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Synthesis and competency of a tartrate-derived dicationic solid–liquid phase-transfer catalyst

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Abstract—A new asymmetric phase-transfer catalyst is described, along with a new, flexible synthetic scheme using a tartaric acid chloride. Alkylations and Michael reactions on a glycine imino ester show the new catalyst to be an effective phase-transfer catalyst with limited enantioselectivity.

1. Introduction

Asymmetric phase-transfer catalysis offers a powerful method for many reactions, including the synthesis of unnatural amino acids.[1–8] Early work focused on Cinchona derivatives,[9–13] though recent reports have described successes with binaphthyl[14–18] and other[19–21] stereogenic units. Most work has utilized a single ammonium group on the catalyst, with a few notable exceptions.[22,23] Our group's interest is in dicationic catalysts,[24] hypothesizing that with the proper alignment of the ammonium centers, a 'reverse chelate' effect may be observed in which the nucleophilic anion interacts with both ammonium centers to provide optimum enantioselectivity. Tartaric acid was chosen as the source of chirality because (1) its derivatives have a successful history in inducing asymmetry in other catalytic processes,[25–27] (2) it allows us to develop a dicationic catalyst, and (3) it is inexpensive. We were encouraged by the relatively good enantioselectivities reported in a recent publication by Shibasaki and co-workers that uses the same tartaric acid stereocenters as in our design.[22] However, the synthesis described therein is limited to attaching carbon groups to the nitrogen from primary alkyl halides.[22] We report herein a new synthetic scheme that allows for more sterically demanding alkyl groups to be attached and the first two catalysts generated using this new scheme (Fig. 1).

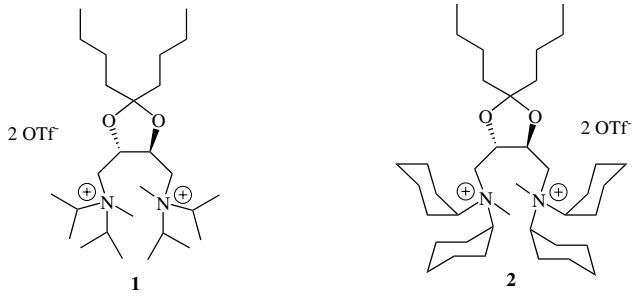

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Figure 1. Tartaric acid derived catalysts.

2. Results and discussion

Key to our synthetic scheme is acid chloride **4**, synthesized by adapting the procedure of Choi et al. (Fig. 2).[28] From diethyl tartrate, nonanone ketal **3** is synthesized in bulk (100 g preparations) and then hydrolyzed with LiOH. The lithium carboxylate can be stored indefinitely and used to generate acid chloride in a single day. Reaction with 3 equiv of TMS–Cl in dry THF proceeds more quickly than for the literature analogue, presumably because of the extra carbons on the ketal, which provide enhanced solubility of the carboxylate salt. Removal of solvent and excess TMS–Cl in vacuo, followed by vigorous reaction with 3 equiv of oxalyl chloride catalyzed by DMF provides acid chloride **4** in good yield. Following solvent and excess oxalyl chloride removal, distillation in vacuo provides the acid chloride in 55% yield as a very viscous oil.

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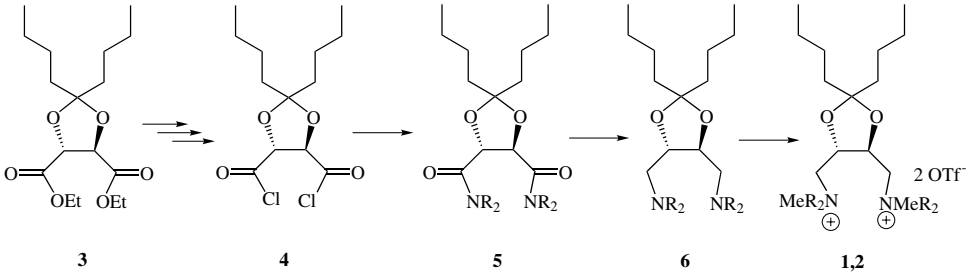

Figure 2. Synthetic scheme for catalysts **1** and **2**. Compounds **5a**, **6a**, **1**: R = ^{i}Pr; **5b**, **6b**, **2**: R = cyclohexyl.

The acid chloride is important because it allows for the introduction of virtually any secondary amine. We chose symmetrical secondary amines to begin our studies, diisopropyl and dicyclohexyl amines, because they add significant steric bulk. One could easily imagine other amines including chiral amines. We hypothesized that the steric bulk of these secondary amines would cause the reaction of the glycine anion with an electrophile to take place near the stereogenic centers of the tartaric acid bridge; the extra carbons also add to the solubility of the final catalyst in organic solvents.

Amines are introduced by reaction of the acid chloride with the secondary amine and a proton acceptor, diisopropylethyl amine. After isolation of the resulting amide, reduction with $LiAlH_4$ yields a tertiary amine. Quaternization of the tertiary amine is best effected by reaction with methyl triflate. The reaction is quite rapid and is usually 95% complete after 2 h at room temperature. Other methylating agents (MeI, Me_2SO_4) gave sluggish reactions.

Preliminary catalytic testing using the literature standard glycine imino ester both for the alkylation[14,15,22] (Fig. 3, Table 1) and Michael reactions[22] (Fig. 4, Table 2) shows both compounds to be effective phase-transfer catalysts. Good yields were obtained with 5% catalyst loading. Integration of the chiral column HPLC traces showed limited enantioselectivity in both reactions. Solubility of the catalysts is good in both CH_2Cl_2 and toluene, and catalytic activity is comparable. While

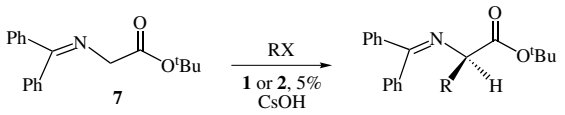

Figure 3. Glycine alkylation.

catalytic activity is better at 0 °C than at −78 °C, activity was observed even at dry ice temperatures.

3. Experimental

3.1. General

All chemicals were purchased from Aldrich and used as received, except THF, which was distilled from sodium potassium alloy just prior to use. 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. Elemental analyses were performed by Desert Analytics. HPLC analyses were performed on a Chiracel OD-H column.

3.2. Synthesis of L-diethyl tartrate, nonanone ketal 3

Diethyl tartrate (100 g, 485 mmol), 5-nonanone (100 g, 703 mmol), *p*-toluenesulfonic acid (1 g, 5.26 mmol) and toluene (150 mL) were added to a 1 L round-bottomed flask. A Dean–Stark trap and condenser were attached

Table 1. Results of glycine imino ester alkylations using CsOH as base

Catalyst	Alkyl halide	Solvent	Temperature (°C)	Time (h)	% Ee	% Conversion
1	$BrCH_2C_6H_5$	CH_2Cl_2	0	1	9	83
1	$BrCH_2C_6H_5$	Toluene	0	1	1	100
1	$BrCH_2C_6H_5$	Toluene	−78	48	4	13
1	$BrCH_2C_6H_5$	CH_2Cl_2	−78	24	2	17
1	$BrCH_2[(2\text{-}CH_3)C_6H_4]$	CH_2Cl_2	0	1	9	94
1	$BrCH_2[(2\text{-}CH_3)C_6H_4]$	CH_2Cl_2	−78	6.5	0	12
1	$BrCH_2[(4\text{-}CH_3)C_6H_4]$	CH_2Cl_2	0	1	2	99
1	$BrCH_2[(4\text{-}CH_3)C_6H_4]$	CH_2Cl_2	−78	6.5	1	43
2	$BrCH_2C_6H_5$	CH_2Cl_2	0	1	6	100
2	$BrCH_2C_6H_5$	Toluene	0	1	9	64
2	$BrCH_2C_6H_5$	CH_2Cl_2	−78	48	0	42
2	$BrCH_2C_6H_5$	Toluene	−78	24	3	17
2	$BrCH_2[(2\text{-}CH_3)C_6H_4]$	CH_2Cl_2	0	1	6	100
2	$BrCH_2[(2\text{-}CH_3)C_6H_4]$	CH_2Cl_2	−78	6.5	2	16
2	$BrCH_2[(4\text{-}CH_3)C_6H_4]$	CH_2Cl_2	0	1	8	99
2	$BrCH_2[(4\text{-}CH_3)C_6H_4]$	CH_2Cl_2	−78	6.5	7	17

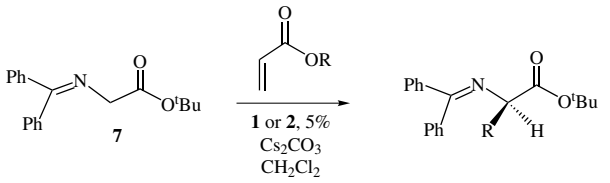

Figure 4. Glycine Michael addition.

Table 2. Results of glycine imino ester Michael reactions using $CsCO_3$ as base, 0 °C

Catalyst	Ester (R)	Time (h)	% Ee	% Conversion
1	Me	24	6	100
1	Et	24	6	100
2	Me	24	11	100
2	Et	24	1	88

and the mixture was allowed to reflux overnight. Solvent was removed in vacuo. The remaining dark brown oil was then attached to a vacuum line and fractionally distilled. Early cuts (boiling below 120 °C) contained starting materials. Ketal **3** distilled between 120 and 125 °C (2 Torr) to yield a colorless oil. Yield: 112.64 g (70%). ^{1}H NMR: δ 4.7 (s, 2H, C(O)C*H*O), 4.3 (q, 4H, OCH_2CH$_3$), 1.7 (dd, 4H, OOCCH_2), 1.3–1.4 (m, 8H, CH_2CH_2CH$_3$), 1.3 (t, 6H, OCH$_2$CH_3), 0.9 (t, 6H, CH$_2$CH$_2$CH_3). ^{13}C NMR: δ 169.3, 117.0, 76.9, 61.5, 36.7, 25.0, 22.5, 14.5. MS: 331 (M+H$^+$), 274.

3.3. Synthesis of diacid chloride 4

Diester **3** (50.0 g, 151 mmol) was dissolved in methanol (300 mL). LiOH·H_2O (15.88 g, 378 mmol) was added and the mixture stirred for 16 h. The resulting mixture was condensed to 75 mL, cooled, filtered, and washed with ether. A small amount was acidified in an ether/water mixture to obtain spectra in order to establish purity. The solid was dried in vacuo until needed. A portion of the dicarboxylate (10.0 g, 35.0 mmol) was taken into freshly distilled THF. TMS–Cl (13.27 mL, 104.9 mmol) was added and the mixture stirred for 20 min after the solid dissolved. Solvent and excess TMS–Cl were removed in vacuo. The resulting waxy solid was stirred with fresh THF and DMF (two drops), after which oxalyl chloride (9.15 mL, 104.9 mmol) was added slowly enough to control the vigorous gas evolution. The mixture was stirred for 20 min after gas evolution ceased and then solvent and excess oxalyl chloride removed in vacuo. Vacuum distillation at 140 °C (2 Torr) of the dark oil gave acid chloride **4** as a pale yellow oil (7.35 g, 68%). ^{1}H NMR: δ 5.1 (s, 2H, ClC(O)C*H*O) 1.6–1.7 and 1.3–1.4 (m, 12H, CH_2CH_2CH_2CH$_3$), 0.9 (t, 6H, CH$_3$). ^{13}C NMR: δ 172.0, 120.9, 83.4, 36.5, 25.9, 22.7, 13.9.

3.4. Synthesis of amide 5-dicyclohexylamide 5b

Diacid chloride **4** (10.87 g, 35.0 mmol) was taken into freshly distilled THF (50 mL) and stirred on ice. Dicyclohexylamine (12.65 g, 70.0 mmol) and diisopropylethylamine (9.02 g, 70 mmol) were combined and added, yielding a heavy white precipitate. The mixture was stirred for an additional hour to allow the reaction to reach completion and then the ^{i}Pr$_2$NEt·HCl filtered and solvent removed in vacuo. Chromatography on basic alumina (hexanes/ether 2:1 then ether) yielded product **5b** as a viscous pale yellow oil. ^{1}H NMR: δ 5.3 (s, 2H, NC(O)C*H*O), 3.9 (br t, 2H, NC*H*(cyclohexyl)), 2.9 (br, 2H, NC*H*(cyclohexyl)), 2.4 (br, 4H, NCHCH_2) 1.0–1.9 (m, 44H, cyclohexyl and butyl), 0.9 (t, 6H, CH_3). ^{13}C NMR: δ 168.3, 114.6, 76.2, 57.5, 56.3, 53.1, 36.7, 31.1, 30.0, 29.7, 29.1, 26.6, 26.3, 25.9, 25.7, 25.4, 22.9, 14.1 MS: 602 (M$^+$), 376, 251, 181.

3.5. Synthesis of tertiary amines 6-dicyclohexyl amine 6b

Diamide **5b** (2.1 g, 3.5 mmol) was dissolved in THF. LAH pellets (1.06 g, 27.9 mmol) were then stirred in distilled THF until a slurry formed. The amide solution was added and the mixture refluxed overnight. After cooling on ice, the mixture was quenched with a sequence determined as x g LAH = x mL H_2O = x mL 3 M NaOH = 3x mL H_2O and stirred until the mixture became white. This was then filtered through a pad of Celite. After solvent removal, the oil was chromatographed on basic alumina with a gradient eluent (hexanes–gradient hexanes/ether–ether). Yield: 1.47 g (74%). ^{1}H NMR: δ 3.6 (br(dd), 2H, NCH$_2$C*H*O), 2.75 (dd, 2H, NC*H*HCHO), 2.73 (dd, 2H, NC*H*HCHO), 2.6 (m, 2H, NC*H*(cyclohexyl))1.0–1.7 (m, 58H, cyclohexyl and butyl). ^{13}C NMR: δ 111.4, 81.2, 58.2, 49.7, 38.0, 32.6, 31.5, 26.7, 26.6, 26.3, 26.2, 23.1, 14.2 MS: 574 (M$^+$), 195. Anal. (calcd): C, 77.42 (77.29); H, 12.38 (12.27); N, 4.74 (4.87).

3.6. Synthesis of quaternary ammonium salts 1 and 2-dicyclohexyl amine 2

Diamine **6b** (1.352 g, 2.4 mmol) was dissolved in CH_2Cl_2 and methyl triflate (850 mg, 5.2 mmol) added. The reaction was stirred overnight (though an NMR scale reaction showed the reaction was at least 95% complete after 2 h). The product was chromatographed on basic alumina with ethyl acetate and then methanol. The product was eluted in the methanol fractions. A 100 mg sample was recrystallized for analysis from CH_2Cl_2/hexane. Yield: 2.5 g (71%). ^{1}H NMR: δ 4.5 (d, 2H, NCH$_2$C*H*O), 3.9 (dd, 2H, NCH*H*CHO), 3.7 (d, 2H, NCH*H*CHO), 3.7 (t, 2H, NC*H*(cyclohexyl)), 3.5 (t, 2H, NC*H*(cyclohexyl)), 3.0 (s, 6H, NCH_3), 1.1–2.3 (m, 52H, cyclohexyl and butyl), 0.9 (t, 6H, CH_3). ^{13}C NMR: δ 116.1, 74.1, 73.8, 62.6, 59.3, 53.5, 43.3, 36.8, 27.8, 27.7, 26.4, 26.3, 26.2, 26.0, 25.9, 25.7, 25.0, 24.9, 24.8, 22.6, 14.1. Mp 146–148 °C. $[\alpha]_D^{25} = -17.0$ (c 0.5, CH_2Cl_2). Anal. (calcd): C, 54.92 (54.65); H, 8.02 (8.28); N, 3.02 (3.11).

Diisopropyl catalyst **1**: ^{1}H NMR: δ 4.5 (d, 2H, NCH$_2$C*H*O), 4.1 (sept, 2H, NC*H*(CH$_3$)$_2$), 4.0 (sept, 2H, NC*H*(CH$_3$)$_2$), 3.9 (dd, 2H, NCH*H*CHO), 3.7 (d, 2H, NCH*H*CHO), 3.0 (s, 6H, NCH_3), 1.2–1.7 (m, 24H, butyl and NCH(CH_3)$_2$), 0.9 (t, 6H, CH_3). Mp 155–157 °C. $[\alpha]_D = -22.9$ (c 0.5, CH_2Cl_2, 25 °C). Anal. (calcd): C, 46.58 (46.88); H, 8.12 (8.14); N, 3.77 (3.77).

3.7. Example procedure for catalytic trials

A 25 mL round-bottomed flask was charged with CH_2Cl_2 (2 mL), CsOH (210 mg, 1.25 mmol), *N*-(diphenylmethylene)glycine *t*-butyl ester (148 mg, 0.50 mmol), and benzyl bromide (102 mg, 0.60 mmol) along with a 1/2 in. stir bar. The mixture was cooled in an ice bath. Catalyst **1** (37 mg, 0.05 mmol) was dissolved in CH_2Cl_2 (1 mL) and added at which point timing was started. Samples were taken at 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 Chiracel OD-H column and a 99:1 hexanes–isopropanol eluent to determine both conversion and enantioselectivity.

Acknowledgements

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