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SYNTHESIS OF NEW N-TETRASUBSTITUTED DERIVATIVES OF *R,R*-TARTARIC ACID AND THEIR USE AS CHIRAL LIGANDS IN OXIDATION CATALYSTS

Kaja ILMARINEN[a], Kadri KRIIS[a], Anne PAJU[a], Tõnis PEHK[b], and Margus LOPP[b,c]

[a] Institute of Chemistry, Tallinn Technical University, Akadeemia tee 15, 12618 Tallinn, Estonia; kkallas@chemnet.ee
[b] National Institute of Chemical Physics and Biophysics, Akadeemia tee 23, 12618 Tallinn, Estonia
[c] Department of Chemistry, Tallinn Technical University, Ehitajate tee 5, 19086 Tallinn, Estonia; lopp@chemnet.ee

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Abstract. N,N,N′,N′-tetraphenyl-*R*,*R*-tartramide, N,N,N′,N′-tetrabenzyl-*R*,*R*-tartramide, and N,N,N′,N′-tetrabenzyl-1,4-diamino-*S*,*S*-2,3-butanediol and their acetals were prepared from commercially available (+)-dimethyl-*R*-*R*-tartrate in good yields. A preliminary screening of the compounds as chiral ligands in catalysts for Baeyer–Villiger oxidation was performed.

Key words: chiral *R*,*R*-tartramides, asymmetric oxidation, reduction.

INTRODUCTION

Asymmetric catalysis is one of the most important areas of synthetic organic chemistry [1]. In recent years many outstanding results in this field have been achieved. A remarkable example is the highly enantioselective epoxidation of allylic alcohols using the Sharpless catalyst [2]. The asymmetric Baeyer–Villiger oxidation has been neglected for a long time. Positive promising results in this field have been obtained only recently [3, 4].

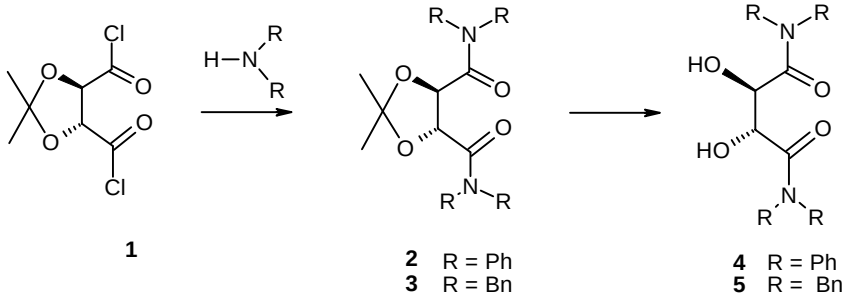
A number of tartaric acid derivatives have been examined as substitutes for tartrate esters in the asymmetric catalysis. N,N′-alkyl-*R*,*R*-tartramides have been used as enantiomerically pure chiral auxiliaries in different catalysts [5–7]. Aminoalcohols have been also used as chiral auxiliaries in asymmetric oxidations (e.g. in dihydroxylation [8, 9]).

In this paper we report the synthesis of different N-containing tartaric acid derivatives: N,N,N′,N′-tetraaryl-*R*,*R*-tartramides **4** and **5**, N,N,N′,N′-tetrabenzyl-

1,4-amino-*S*,*S*-2,3-butanediol **7**, and their acetals (**2**, **3**, and **6**). Also, the results of preliminary experiments on Baeyer–Villiger oxidation of ketones using synthesized compounds as chiral ligands in the asymmetric catalysts are presented.

RESULTS AND DISCUSSION

N,N,N′,N′-tetraaryl-*R*,*R*-tartramides **4** and **5** were prepared from 2,3-O-isopropylidene-*R*,*R*-tartryl chloride **1** by aminolysis of the corresponding secondary amines (Scheme 1). The preparation of 2,3-O-isopropylidene-*R*,*R*-tartryl chloride involves a certain problem because of labile acetal group in the molecule. However, the acid chloride **1** was successfully synthesized from (+)-dimethyl-2,3-O-isopropylidene-*R*,*R*-tartrate [10] according to a method suggested by Choi et al. [11].



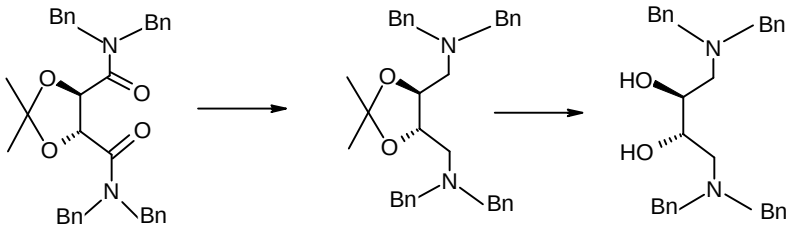
Scheme 1. Synthesis of N,N,N′,N′-tetraaryl-*R*,*R*-tartramides **2**, **3**, **4**, and **5**.

In order to obtain N,N,N′,N′-tetrabenzyl-1,4-amino-*S*,*S*-2,3-butanediols **6** and **7** we tried the reduction of N,N,N′,N′-tetrabenzyl-2,3-O-isopropylidene *R*,*R*-tartramide **3** with various reducing agents. The mixed reducing agent $LiAlH_4$–$AlCl_3$ and AlH_3 [12] reduced **3** in good yield (Table 1, Nos. 2, 3). A mild reduction of **3** with diborane [13] resulted in amine **6** in high yield (Table 1, No. 1). $LiAlH_4$ alone did not give the target amine (Table 1, No. 4). After the removal of the protecting group (Scheme 2) we obtained N,N,N′,N′-tetrabenzyl-1,4-amino-*S*,*S*-2,3-butanediol **7** in good yield.

Table 1. The reduction of N,N,N′,N′-tetrabenzyl-2,3-O-isopropylidene *R*,*R*-tartramide **3**

Entry	Reducing agent	Solvent	Temperature, °C	Time, h	Yield of amine **6**, %
1	B_2H_6	THF	60	1.5	94
2	AlH_3	Et_2O, THF	0	1.5	70
3	$LiAlH_4$–$AlCl_3$	Et_2O, THF	0	1.5	86
4	$LiAlH_4$	THF	0	1.0	*

* Only amide-cleavage products were detected.

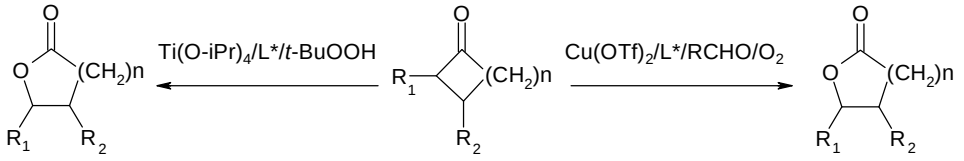


3 **6** **7**

Scheme 2. Synthesis of the 1,4-amino-N,N,N′,N′-tetrabenzyl-*S*,*S*-2,3-butanediol **7**.

The behaviour of new synthesized compounds (**2**–**7**) as ligands in metal-catalyzed Baeyer–Villiger oxidation was checked. Often a stoichiometric amount of the catalyst is required for Baeyer–Villiger oxidation of ketones [14, 15]. However, in some cases excellent catalytic processes have been developed with moderate to good enantioselectivity (up to 95% *ee*) [4, 16].

Two different oxidative systems were investigated on Baeyer–Villiger oxidation of cyclic ketones (Scheme 3).



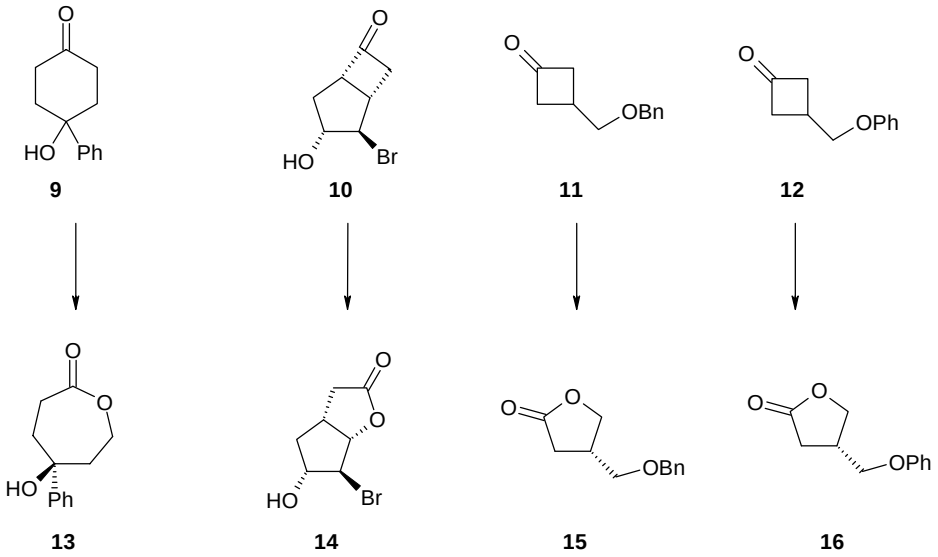
n = 1-3

L* = chiral ligands

RCHO = PhCHO or *t*-BuCHO

Scheme 3. Baeyer–Villiger oxidation of ketones using Ti- and Cu-based chiral catalysts.

We found that the copper(II)triflate/aldehyde/O_2 system with an N-containing chiral ligand in a catalytic amount (5–10 mol% of catalyst) oxidizes ketones **9**–**12** into lactones **13**–**16**, correspondingly, with moderate yield (Scheme 4, Table 2, Nos. 1, 2, 6–14). Only in one case, with substrate **9**, a certain enantioselectivity was achieved (26% *ee*, Table 2, No. 1). The isolated yield of lactone **13** was, however, very low (5%). The catalytic activity of the complex depends considerably on the aldehyde used (Table 2, Nos. 6, 9). Oxidation of ketone **11** with molecular oxygen in the presence of various ligands **2**–**8**, copper(II)triflate, and aldehyde led to racemic lactone **15**. In the case of a titanium based catalyst, a stoichiometric amount of the catalyst was required (Table 2, Nos. 4, 5). Poor to moderate diastereodifferentiation (9 and 37% *ee*; kinetic resolution) with moderate yield was obtained.



Scheme 4. Oxidation substrates and products.

Table 2. The results of Baeyer–Villiger oxidation of ketones **9**–**12** by using chiral ligands **2**–**8***

Entry	Substrate	Oxidant	Chiral ligand	Metal compound	Amount of catalyst	Yield,%	Enantiomeric excess *ee***
1	**9**	PhCHO, O_2	**3**	$Cu(OTf)_2$	5 mol%	5	26%
2	**10**	PhCHO, O_2	**6**	$Cu(OTf)_2$	5 mol%	43	Rac + regio-isomers
3	**10**	PhCHO, O_2	**2**	$Cu(OTf)_2$	1.0 eq	7	Rac + regio-isomers
4***	**10**	*t*-BuOOH	**5**	$Ti(O\text{-}iPr)_4$	1.4 eq	16	37%
5***	**10**	*t*-BuOOH	**8**	$Ti(O\text{-}iPr)_4$	1.5 eq	12	9%
6	**11**	PhCHO, O_2	**3**	$Cu(OTf)_2$	10 mol%	12	Rac
7	**11**	PhCHO, O_2	**5**	$Cu(OTf)_2$	10 mol%	19	Rac
8	**11**	PhCHO, O_2	**8**	$Cu(OTf)_2$	10 mol%	19	Rac
9	**11**	*t*-BuCHO, O_2	**3**	$Cu(OTf)_2$	10 mol%	52.5	Rac
10	**11**	*t*-BuCHO, O_2	**2**	$Cu(OTf)_2$	10 mol%	30	Rac
11	**11**	*t*-BuCHO, O_2	**4**	$Cu(OTf)_2$	10 mol%	31	Rac
12	**11**	*t*-BuCHO, O_2	**5**	$Cu(OTf)_2$	10 mol%	24	Rac
13	**11**	*t*-BuCHO, O_2	**7**	$Cu(OTf)_2$	10 mol%	33.5	Rac
14	**12**	*t*-BuCHO, O_2	**3**	$Cu(OTf)_2$	10 mol%	46	Rac

* For the experimental procedure see [16]; the oxidation process was terminated after a sufficient amount of products for analysis was obtained;
** The *ee* values were determined by HPLC with the column Daicel ODH (4.6 × 250 mm);
*** For the experimental procedure see [14].

EXPERIMENTAL

The glassware was dried in an oven and cooled under argon atmosphere. Toluene was distilled over sodium under argon atmosphere and THF was distilled

over $LiAlH_4$. The dried solvents were stored under dry argon. Commercial reagents, dibenzylamine (Aldrich, 97%), (+)-dimethyl-*R*,*R*-tartrate (Merck, 99%), 2,2-dimethoxypropane (Aldrich, 98%), *p*-TsOH (Reachim), B_2H_6 (Lancaster 1M solution in THF), $AlLiH_4$ (Reachim), $AlCl_3$ (Aldrich, 98%), and acetonitrile (Fisher Scientific, HPLC grade) were used without purification. K_2CO_3 (Reachim) was freshly dried and diphenylamine (Reachim) was recrystallized from petrolether. (+)-Dimethyl-2,3-O-isopropylidene-*R*,*R*-tartrate was prepared via a published procedure [10]. For flash-column chromatography 40–100 μm KKC 120 silica gel was used. A Pye Unicam PU 4500 gas chromatograph (GC) (Philips) equipped with a flame ionization detector and an Alltech ECONO-CAP EC-5, 15 m × 0.53 mm ID × 1.2 μm was utilized for all GC analyses. The system was operated using helium as the carrier gas with a linear velocity of 10 mL/min. The injector and detector temperatures were set at 120 and 250 °C respectively. HPLC was performed with an instrument of Shimadzu LC-10AT VP with a system controller SCL-10A and a UV-VIS detector SPD-10A VP (λ = 254 nm), FCV-10AL VP at ambient temperature. The column was Symmetry C18 5 μm, 4.6 × 250 mm; and the mobile phase used was acetonitrile/H_3PO_4, H_2O 0.5 mL/L, TEA, pH = 7.0, with a program that runs 60% CH_3CN for 10 min and during 20 min the mobile phase was changed to 100% CH_3CN.

New compounds were characterized by ^1H and ^{13}C NMR spectroscopy with an AMX500 MHz Bruker instrument. The optical rotations were measured with a polarimeter Polamat A.

(+)-Dimethyl-2,3-O-isopropylidene-*R*,*R*-tartrate

To the solution of (+)-dimethyl-*R*,*R*-tartrate (45.5 mmol) in toluene (100 mL) 2,2-methoxypropane (95.6 mmol) and *p*-TsOH (5 mol%) were added. The reaction mixture was kept at 60–70 °C for 3 h. After azeotropic distillation (toluene–methanol) with a Vigreux column (15 cm) at 64 °C the reaction mixture was stirred for 4 h and it was left overnight at room temperature. To the reaction mixture (1.05 g) K_2CO_3 was added and the mixture was stirred for 1 h at room temperature. After filtration and concentration the crude product (purity 86.3% by GC) was distilled under vacuum at 115–122 °C (2–3 mmHg). The yield of the product was 85.2% with 97.4% purity by GC.

^1H NMR ($CDCl_3$) δ (ppm): 1.35 s (–CH_3); 3.71 s (–O–CH_3); 4.67 s (–CH–).

^{13}C NMR ($CDCl_3$) δ (ppm): 25.92 (–CH_3); 52.34 (–O–CH_3); 76.64 (–CH–); 113.41 (*tert*-C); 169.69 (C=O).

N,N,N′,N′-tetraphenyl-2,3-O-isopropylidene *R*,*R*-tartramide 2

To the solution of chloride **1** (3.68 mmol) in THF (2 mL) a solution of diphenylamine (19.08 mmol) in THF (5 mL) was added dropwise at 0 °C. The reaction mixture was refluxed for 1 h and stirring was continued for 4 days at room temperature. After work-up the organic layer was dried on $MgSO_4$ and concentrated with rotavap. The crude product was purified by flash-column

chromatography on silica gel (petrolether:ethylacetate 15:1). The preparative yield of the product was 66% (purity of the product was 99.2% by HPLC).

^{1}H NMR ($CDCl_3$) δ (ppm): 1.22 s (–CH_3); 5.01 s (–CH–); 7.15–7.37 (exchange broadened arom.).

^{13}C NMR ($CDCl_3$) δ (ppm): 26.23 (–CH_3); 76.59 (–CH–); 112.57 (*tert*-C); 126.7–129.2 and 142.0 (exchange broadened arom.); 168.35 (–C=O).

N,N,N′,N′-tetrabenzyl-2,3-O-isopropylidene *R,R*-tartramide 3

To the solution of chloride **1** (1.1 mmol) in THF (2.5 mL) a solution of dibenzylamine (3.3 mmol) in THF (1.5 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature. After filtration and concentration with rotavap, the product was purified by flash-column chromatography on silica gel (petroether:ethylacetate 10:1). The preparative yield of the product was 88% (purity of the product was 85% by HPLC).

^{1}H NMR ($CDCl_3$) δ (ppm): 1.48 s (–CH_3); 5.59 s (–CH–); 4.48 d and 4.63 d, 4.68 d and 4.73 d (2 CH_2–Ph).

^{13}C NMR ($CDCl_3$) δ (ppm): 26.41 (–CH_3); 47.49 and 49.65 (2 –CH_2Ph); 76.06 (–OCH); 112.42 (*tert*-C); 127.55 and 128.09 (*ortho*), 128.60 and 128.77 (*meta*), 127.36 and 127.69 (*para*), 136.28 and 136.61 (*s*); 168.83 (C=O).

General procedure for deprotection [17]

To the solution of the corresponding 2,2-dimethyl-1,3-dioxolanes in CH_3CN (40 mL) 6 N H_2SO_4 (20 mL) was added. After refluxing for 1.5 h the reaction was stopped by adding ice-cold water and the mixture was extracted with EtOAc (4 × 15 mL). The organic layer was collected and concentrated with rotavap. After flash-column chromatography on silica gel (petrolether:ethylacetate 5:3) the corresponding product was obtained.

N,N,N′,N′-tetraphenyl *R,R*-tartramide 4

The deprotection of N,N,N′,N′-tetraphenyl-2,3-O-isopropylidene *R,R*-tartramide **2** gave 83% yield of white crystals with 84% purity by HPLC.

$[\alpha]_{546}^{21\,°C}$ = –133 (c = 1.646, DMF).

^{1}H NMR ($CDCl_3$) δ (ppm): 4.12 s (O–CH); 4.25 (OH); 7.1–7.3 m (exchange broadened arom.).

^{13}C NMR ($CDCl_3$) δ (ppm): 69.90 (HO–CH); 126.33 (2), 126.68 (1), 128.13 (3), 129.07 (2), 129.87 (2), 140.42 (*s*), 142.75 (*s*) (arom.); 170.75 (C=O). Aromatic carbon atoms showed at room temperature exchange broadening between E and Z phenyl groups. Equivalence of phenyl groups occurred at temperatures above 60 °C.

N,N,N′,N′-tetrabenzyl *R,R*-tartramide 5

The deprotection of N,N,N′,N′-tetrabenzyl-2,3-O-isopropylidene *R,R*-tartramide **3** gave 85% yield of white crystals with 95% purity by HPLC. $[\alpha]_{546}^{21.5\,°C}$ = 13.3 (c = 2.15 EtOAc).

^{1}H NMR ($CDCl_3$) δ (ppm): 4.40 d, 4.47 d, 4.67 d, and 4.78 d (–CH_2–Ph); 4.79 s (HO–CH–); 7.14–7.34 m (arom.).

^{13}C NMR ($CDCl_3$) δ (ppm): 48.47 and 49.32 (–CH_2–Ph); 70.19 (HO–CH–); 126.70, 127.62 (*para*), 127.86 (*para*), 128.36, 128.68, 129.01, 135.48 (*s*), 136.10 (*s*) (arom.); 171.69 (C=O).

1,4-amino-N,N,N′,N′-tetrabenzyl-2,3-O-isopropylidene-*S*,*S*-2,3-butanediol 6 (Table 1)

^{1}H NMR ($CDCl_3$) δ (ppm): 1.28 s (–CH_3), 2.48 and 2.59 m (–N–C**H$_2$**–CHO–); 3.55 d and 3.60 d (J = 13.9 Hz) (–CH_2–Ph), 3.83 m (–CH–O–), 7.18–7.32 m (arom.).

^{13}C NMR ($CDCl_3$) δ (ppm): 27.16 (–CH_3), 55.32 (–N–**C**H_2–CHO–), 58.73 (–N–CH_2–Ph), 78.50 (–CH_2–**C**H–O), 108.66 (*tert*-C), 126.79 (*para*), 128.10 (*meta*), 128.90 (*ortho*), and 139.25 (*s*) (arom.).

1,4-amino-N,N,N′,N′-tetrabenzyl-*S*,*S*-2,3-butanediol 7

Deprotection of 1,4-amino-N,N,N′,N′-tetrabenzyl-2,3-O-propylidene-*S*,*S*-2,3-butanediol **6** gave 99% yield of white crystals with 93% purity by HPLC.

$[\alpha]_{546}^{21.5^\circ C}$ = –11.8 (c = 1.52, DMF).

^{1}H NMR ($CDCl_3$) δ (ppm): exchange broadened spectrum: 2.55 and 2.65 m (–OCH–C**H$_2$**–N–); 3.50 and 3.79 m (N–CH_2–Ph); 3.65 m (–CHO); 7.2–7.4 m (arom.).

^{13}C NMR ($CDCl_3$) δ (ppm): exchange broadened spectrum: 56.43 (–OCH–**C**H_2–N); 59.01 (–CH_2–Ph); 69.32 (HO–CH–); 127.40 (*para*), 128.46 (*meta*), 129.32 (*ortho*); 138.05 (*s*) (arom.).

General oxidation procedure with a copper(II)triflate/aldehyde/O_2 system

To a solution of chiral ligand (0.05 eq) in CH_2Cl_2 (0.01 M) copper(II)triflate (0.05 eq) was added and the mixture was stirred for 3 h at room temperature. Then ketone (1 eq) and aldehyde (3 eq) were added. The mixture was stirred under an oxygen atmosphere for 2–4.5 days. The reaction was quenched with a saturated solution of $NaHCO_3$ and the aqueous layer was extracted three times with CH_2Cl_2. The organic phase was dried over $MgSO_4$. After the removal of the solvent, the crude product was chromatographed on silica gel. The enantiomeric excesses for lactones were determined by HPLC with the column Daicel ODH (4.6 × 250 mm).

CONCLUSION

The preliminary results of the Baeyer–Villiger oxidation reaction were promising. The easily prepared new derivatives of tartaric acid with titanium and copper complexes show a good ability to catalyze the Baeyer–Villiger oxidation reaction. However, moderate enantioselectivity was achieved only in one case

with the catalytic Cu(II) system and with stoichiometric Ti-system. The other metals as well as other oxidation systems should be tested together with the synthesized chiral ligands.

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R,*R*-VIINHAPPE N-TETRAASENDATUD DERIVAATIDE SÜNTEES JA KASUTAMINE KIRAALSETE LIGANDIDENA OKSÜDATSIOONI KATALÜSAATORITES

Kaja ILMARINEN, Kadri KRIIS, Anne PAJU, Tõnis PEHK ja Margus LOPP

Optiliselt puhtad N,N,N′,N′-tetrafenüül-*R*,*R*-viinhappeamiid, N,N,N′,N′-tetrabensüül-*R*,*R*-viinhappeamiid ja N,N,N′,N′-tetrabensüül-1,4-amino-*S*,*S*-2,3-butaandiool ning nende atsetaalid sünteesiti (+)-dimetüül-*R*,*R*-viinhappe estrist heade saagistega. Esialgsete tulemuste järgi katalüüsisid nende baasil loodud kompleksid Baeyeri–Villigeri oksüdatsiooni ja neil oli ühel juhul ka enantioselektiivne toime.