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Synthesis and competency of a novel dicationic phase-transfer catalyst

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Abstract—Synthesis and characterization of a novel phase-transfer catalyst, 6,6′ di(triethylammoniummethyl)-2,2′-dihexyloxy-bi-1,1′-naphthalene, are reported. Preliminary catalytic studies on the alkylation of a glycine derivative show the catalyst to be an effective phase-transfer catalyst but with no enantioselectivity.

1. Introduction

Asymmetric phase-transfer catalysis represents an important developing field for many reactions.[1–3] In particular the possibility of designer peptides through the controlled synthesis of unnatural amino acids is of significant interest.[4–8] Most reports of successful phase-transfer catalysts revolve around quaternization of Cinchona alkaloids.[4–6,9–13] Recent reports have introduced the binaphthyl moiety into the mix.[8,14–17] The majority of these catalysts have a single quaternized ammonium site, with only very few exceptions.[7,18] In contrast a dicationic catalyst has the potential to pseudo-chelate an anion, perhaps then influencing its nucleophilic attack and generating enantioselectivity. Herein we report the synthesis and catalytic competency of a novel compound with two quaternary ammonium groups positioned to act cooperatively.

2. Results and discussion

The diammonium salt **1** can be synthesized in five steps from (*R*)-1,1′-bi-2,2′-naphthol[19] (BINOL) (Scheme 1). After a standard Williamson ether synthesis, bromination follows the procedure of Persoons and Bjornholm.[20] Double cyanation of the dibromodihexyloxy derivative **4** with CuCN gives dicyanodihexyloxy BINOL derivative **5**.[21] Reduction of **5** proved difficult, owing to both over- and under-reduction, but modification of a procedure by Lemaire gave diamine **6**.[22] Purification by column chromatography using a gradient eluant of ether followed by 100:100:1 CH_2Cl_2/MeOH/NH_3 and finally 2:2:1 CH_2Cl_2/MeOH/NH_3[23] gave pure diamine. Quaternization with ethyl iodide gave **1a** initially, but upon further reflux, the salt decomposed to give tetraethylammonium iodide. This led us to replace ethyl iodide with ethyl tosylate, which required longer reaction times, but gave **1b** in good yield. Gradient chromatography on alumina (ethyl acetate followed by 20:1 ethyl acetate/methanol and finally 1:1 ethyl acetate/methanol) surprisingly yielded **1c** (Fig. 1).

Preliminary catalytic testing on glycine imino ester **7** alkylation (Scheme 2) showed compound **1** to be a good phase-transfer catalyst with rates comparable to those reported in the literature for the same reaction.[8,15,16] Table 1 summarizes our results. Integration of the chiral column HPLC traces showed enantioselectivities to be below 5% for all substrates and conditions. Following literature procedures[8,15,16] we used a variety of active alkyl halides: methyl iodide, benzyl bromide, allyl bromide, and 2-(bromomethyl)naphthalene. Even methyl iodide, reported in the literature to give slow rates even with fivefold excess, gave a significant yield in 1 h. After 1 h the methyl iodide was fully consumed, presumably hydrolyzed to methanol.

To test the ability of our compound to act as a solid–liquid and a liquid–liquid phase-transfer catalyst, both 50% KOH (for liquid–liquid catalysis) and $CsOH{\cdot}H_2O$ (for solid–liquid catalysis) were used as base. Solid CsOH consistently gave faster rates, though the KOH solution was still effective.

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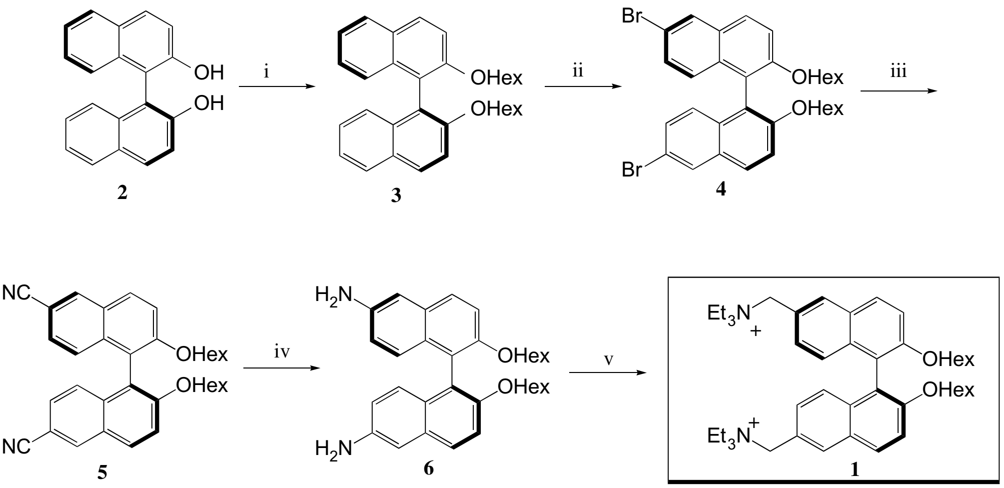


Scheme 1. Synthesis of phase-transfer catalyst **1**. Reagents and conditions: (i) 1-bromohexane, NaOH, acetone; (ii) Br_2, CH_2Cl_2, 0 °C; (iii) CuCN, DMF; (iv) LAH, THF; (v) EtOTos, dioxane, Na_3PO_4.

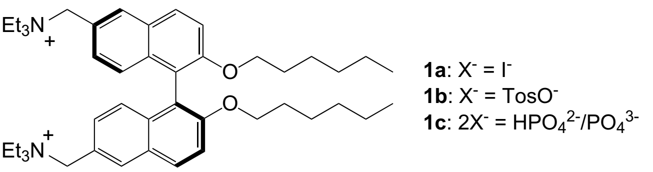
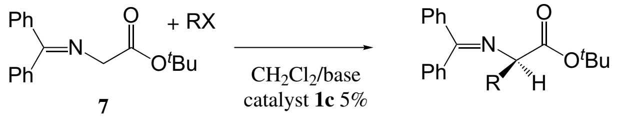


Figure 1. Chiral phase-transfer catalyst **1**.



Scheme 2. General imino ester alkylation with phase-transfer catalyst **1c**.

The catalyst was soluble in dichloromethane and acetonitrile; the alkylation reaction ran well in both solvents. In toluene, however, the catalyst was insoluble with the alkylation proceeding only at the background rate.

In conclusion, we have reported the synthesis of a novel phase-transfer catalyst, the first of its class of 6,6′ substituted 2,2′-dihexyloxybi-1,1′-naphthalene dications. The catalytic alkylation of the imino ester **7** showed that the compound was an efficient phase-transfer catalyst. Further studies on other related compounds are currently under way.

3. Experimental

3.1. General

All chemicals were purchased from Aldrich and used as received, except THF, which was distilled from sodium metal just prior to use. (*R*)-BINOL was synthesized from 2-naphthol[24] and resolved[19] according to literature procedures. NMR spectra were obtained on a Bruker Avance 400. GC/MS data were obtained on a Varian Saturn 2100T. Optical rotations were obtained on a Perkin–Elmer 341 polarimeter. IR spectra were obtained on a ThermoNicolet 200. Elemental analyses were performed by Desert Analytics. HPLC analysis was performed on a Chiracel OD column.

3.2. Synthesis of (*R*)-2,2′-dihexyloxybi-1,1′-naphthalene 3

To a solution of (*R*)-BINOL (6.0 g, 20.1 mmol) in acetone (150 mL) was added NaOH (1.76 g, 44.1 mmol,

Table 1. Results of imino ester alkylation with 5% catalyst loading

Alkyl halide RX	Solvent	Base	Temperature (°C)	Time (min)	% Completion
$PhCH_2Br$	CH_2Cl_2	50% KOH	0	60	79.6
$PhCH_2Br$	CH_2Cl_2	CsOH	0	20	89.4
$PhCH_2Br$	CH_2Cl_2	50% KOH	20	60	77.5
$PhCH_2Br$	CH_3CN	CsOH	0	20	82.7
CH_2CHCH_2Br	CH_2Cl_2	50% KOH	0	60	43.0
CH_2CHCH_2Br	CH_2Cl_2	CsOH	0	20	82.3
CH_3I	CH_2Cl_2	CsOH	0	60	68.9
CH_3I	CH_2Cl_2	50% KOH	0	60	22.2
Bromomethylnaphthalene	CH_2Cl_2	CsOH	0	60	93.4
Bromomethylnaphthalene	CH_2Cl_2	50% KOH	0	60	33.7

2.1 equiv) in water. 1-Bromohexane (7.27 g, 44.1 mmol) was then added and the solution refluxed with stirring for 18 h. The reaction was monitored by TLC (1:1 ether/hexanes eluant) with additional bromohexane added if needed. The reaction mixture was then cooled and solvent removed in vacuo. The resulting oil was taken into ether and extracted with 1 M NaOH. After drying over $CaCl_2$, solvent was removed to yield the product as an oil (9.11 g, 95.6%). ^{1}H NMR: δ 7.9 (d, 2H, ArH), 7.8 (d, 2H, ArH), 7.4 (d, 2H, ArH), 7.3 (m, 2H, ArH), 7.2 (m, 4H, ArH), 3.9 (m, 4H, $\mathrm{OC}\mathit{H}_2$), 0.7–1.4 (m, 11H, hexyl). ^{13}C NMR: δ 154.5, 134.2, 129.3, 129.0, 127.7, 125.5, 123.4, 120.7, 115.9, 69.8, 31.3, 29.4, 25.3, 22.4, 13.9. MS: 455 (M^++H); $[\alpha]_D$ +36 (*c* 1.0, THF).

3.3. Synthesis of (*R*)-6,6′-dibromo-2,2′-dihexyloxybi-1,1′-naphthalene 4

(*R*)-2,2′-Dihexyloxybi-1,1′-naphthalene **3** (8.35 g, 18.6 mmol) was dissolved in CH_2Cl_2 (150 mL) and cooled to 0 °C. Bromine was added in increments, starting with 1.8 equiv. The reaction was followed by GC/MS, with bromine added until the reaction went to completion. The reaction mixture was then extracted with 10% sodium hydrosulfite and brine. After drying over $CaCl_2$ and filtering, the solvent was removed to yield the product as an oil (11.3 g, 99%). ^{1}H NMR: δ 8.0 (d, 2H, ArH),7.8 (d, 2H, ArH), 7.4 (d, 2H, ArH), 7.3 (dd, 2H, ArH), 7.0 (d, 2H, ArH), 3.9 (m, 4H, $\mathrm{OC}\mathit{H}_2$), 0.7–1.4 (m, 11H, hexyl). ^{13}C NMR: δ 154.8, 132.6, 130.2, 129.7, 129.4, 128.4, 127.1, 120.0, 117.2, 116.4, 69.5, 31.3, 29.7, 29.2, 25.3, 22.5, 13.9. MS: 612 (M^+).

3.4. Synthesis of (*R*)-6,6′-dicyano-2,2′-dihexyloxybi-1,1′-naphthalene 5

(*R*)-6,6′-Dibromo-2,2′-dihexyloxybi-1,1′-naphthalene **4** (6.7 g, 11.0 mmol) and CuCN (3.94 g, 44.0 mmol) were taken into DMF and degassed with nitrogen. The nitrogen line was replaced with a vent needle and the reaction mixture refluxed for 16 h. The reaction mixture was then poured into a 1:1 H_2O/concd NH_3 solution (500 mL) and stirred for 2 h to remove any copper salts. Filtration yielded the crude product as a sticky solid. This solid was extracted with ethyl acetate. The ethyl acetate solution was then further extracted with 1 M NH_3 until the aqueous layer was colorless. After drying over $CaCl_2$ and filtering, the solvent was removed in vacuo. The resulting crude product was recrystallized from MeOH and again from heptane to yield white needles (3.18 g, 57.4%). ^{1}H NMR: δ 8.25 (d, 2H, ArH), 8.0 (d, 2H, ArH), 7.5 (d, 2H, ArH), 7.3 (dd, 2H, ArH), 7.1 (d, 2H, ArH), 4.0 (m, 4H, $\mathrm{OC}\mathit{H}_2$), 0.7–1.4 (m, 11H, hexyl). ^{13}C NMR: δ 156.9, 135.5, 134.4, 130.4, 127.7, 126.8, 126.1, 119.6, 119.0, 106.6, 69.2, 31.2, 29.7, 25.2, 22.4, 13.8. IR: 2221 cm^{-1} (CN). MS: 505 (M^+). Anal. Calcd: %C 81.03 (80.92), %H 7.29 (7.19), %N 5.31 (5.55).

3.5. Synthesis of (*R*)-6,6′-di(aminomethyl)-2,2′-dihexyloxybi-1,1′-naphthalene 6

(*R*)-6,6′-Dicyano-2,2′-dihexyloxybi-1,1′-naphthalene **5** (3.0 g, 6.0 mmol) was taken into freshly distilled THF; pelletized LAH (3.0 g, 59 mmol) was also taken into a separate flask of freshly distilled THF and vigorously stirred until the pellet was fully dispersed. Both solutions were degassed with bubbling nitrogen for 20 min and the dinitrile solution added via cannula to the LAH solution. The mixture was stirred for 90 min; longer reaction times yielded over-reduction. The reaction was quenched with water, 15% NaOH, Celite, and toluene following a simple formula: g LAH = mL H_2O = mL 15% NaOH = g Celite. Celite was added to aid filtering; toluene (25 mL) was added. The role toluene plays is unclear but it is a critical addition. This quenched mixture was stirred for 1 h and then filtered. Solvents were removed in vacuo to yield the product as a pale yellow, highly viscous oil (2.7 g, 88%). If further purification was needed, column chromatography on silica was performed using a gradient eluant (ether; 100:100:1 CH_2Cl_2/MeOH/NH_3; 2:2:1 CH_2Cl_2/MeOH/NH_3). ^{1}H NMR: δ 7.9 (d, 2H, ArH), 7.7 (s, 2H, ArH), 7.4 (d, 2H, ArH), 7.1 (m, 4H, ArH), 3.95 (s, 4H, NH_2 $\mathrm{C}\mathit{H}_2$), 3.9 (m, 4H, $\mathrm{OC}\mathit{H}_2$), 0.6–1.7 (m, 11H, hexyl). ^{13}C NMR: δ 154.4, 138.1, 133.3, 129.3, 128.7, 126.0, 125.9, 125.1, 120.7, 116.1, 69.8, 46.5, 31.3, 30.0, 25.3, 22.7, 13.9. $[\alpha]_D$ −8.6 (*c* 0.6, THF). MS: 513 (M^+). Anal. Calcd: %C 79.67 (79.65), %H 8.71 (8.65), %N 5.30 (5.46).

3.6. Synthesis of (*R*)-6,6′-bis(triethylammoniummethyl)-2,2′-dihexyloxyBINOL hydrogen phosphate/phosphate 1c

(*R*)-6,6′-Di(aminomethyl)-2,2′-dihexyloxybi-1,1′-naphthalene **6** (4.0 g, 7.8 mmol), ethyl tosylate (18.7 g, 93.5 mmol, 12 equiv), and Na_3PO_4 (7.6 g, 46.5 mmol, 6 equiv) were combined in dioxane and refluxed for 48 h. The reaction mixture was then cooled and poured onto an alumina column filled with ethyl acetate. The column was eluted with 20:1 ethyl acetate/MeOH to remove any amine impurities, then 4:1 ethyl acetate/MeOH, and finally pure MeOH. The product was found in methanol-rich cuts (3.6 g, 69%). ^{1}H NMR: δ 8.1 (s, 2H, ArH), 8.0 (d, 2H, ArH, $J = 9$ Hz), 7.5 (d, 2H, ArH, $J = 9$ Hz), 7.3 (d, 2H, ArH, $J = 9$ Hz), 7.0 (d, 2H, ArH, $J = 9$ Hz), 4.8 (d, 2H, $\mathrm{C}\mathit{H}_2\mathrm{NEt}_3$, $J = 14$ Hz), 4.7 (d, 2H, $\mathrm{C}\mathit{H}_2\mathrm{NEt}_3$, $J = 14$ Hz), 4.0 (m, 4H, $\mathrm{OC}\mathit{H}_2$), 3.4 (br, 6H, $\mathrm{NC}\mathit{H}_2\mathrm{CH}_3$), 0.7–1.5 (m, hexyl and $\mathrm{NCH}_2\mathrm{C}\mathit{H}_3$). ^{13}C NMR: δ 156.0, 134.6, 133.2, 130.1, 128.8, 128.5, 126.4, 121.7, 119.3, 116.2, 69.4, 63.6, 61.3, 52.8, 31.9, 31.3, 30.9, 30.3, 30.0, 29.7, 29.4, 29.2, 25.3, 22.7, 22.4, 14.1, 13.9, 8.4. Anal. Calcd: %C 72.06 (70.9), %H 9.41 (9.19). Analysis is consistent with a 60% HPO_4^{2-}/40% PO_4^{3-} mixture of counter ions (calcd C 72.0, H 9.49).

3.7. Example procedure for catalytic trials

A 25 mL round bottomed flask was charged with CH_2Cl_2 (2 mL), 50% KOH (1 mL), *N*-(diphenylmethylene)glycine *t*-butyl ester (0.148 g, 0.50 mmol), and benzyl bromide (102 mg 0.60 mmol) along with a 1/2 in. stirrer bar. The mixture was cooled in an ice bath. Catalyst **1c** (0.039 g, 0.05 mmol) was first dissolved in CH_2Cl_2 (1 mL) and then added to the mixture at which point timing was started. Samples were taken after 10, 20, 30, 60, and 180 min. Samples were quenched by the addition of a 1:1 ether/water mixture (2 mL) followed by extraction of the ether layer. Samples were analyzed by HPLC using a Chiralcel OD–H column and a 99:1 hexane/isopropanol eluent to determine both yield and % ee.

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