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Stereoselectivity of Grignard Reaction in the Presence of Chiral Podands and Crown Ethers

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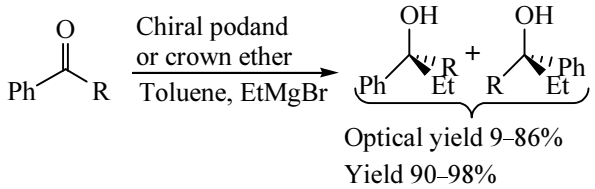
Abstract—Reactions of ethylmagnesium bromide with benzaldehyde and acetophenone in toluene proceed stereoselectively in the presence of catalytic amounts of chiral podands and crown ethers. Under catalytic conditions theyield of the corresponding alcohols is nearly quantitative. The optical yield varies in the range 9–86% depending on the catalyst structure.

Enantiodifferentiating qualities of chiral crown ethers and their acyclic analogs, podands, provide versatile opportunities for their application as enantioselective sensors, enantiodifferentiating agents, models of biologic systems, and catalysts of asymmetrical reactions [1]. Optically active crown ethers relatively seldom were used as catalysts of phase-transfer catalysis [2]. However examples are known of their successful application as stereoselective phase-transfer catalysts in aromatic ketones reduction with aminoborane NH_3BH_3 [3], Michael [4], and Darzen reactions [5]. Up till now the possibility of application of chiral podands and crown ethers as stereoselective catalysts for Grignard reaction virtually is not investigated. Only reactions of asymmetrical addition of alkylmagnesium halides to enones [6] and γ-ketoesters [7] were described. In the first study the catalysis was carried out using complexes of Zn^{2+}, Pd^{2+} and Eu^{3+} with chiral thiazacrown ethers, in the second were applied chiral podands originating from binaphthol.

We demonstrated formerly that crown ethers in solution form stable complexes with aryl(alky)magnesium halides (1:1) that were isolated as individual compounds [8]. These complexes mildly and highly selectively react with carbonyl compounds both in ether traditional for the Grignard reaction and in hydrocarbon solvents. The Grignard reaction may be performed also under phase-transfer conditions in the presence of 5–10 mol% of crown ether [9].

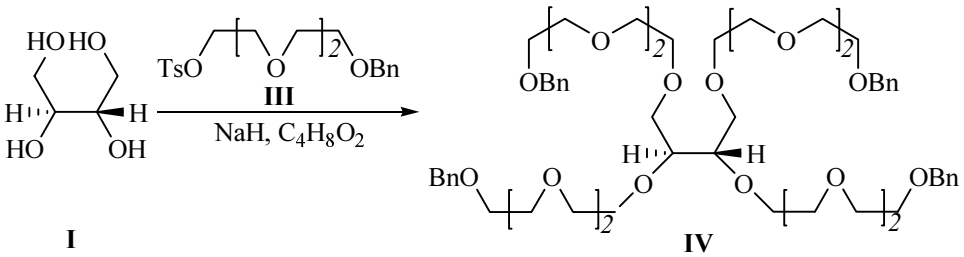


We report here on the synthesis of new chiral podands and results of investigating Grignard reaction in the presence of chiral podands and crown ethers as catalysts of asymmetricl induction.

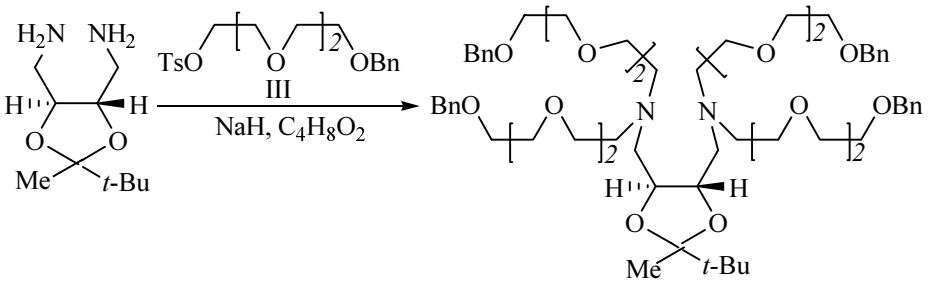
As starting chiral synthons for podands synthesis served tetrol **I** and diamine **II** that by alkylation with tosylate **III** in dioxane were converted into podand **IV** and azapodand **V** (see the scheme).

The catalytic and enantiodifferentiating activity of podands **IV** and **V** and chiral compounds that we had prepared before (chiral podand **VI**, crown ethers **VII** and **VIII** [10], **IX** and **X** [11], and azacrown ethers **XI** [12], XII, and **XIII** [13]) was investigated by an example of ethylmagnesium bromide reactions with benzaldehyde and acetophenone in toluene at 0°C in the presence of 10 mol% of the catalyst. The catalytic activity was evaluated by the time of complete conversion of the initial carbonyl compound. Yields of the corresponding alcohols in all cases attained 90–98% (GLC data). The alcohol yield in the absence of the catalyst did not exceed 1–2%, and therefore the non-catalyzed process was disregarded.

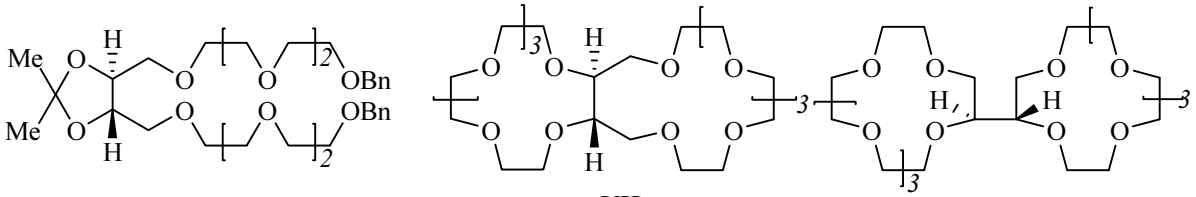
The preliminary runs showed that the maximum yield of the corresponding alcohols was obtained at the ratio of ethylmagnesium bromide to the carbonyl compound of 2:1. Under catalysis the yield of the target alcohol calculated on the reacted carbonyl compound reached a quantitative value, and any side products are virtually lacking. The catalytic activity of all crown ethers **VII–X** and azacrown ethers **XI–XIII** studied considerably



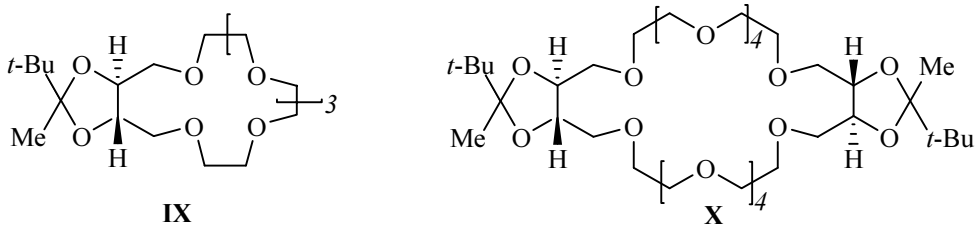
I **IV**



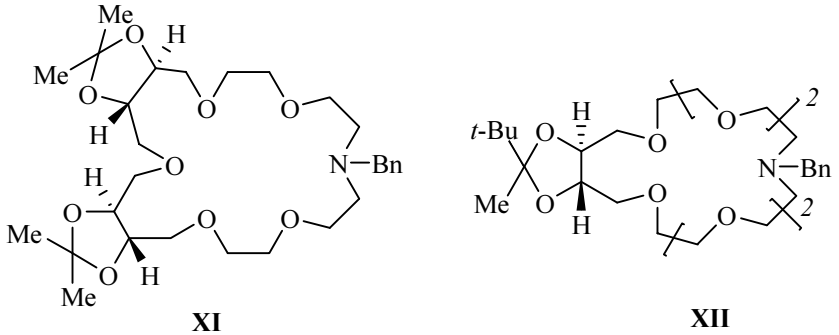
II **V**



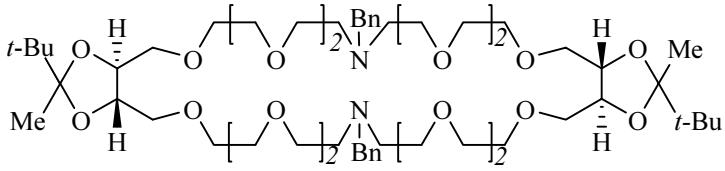
VI **VII** **VIII**



IX **X**



XI **XII**



XIII

Process time, yields, and enantioselectivity of reaction of ethylmagnesium bromide with benzaldehyde and acetophenone in the presence of chiral ligands **IV–XIII** in toluene at the ratio of ethylmagnesium bromide to carbonyl compound 2 : 1

Catalyst	Reaction time, h		Chemical yield, %		$[\alpha]_D^{20}$, deg. (prevailing enantiomer)		Optical yield,[a] %	
	benzaldehyde	acetophenone	1-phenyl-1-propanol	2-phenyl-2-butanol	1-phenyl-1-propanol	2-phenyl-2-butanol	1-phenyl-1-propanol	2-phenyl-2-butanol
IV	24	28	92	94	–10.1 (*S*)	–5.4 (*S*)	25.3	29.2
V	18	20	96	98	13.4 (*R*)	7.0 (*R*)	33.4	38.1
VI	30	36	90	92	–3.5 (*S*)	–2.0 (*S*)	8.8	10.6
VII	10	12	91	94	15.4 (*R*)	7.7 (*R*)	38.5	41.7
VIII	14	16	94	96	–24.8 (*S*)	–13.6 (*S*)	62.0	74.1
IX	15	17	95	97	15.9 (*R*)	8.2 (*R*)	39.7	44.3
X	10	11	94	96	–17.9 (*S*)	–9.1 (*S*)	44.8	49.3
XI	10	12	93	96	–31.4 (*S*)	–15.9 (*S*)	78.6	86.2
XII	9	10	95	98	–28.5 (*S*)	–14.3 (*S*)	71.2	77.5
XIII	5	6	95	97	27.5 (*R*)	13.7 (*R*)	68.8	74.4

[a] Ratio of specific rotation of reaction product to the specific rotation of a pure enantiomer expressed as percent. The values $[\alpha]_D^{20}$ for pure enantiomers of 1-phenyl-1-propanol and 2-phenyl-2-butanol were taken as ± 40.0° [14] and ±18.4° [15] respectively.

exceeded that of acyclic podands **IV–VI** demonstrating the decisive contribution of the cyclic structure to formation of soluble complexes with the reagent (see table).

The yield of the corresponding alcohols from acetophenone was regularly by 2–3% higher than from benzaldehyde; the latter was more disposed to form side products. The comparison in pairs of catalysts with similar structures (**IV** and **V**, **IX** and **XII**, **X** and **XIII**) shows that azapodand **V** and azacrown ethers **XII** and **XIII** are considerably more efficient catalysts than their oxygen-containing analogs.The value of the asymmetrical induction (the optical yield of the product) changes within these pairs in the same direction as their catalytic activity. The higher rate and enantiselectivity of the reaction in the presence of chiral azapodand and azacrown ethers is likely to be caused by formation of more stable complexes with reagent molecules than those with the oxygen-containing analogs.

Reactions with acetophenone as compared to those with benzaldehyde were always slower but afforded the corresponding alcohol with a higher optical yield. The reason of this fact is apparently the higher shielding of the reaction site in the acetophenone.

The catalytic activity of crown ethers **VII** and **X** as compared to that of crown ether **IX**, and that of compound **XIII** relative to the activity of azacrown ether **XII** is 1.5–2 times greater whereas the capability to asymmetrical induction is of similar order of magnitude. The highest optical yields in the Grignard reaction were obtained at the use as catalyst of crown ether **XI** probably due to the presence in its molecule of four closely located asym-metrical centers.

It should be noted in conclusion that we demonstrated the possibility to perform asymmetrical Grignard reaction at the use of chiral podands and crown ethers as catalysts. The results obtained show sufficiently high enantioselectivity of some crown ethers, for instance, **VIII**, **XI–XIII**. Therefore their application to asymmetrical synthesis involving organomagnesium compounds is promising.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometer Bruker AM-250 (250 MHz) in $CDCl_3$, internal reference HMDS. Mass spectra were measured on Varian MAT-112 and MKh-1321 instruments with direct sample admission into the ion source, ionizing electrons energy 70 eV. Values of $[\alpha]_D^{20}$ were determined on polarimeter Perkin Elmer 241-MC.

GLC analyses were carried out on Chrom-5 device equipped with flame-ionization detector, glass column 1200×3 mm, stationary phase SE-30 (5%) on a carrier Inerton AW-DMCS (0.100–0.125 mm). TLC was performed on Silufol plates, development with ninhydrine

solution in ethyl ether, and also glass plates with fixed layer of neutral aluminum oxide (L 5/40) were used, development in iodine vapor. The preparative liquid chromatography was carried out on glass columns packed with silica gel (L 40/100) or neutral aluminum oxide (L 40/250).

(2*S*,3*S*)-1,2,3,4-Butanetetrol **I** and 1-benzyloxy-8-tosyloxy-3,6-dioxaoctane **III** were prepared as described before [10, 16].

(4*S*,5*S*)-4,5-Bis(aminomethyl)-2-*tert*-butyl-2-methyl-1,3-dioxolane (II). To a solution of 10.2 g (0.6 mol) of ammonia and 0.2 g (8.7 mmol) of sodium metal in 100 ml of anhydrous methanol was added 28.8 g (0.1 mol) of diethyl (4*R*,5*R*)-2-*tert*-butyl-2-methyl-1,3-dioxolane-4,5-dicarboxylate [11]. The mixture was stirred for 3 h at 18–20°C and left overnight. Then the reaction mixture was evaporated by half, the precipitate was filtered off and recrystallized from 40 ml of anhydrous methanol. Yield of (4*R*,5*R*)-2-*tert*-butyl-2-methyl-1,3-dioxolane-4,5-dicarboxamide 17.5 g (76%), colorless crystals, mp 148–149°C, $[\alpha]_D^{20}$ 11.1° (*c* 1.0, C_2H_5OH). ^1H NMR spectrum, δ, ppm: 0.98 s (9H, *t*-Bu), 1.32 s (3H, CH_3), 4.29 q (2H, CH), 7.10 s (2H, NH), 7.28 s (2H, NH). Found, %: C 52.19; H 7.92; N 12.21. M^+ 230. $C_{10}H_{18}N_2O_4$. Calculated, %: C 52.16; H 7.88; N 12.17. *M* 230.26.

To a dispersion of 5.6 g (148 mmol) of lithium aluminum hydride in 100 ml of anhydrous THF under argon atmosphere at vigorous stirring was added by small portions 15.6 g (68 mmol) of (4*R*,5*R*)-2-*tert*-butyl-2-methyl-1,3-dioxolane-4,5-dicarboxamide, the stirring was continued for 2 h, then the temperature was raised to boiling, and the mixture was heated at reflux for 8 h and left overnight. Then at stirring while cooling with an ice bath was added dropwise 5.6 ml of ice water, the precipitate was filtered off, treated with boiling THF (3∞ 75 ml), the extract was combined with the filtrate, the solution was dried on NaOH, THF was distilled off at reduced pressure, and the residue was distilled in a vacuum. Yield of diamine **II** 10.1 g (74%), bp. 90–91°C (2 mm Hg), $[\alpha]_D^{20}$ 2.6° (*c* 2.5, C_2H_5OH). ^1H NMR spectrum, δ, ppm: 0.92 s (9H, *t*-Bu), 1.22 s (3H, CH_3), 2.40 br.s (4H, NH_2), 2.68–2.79 m (4H, NCH_2), 3.47–3.80 m (2H, CH). Found, %: C 59.41; H 10.94; N 13.81. M^+ 202. $C_{10}H_{22}N_2O_2$. Calculated, %: C 59.37; H 10.96; N 13.85. *M* 202.30.

Podands IV and V. To a dispersion of 1.9 g (79 mmol) of sodium hydride in 20 ml of anhydrous dioxane was added in small portions under argon atmosphere while stirring 1.0 g (8.2 mmol) of tetrol **I** or was added dropwise a solution of 1.6 g (7.9 mmol) of diamine **II** in 5 ml of anhydrous dioxane, and the stirring was continued for 1 h at 18–20°C. To the mixture thus obtained was added dropwise a solution of 13.8 g (35 mmol) of tosylate **III** in 25 ml of anhydrous dioxane, the temperature was raised to 90–95°C, and the stirring was continued for 16 h. The reaction mixture cooled to 18–20°C was poured by portions to stirred ice water (50 ml), and the reaction products were extracted into chloroform (3×50 ml). The combined extracts were dried over Na_2SO_4, the solvent was removed at a reduced pressure. The individual podands **IV** and **V** were isolated as colorless oily substances by column chromatography on neutral aluminum oxide, eluent chloroform–benzene–methanol–propanol, 8:3:0.3:0.3.

(13*S*,14*S*)-13,14-Bis(2-{2-[2-(benzyloxy)-ethoxy]ethoxy}ethoxy)-1,26-diphenyl-2,5,8,11,16,19,22,25-octaoxahexacosane (IV). Yield 5.1 g (62%), $[\alpha]_D^{20}$ –6.0° (*c* 4.0, C_2H_5OH). ^1H NMR spectrum, δ, ppm: 3.52–3.68 m (52H, CH_2), 3.70–3.85 m (2H, CH), 4.49 s (8H, CH_2Ph), 7.19–7.31 m (20H, Ph). Found, %: C 66.60; H 8.23. M^+ 1010. $C_{56}H_{82}O_{16}$. Calculated, %: C 66.52; H 8.17. *M* 1011.17.

***N*,*N*-Bis(2-{2-[2-(benzyloxy)ethoxy]ethoxy}-ethyl)-*N*-{[(4*S*,5*S*)-5-[2-(2-{2-[2-(benzyloxy)-ethoxy]ethoxy}ethyl)-12-phenyl-5,8,11-trioxa-2-azadodec-1-yl]-2-(*tert*-butyl)-2-methyl-1,3-dioxolan-4-yl]methyl}amine (V).** Yield 6.2 g (72%), $[\alpha]_D^{20}$ –3.9° (*c* 5.0, C_2H_5OH). ^1H NMR spectrum, δ, ppm: 0.89 s (9H, *t*-Bu), 1.19 s (3H, CH_3), 2.64–2.81m (12H, NCH_2), 3.42–3.58 m (40H, OCH_2), 3.60–3.82 m (2H, CH), 4.48 s (8H, CH_2Ph), 7.18–7.29 m (20H, Ph). Found, %: C 68.28; H 8.61; N 2.63. M^+ 1090. $C_{62}H_{94}N_2O_{14}$. Calculated, %: C 68.23; H 8.68; N 2.57. *M* 1091.43.

Reaction of ethylmagnesium bromide with benzaldehyde and acetophenone in the presence of chiral ligands. A solution of 0.5 mmol of a ligand in 5 ml of anhydrous toluene preliminary saturated with nitrogen was added to 0.24 g (10 mmol) of magnesium turnings activated with iodine vapour. To this mixture was added 0.22 g (2 mmol) of freshly distilled ethyl bromide, and the mixture was stirred at 18–20°C till the reaction started (as was seen from the darkening of the metal surface). Then a mixture of 0.87 g (8 mmol) of ethyl bromide and 0.53 g (5 mmol) of benzaldehyde or 0.6 g (5 mmol) of acetophenone in 20 ml of anhydrous toluene was added dropwise within 0.5 h. The stirring under nitrogen atmosphere was continued till complete conversion of the substrate (GLC monitoring). The

reaction mixture was treated with a saturated solution of ammonium chloride, the organic layer was separated, and the water layer was extracted with ether (3×10 ml). The ether extracts were combined with the toluene solution, the solution obtained was washed in succession with a saturated solution of sodium thiosulfate, with 10% solution of sodium hydrogen carbonate, and with a little water till neutral reaction. The solution was then dried with $MgSO_4$, the solvents were distilled off at the atmospheric pressure, and the residue was subjected to column chromatography on silica gel, eluent pentane–ethyl ether, 5:2. Thus a mixture of enantiomeric alcohols was isolated, and their $[\alpha]_D^{20}$ was measured (see table).

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