.7, 30.8, 26.5, 24.3, 20.5; FAB-MS *m*/*z*: (1502.55) [M+Na]$^+$. Anal. Calcd for $C_{88}H_{110}N_4O_6Br_2$ (1479.65): C, 71.43; H, 7.49; N, 3.79; Br, 10.80. Found: C, 71.94; H, 8.27; N, 3.35; Br, 9.83.

4.2.3. Compound 3c. Yield 96%; pale brown solid; mp 236 °C (decomp.); $[\alpha]_D^{25} = -35$ (*c* 0.2, MeOH). IR (KBr): 3381, 2959, 1630, 1583, 1475, 1113, 868 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.81 (d, 2H, $J = 4.4$ Hz, NC*H* of quin), 8.05 (d, 2H, $J = 8.4$ Hz, NCC*H* of quin), 8.01 (d, 2H, $J = 8.4$ Hz, NCCHCHCHC*H* of quin), 7.63 (d, 2H, $J = 4.4$ Hz, NCCHC*H* of quin), 7.58 (dd, 2H, $J = 7.8$ Hz, NCCHCHC*H* of quin), 7.48 (t, 2H, $J = 7.3$ Hz, NCCHC*H* of quin), 7.46 (s, 2H, ArO*H*), 7.06 (s, 4H, Ar*H*), 6.85 (s, 4H, Ar*H*), 6.51–6.50 (m, 2H, C*H*CH$_2$ of eth), 6.39 (d, 2H, $J = 5.4$ Hz, C*H*OH), 5.44–5.79 (m, 2H, CHO*H* of alcohol), 5.04 (d, 2H, $J = 17.2$, CHCH_2 of eth), 4.89 (d, 2H, $J = 10.5$; CHCH_2 of eth), 4.70–4.66 (m, 4H, CH_2), 4.50–4.39 (m, 2H, CH_2CH$_2$ of met), 4.29 (d, 4H, $J = 12.7$ Hz, ArCH_2Ar), 4.22–4.12 (m, 2H, NC*H*-

CHOH), 4.05–3.82 (m, 6H, CH_2), 3.68 (t, 2H, $J = 8.5$ Hz, CH_2), 3.52 (m, 2H, CH_2), 3.36 (t, 4H, $J = 12.7$ Hz, $ArCH_2$-Ar), 2.78 (br, 2H, CH_2), 2.42–2.18 (m, 12H, CH_2), 2.05–1.82 (m, 6H, CH_2), 1.29 (s, 18H, $C(CH_3)_3$), 1.00 (s, 18H, $C(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm): 149.1, 149.0, 148.3, 146.8, 146.5, 143.6, 141.3, 135.4, 131.5, 129.4, 128.2, 127.1, 127.0, 126.4, 124.8, 124.4, 124.2, 123.3, 121.3, 119.2, 116.4, 74.7, 65.9, 63.4, 58.7, 36.6, 33.0, 32.9, 30.9, 30.8, 30.7, 30.0, 26.1 25.0, 24.2, 20.3, 19.3; FAB-MS m/z: (1530.60) $[M+Na]^+$. Anal. Calcd for $C_{90}H_{114}N_4O_6Br_2$ (1507.70): C, 71.70; H, 7.62; N, 3.72; Br, 10.60. Found: C, 72.24; H, 7.86; N, 3.21; Br, 9.86.

4.3. Representative procedure for enantioselective phase-transfer alkylation (benzylation)

To a mixture of *N*-(diphenylmethylene)glycine ethyl ester **4** (50.0 mg, 0.17 mmol) and chiral catalysts **3a–c** (0.0085 mmol) in toluene/$CHCl_3$ (volume ratio 7:3, 0.75 mL) was added benzyl bromide (0.1 mL, 0.85 mmol). The reaction mixture was then cooled to 0 °C, 50% aqueous KOH (0.25 mL) was added, and the reaction mixture was stirred at 0 °C until the starting material had been consumed. The suspension was diluted with ether (20 mL), washed with water (2×5 mL), dried over $MgSO_4$, filtered, and solvent evaporated under reduced pressure, as well as excess benzyl bromide was removed. The crude product was passed through a short silica column using hexane/EtOAc 30:1 as an eluent to remove chiral catalysts and afforded the desired product **5** as a colorless oil. IR (KBr): 2965, 2935, 1733, 1620 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, $J = 7.0$ Hz, 2H), 7.26–7.21 (m, 8H), 7.10 (t, $J = 7.3$ Hz, 3H), 6.90 (d, $J = 6.8$ Hz, 2H), 4.17–4.07 (m, 3H), 3.12–3.03 (m, 2H), 1.19 (t, $J = 7.2$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 170.5, 139.3, 137.9, 136.1, 130.1, 129.6, 128.7, 128.2, 128.0, 127.9, 127.6, 126.2, 67.2, 60.9, 39.6, 14.1 ppm. Enantiomeric excess was determined by HPLC using Chiralcel OD-H column with eluent hexane/isopropanol (99:1). With a 1.0 mL/min flow rate the retention time was 7.2 min for the (*R*)-isomer and 12.3 min for the (*S*)-isomer.

4.4. Hydrolysis of the imino functional group of the *N*-(diphenylmethylene)glycine ethyl ester

Imino ester **5** (1 mmol) was added to 10 mL ethanolic hydrogen chloride (1 M) and stirred vigorously overnight at room temperature. After this time, the solvent was removed under reduced pressure and product **6** was isolated as a white solid powder. Chemical yields: 195–205 mg (85–90%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.31–7.18 (m, 5H), 4.15 (q, $J = 7.3$ Hz, 2H), 3.69 (t, $J = 7.3$ Hz, 1H), 3.10–2.96 (m, 2H), 1.50 (s, 3H), 1.23 (t, $J = 7.3$ Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 137.2, 129.2, 128.3, 126.6, 60.7, 55.7, 41.0, 14.0 ppm. Measured optical rotation values: $[\alpha]_D^{25} = +19.2$ to $+2.4$ (c 2.0, EtOH).

Acknowledgments

This work was supported by the Scientific and Technical Research Council of Turkey (TUBITAK–106T091) and Research Foundation of Selçuk University (BAP–06401067).

References

1. Lee, J.-H.; Yoo, M.-S.; Jung, J.-H.; Jew, S.-s.; Park, H.-g.; Jeong, B.-S. *Tetrahedron* **2007**, *63*, 7906–7915.
2. (a) Chinchilla, R.; Mazón, P.; Nájera, C. *Adv. Synth. Catal.* **2004**, *346*, 1186–1194; (b) Chinchilla, R.; Nájera, C.; Ortega, F. J. *Eur. J. Org. Chem.* **2007**, 6034–6038.
3. (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, 1993; (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase-Transfer Catalysis*; Chapman & Hall: New York, NY, 1994; (c) *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; (d) *Phase-Transfer Catalysis*; Halpern, M. E., Ed. ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997; (e) Shioiri, T. In *Handbook of Phase-Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997, Chapter 14; (f) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Chemie: New York, NY, 2000, Chapter 10; (g) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549–1551.
4. For excellent reviews: (a) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3–15; (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028; (c) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506–517; (d) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525; (e) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526–533; (f) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682.
5. O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663–2666.
6. O'Donnell, M. J.; Delgado, F.; Pottorf, R. S. *Tetrahedron* **1999**, *55*, 6347–6362.
7. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598; (b) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, 2391–2402; (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; (d) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347–5350; (e) Lee, J.-H.; Yoo, M.-S.; Jung, J.-H.; Jew, S.-s.; Park, H.-g.; Jeong, B.-S. *Tetrahedron* **2007**, *63*, 7906–7915.
8. Jew, S.-s.; Jeong, B. S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244–1245.
9. Park, H.-g.; Jeong, B. S.; Yoo, M.-S.; Park, M. K.; Huh, H.; Jew, S. S. *Tetrahedron Lett.* **2001**, *42*, 4645–4648.
10. Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832–2834.
11. (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520; (b) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551–1554; (c) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139–5151.
12. (a) Manabe, K. *Tetrahedron Lett.* **1998**, *39*, 5807–5810; (b) Manabe, K. *Tetrahedron* **1998**, *54*, 14465–14476.
13. (a) Belokon, Y. N.; Kotchetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, A. V.; Parmar, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851–857; (b) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, A. V.; Singh, I.; Parmar, V. S.; Vyskocil, S.; Kagan, H. B. *J. Org. Chem.* **2000**, *65*, 7041–7048.
14. Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535–9537.

15. (a) Belokon, Y. N.; Davies, R. G.; North, M. *Tetrahedron Lett.* **2000**, *41*, 7245–7248; (b) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, S.; Vyskocil, H. B. *Tetrahedron: Asymmetry* **1999**, *10*, 1723–1728; (c) Belokon, Y. N.; North, M.; Churkina, T. D.; Ikonnikov, S.; Maleev, V. I. *Tetrahedron* **2001**, *57*, 2491–2498; (d) Tzalis, D.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 3685–3688; (e) Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; Maleev, V.; North, M.; Pertrosyan, A. *Tetrahedron Lett.* **2003**, *44*, 2045–2048.
16. (a) Srivastava, P.; Srivastava, R. *Tetrahedron Lett.* **2007**, *48*, 4489–4493; (b) Shimizu, S.; Kito, K.; Sasaki, Y.; Hirai, C. *Chem. Commun.* **1997**, 1629–1630; (c) Shimizu, S.; Shirakawa, S.; Suzuki, T.; Sasaki, Y. *Tetrahedron* **2001**, *57*, 6169–6173; (d) Baur, M.; Frank, M.; Schatz, J.; Schildbach, F. *Tetrahedron* **2001**, *57*, 6985–6991.
17. Ji, H.-F.; Brown, G. M.; Dabestani, R. *Chem. Commun.* **1999**, 609–610.
18. (a) Luo, J.; Zheng, Q.-Y.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron* **2005**, *61*, 8517–8528; (b) Yakovenko, A. V.; Boyko, V. I.; Danylyuk, O.; Suwinska, K.; Lipkowski, J.; Kalchenko, V. I. *Org. Lett.* **2007**, *9*, 1183–1185.
19. (a) You, J.-S.; Yu, X.-Q.; Zhang, G.-L.; Xiang, Q.-X.; Lan, J.-B.; Xie, R.-G. *Chem. Commun.* **2001**, 1816–1817; (b) Arena, G.; Contino, A.; Gulino, F. G.; Magri, A.; Sansone, F.; Sciotto, D.; Ungaro, R. *Tetrahedron Lett.* **1999**, *40*, 1597–1600.
20. (a) Guo, W.; Wang, J.; Wang, C.; He, J.-Q.; He, X.-W.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 5665–5667; (b) Xu, H.; Kinsel, G. R.; Zhang, J.; Li, M.; Rudkevich, D. M. *Tetrahedron* **2003**, *59*, 5837–5848.
21. (a) Zheng, Y.-S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189–1192; (b) Quintard, A.; Darbost, U.; Vocanson, F.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1926–1933.
22. (a) Budka, J.; Tkadlecová, M.; Lhoták, P.; Stibor, I. *Tetrahedron* **2000**, *56*, 1883–1887; (b) Grazia, M. L.; Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Mecca, T.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 7467–7470; (c) Schädel, U.; Sansone, F.; Casnati, A.; Ungaro, R. *Tetrahedron* **2005**, *61*, 1149–1154.
23. Yuan, H.-S.; Huang, Z.-T. *Tetrahedron: Asymmetry* **1999**, *10*, 429–437.
24. Pinkhassik, E.; Stibor, I.; Casnati, A.; Ungaro, R. *J. Org. Chem.* **1997**, *62*, 8654–8659.
25. Neri, P.; Bottino, A.; Geraci, C.; Piattelli, M. *Tetrahedron: Asymmetry* **1996**, *7*, 17–20.
26. Soi, A.; Pfeiffer, J.; Jauch, J.; Schurig, V. *Tetrahedron: Asymmetry* **1999**, *10*, 177–182.
27. (a) Liu, F.; Lu, G.-Y.; He, W.-J.; Liu, M.-H.; Zhu, L.-G. *Thin Solid Films* **2004**, *468*, 244–249; (b) Sansone, F.; Dudic, M.; Donofrio, G.; Rivetti, C.; Baldini, L.; Casnati, A.; Cellai, S.; Ungaro, R. *J. Am. Chem. Soc.* **2006**, *128*, 14528–14536.
28. (a) Gaeta, C.; De Rosa, M.; Fruilo, M.; Soriente, A.; Neri, P. *Tetrahedron: Asymmetry* **2005**, *16*, 2333–2340; (b) Marson, A.; Freixa, Z.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem.* **2007**, 4587–4591; (c) Dieleman, C.; Steyer, S.; Jeunesse, C.; Matt, D. *J. Chem. Soc., Dalton Trans.* **2001**, 2508–2517.
29. (a) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinheim, 1995; (b) Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Soc. Rev.* **2007**, *36*, 254–266; (c) Kim, S. K.; Lee, S. H.; Lee, J. Y.; Lee, J. Y.; Bartsch, R. A.; Kim, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 16499–16506.
30. (a) Sirit, A.; Karakucuk, A.; Memon, S.; Kocabas, E.; Yilmaz, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3595–3600; (b) Sirit, A.; Kocabas, E.; Memon, S.; Karakucuk, A.; Yilmaz, M. *Supramol. Chem.* **2005**, *17*, 251–256; (c) Karakucuk, A.; Durmaz, M.; Sirit, A.; Yilmaz, M.; Demir, A. S. *Tetrahedron: Asymmetry* **2006**, *17*, 1963–1968.
31. (a) Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2322–2327; (b) Kocabas, E.; Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Chirality* **2008**, *20*, 26–34.
32. (a) Kocabas, E.; Karakucuk, A.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1514–1520; (b) Durmaz, M.; Alpaydin, S.; Sirit, A.; Yilmaz, M. *Tetrahedron: Asymmetry* **2007**, *18*, 900–905.
33. Li, Z.-T.; Ji, G.-Z.; Zhao, C.-X.; Yuan, S.-D.; Ding, H.; Huang, C.; Du, A.-L.; Wei, M. *J. Org. Chem.* **1999**, *64*, 3572–3584.
34. (a) Gutsche, C. D. *Acc. Chem. Res.* **1983**, *16*, 161–170; (b) Gutsche, C. D. In *Calixarenes Revisited*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998.
35. Chemical Catalog, Acros Organics, 2004–2005, p 1706.
36. Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222–4266.
37. (a) Dehmlow, E. V.; Wagner, S.; Müller, A. *Tetrahedron* **1999**, *55*, 6335–6346; (b) Abellán, T.; Chinchilla, R.; Galindo, N.; Guillena, G.; Nájera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2000**, *15*, 2689–2697; (c) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 1675–1678.
38. Lanitou, O.; Dimotikali, D.; Yannakopoulou, E.; Papadopoulos, K. *Chem. Eng. J.* **2007**, *134*, 72–77.