Metal complexes as phase transfer catalysts in the synthesis of *O*-acetylmandelonitrile

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The asymmetric synthesis of *O*-acetylated mandelonitrile derivative was accomplished from PhCHO, KCN, and Ac_2O in a toluene—water system in the presence of transition metal complexes of Schiff´s bases as phase transfer catalysts.

Key words: benzaldehyde, cyanohydrins, phase transfer catalysis, transition metal complexes.

Cyanohydrin fragments have been found in the molecules of a large number of commercially important compounds. Pyrethroids can be mentioned as the most vivid example.[1] Cyanohydrins by themselves are versatile synthetic intermediates used to prepare α-hydroxy acids, α-amino acids, and α-amino alcohols.[2—4] Since cyanohydrins are unstable, they are mainly used in practice as *O*-substituted derivatives. Therefore, development of the methods of synthesis of these compounds appears to be quite topical.

Cyanohydrins can be synthesized using various sources of cyanide ions,[3] KCN or NaCN being the most convenient starting compounds. Stable *O*-acetyl derivatives of cyanohydrins are formed under conditions we found previously and used in the asymmetric synthesis of *O*-acetylcyanohydrins catalyzed by asymmetric metal complexes.[5] The reaction occurs most efficiently in CH_2Cl_2 on treatment of aldehydes with KCN and Ac_2O in the presence of water additives. The conduction of reactions of organic compounds with inorganic salts in two-phase organic solvent—water systems offers a number of advantages. The key advantage is the possibility of using rather concentrated (in some cases, saturated) solutions, which provides a substantial increase in the reaction rates. Two types of these reactions are known. According to the first one, inorganic salts are transferred into the bulk of the organic solvent (classical phase transfer reactions), while in the second one, organic reagents pass to the aqueous phase. The latter case is encountered more rarely, but this version is now under intensive research (see reviews[6,7]).

In this study, we attempted to prepare the *O*-acetyl derivative of mandelic acid nitrile in a two-phase water—organic medium using anionic Co^{III} complexes **1**—**3** as phase transfer catalysts for transferring PhCHO into the aqueous phase. Complexes **1**—**3** are readily soluble in water and are mainly accumulated in the aqueous phase when placed in a toluene—water system.

The reaction of PhCHO with KCN and Ac_2O is depicted in Scheme 1. Apart from complexes **1**—**3**, a number of other transition metal complexes (**4**—**7**) were used as catalysts and, for comparison, several classical phase transfer catalysts were employed, namely, diols **8**—**10** (the mechanism of their action is the same as that of crown ethers) and quaternary ammonium salt **11**, which carry inorganic anions into the bulk of an organic solvent.[8]

The results are listed in Table 1. In all cases, the reaction is catalyzed rather efficiently by both anionic complexes **1**—**3** (see Table 1, runs *4*—*6*) and formally neutral

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Scheme 1

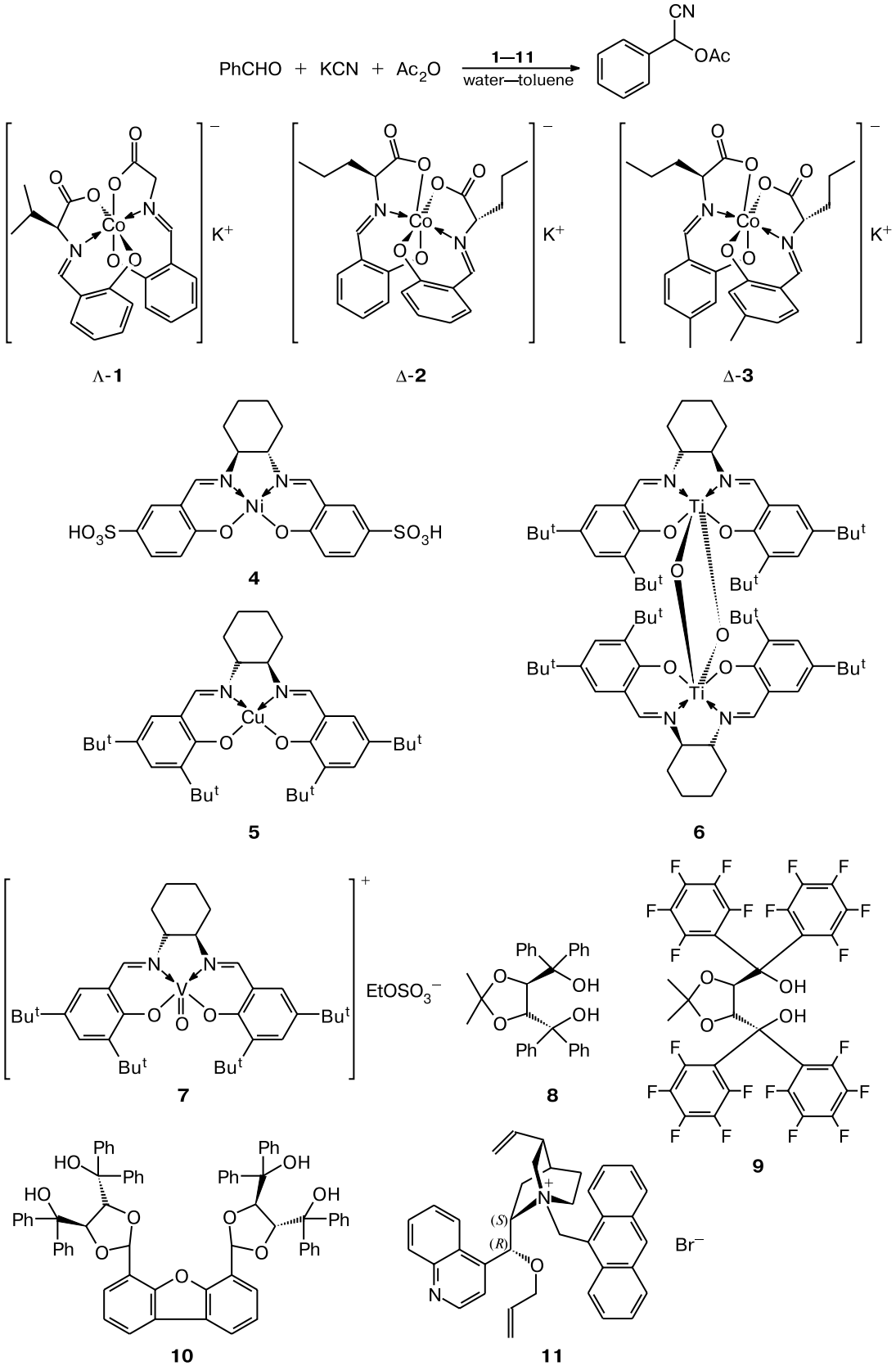

Table 1. Yield and enantiomeric purity of *O*-acetylmandelonitrile based on the results of reaction under conditions of phase transfer catalysis by compounds **1**—**11**

Run	Solvent	Catalyst (mol.%)	Yield[a]	*ee*[a,b]
			%	
1	Toluene	—	3	0
2	Water	—	—	—
3	Toluene—water (9 : 1)	—	27	0
4	The same	**1** (5)	90	0
5	«»	**2** (3) + Bu_4NBr (3)	100	0
6	«»	**3** (5)	90	0
7	«»	**4** (5)	90	0
8	«»	**5** (5) + imidazole (10)	60	0
9	«»	**6** (1)	75	20 (*S*)
10	«»	**7** (2)	75	25 (*S*)
11	«»	**8** (5)	90 (50[c])	0
12	«»	**9** (5)	90 (40[c])	0
13	«»	**10** (5)	90	0
14	«»	**11** (5)	95	0
15	Toluene	**6** (1)	20	52 (*S*)
16	The same	**7** (2)	30	74 (*S*)

[a] The yield and enantiomeric purity were determined by GLC on a chiral column calibrated preliminarily against the starting compound and the racemic product.
[b] The product configuration is given in parentheses.
[c] For the reaction carried out at −10 °C.

compounds **4**—**6** (runs *7*—*9*) and also by cationic complex **7** (runs *10*). The process is catalyzed equally efficiently by diol **8**, its derivatives **9** and **10**, and by quaternary ammonium salt **11**, which are classical catalysts of asymmetric phase transfer catalysis.

Although the catalysts used were chiral enantiomeric compounds, asymmetric induction was observed only with complexes **6** and **7**. The quaternary ammonium salt of cinchonidine **11**, which efficiently catalyzes the asymmetric formation of the C—C bond under phase transfer conditions, did not show stereodifferentiation either.[9—11]

The asymmetric induction observed in the reaction carried out in the toluene—water system (see Table 1, runs *9* and *10*) was lower than that in toluene (runs *15* and *16*), although the yield was substantially higher under the phase transfer conditions.

We hope that optimization of the reation conditions and catalyst structures would allow one to attain high asymmetric induction and high yields in the synthesis of *O*-acetyl derivatives of cyanohydrins with asymmetric phase transfer catalysis.

Experimental

Commercial chemicals and catalyst **11** (Aldrich) and 4,6-diformyldibenzo[*b*,*d*]furan (Acros) were used. GLC analysis was performed on a 3700 chromatograph (Russia) with a 40 m × 0.23 mm quartz capillary column (2,6-di-*n*-pentyl-3-trifluoroacetyl-γ-cyclodextrin as the chiral phase, film thickness 0.12 μm). The yield and the enantiomeric purity of the obtained *O*-acetylmandelonitrile were determined under isothermal conditions at a column temperature of 105 °C with helium as the carrier gas. The column was preliminarily calibrated against the starting compound and the racemic product.

Compounds **1**—**5**,[12] **6**,[5] **7**,[5] **8**,[13] and **9** [14] were prepared by reported procedures, while complex **10** was synthesized by analogy with complex **9** starting from 4,6-diformyldibenzo[*b*,*d*]furan.

4,6-Di[(4*R*,5*R*)-4,5-bis(isopropyloxycarbonyl)-1,3-dioxolan-2-yl]dibenzo[*b*,*d*]furan (12). 4,6-Diformyldibenzofuran (1 g, 4.46 mmol) in 20 mL of benzene, diisopropyl (*R*)-tartrate (1.88 mL, 8.92 mmol), and *p*-toluenesulfonic acid (0.0154 g, 0.01 mmol) were placed in a two-necked flask equipped with a Dean—Stark trap and a reflux condenser. The reaction mixture was refluxed for 48 h and neutralized with a saturated solution of $NaHCO_3$, the organic layer was concentrated, and product **12** was recrystallized from MeOH. Yield 0.7 g (24%), m.p. 103—105 °C, $[\alpha]_D^{20}$ −49.5 (*c* 1, $CHCl_3$). Found (%): C, 62.18; H, 6.07. $C_{34}H_{40}O_{13}$. Calculated (%): C, 62.19; H, 6.14. ^{1}H NMR, δ: 1.23, 1.28 (both d, 6 H each, ^3J = 6.8 Hz); 1.36 (d, 12 H, ^3J = 5.8 Hz); 4.85, 4.98 (both d, 2 H each, $^3J \approx 3$ Hz); 5.18 (br.m, 4 H); 6.85 (s, 2 H); 7.39 (t, 2 H, ^3J = 7.3 Hz, ^3J = 7.5 Hz); 7.83 (d, 2 H, ^3J = 7.3 Hz); 7.98 (d, 2 H, ^3J = 7.5 Hz).

4,6-Di{(4*R*,5*R*)-4,5-bis[hydroxy(diphenyl)methyl]-1,3-dioxolan-2-yl}dibenzo[*b*,*d*]furan (10). Metallic Mg (0.28 g, 12.00 mmol) was placed in an argon-filled two-necked flask, THF (10 mL) was added, and a solution of PhBr (1.88 g, 12 mmol) in 60 mL of THF was slowly added. Then a solution of diester **12** (0.9 g, 1.37 mmol) in 30 mL of THF was added with stirring and cooling (0 °C). After a temperature of ~20 °C was reached, the reaction mixture was refluxed for 2 h and neutralized with a saturated solution of NH_4Cl. The organic layer was separated, concentrated, and recrystallized from MeOH. Yield 0.19 g (14%), dec.p. 232 °C, $[\alpha]_D^{20}$ +159.3 (*c* 0.5, $CHCl_3$). Found (%): C, 80.71; H, 5.42. $C_{70}H_{56}O_9$. Calculated (%): C, 80.75; H, 5.42. ^{1}H NMR, δ: 2.41, 3.54 (both s, 2 H each); 5.35 (d, 2 H, ^3J = 4.4 Hz); 5.54 (d, 2 H, ^3J = 4.0 Hz); 6.14 (s, 2 H); 7.07—7.39 (m, 32 H); 7.44 (t, 4 H, ^3J = 7.5 Hz); 7.61 (m, 8 H); 7.82 (d, 2 H, ^3J = 7.5 Hz). ^{13}C NMR, δ: 79.27 (2 CH); 79.65 (2 CH); 81.22 (2 CH); 82.02 (2 CH); 102.47 (2 CH); 121.58 (2 C); 122.05 (2 CH); 123.25 (2 CH); 124.79 (2 C); 126.90 (2 C); 127.14 (2 CH); 127.17 (2 CH); 127.38 (t); 127.90 (2 C); 128.17 (2 CH); 128.22 (2 CH); 128.42 (4 CH); 128.50 (4 CH); 144.16 (2 C); 144.52 (2 C); 145.36 (2 C); 145.40 (2 C); 154.18 (2 C).

Preparation of *O*-acetylmandelonitrile (general procedure). Water (0.5 mL) was added to finely ground KCN (0.2 g, 3.1 mmol), the mixture was stirred until a homogeneous suspension formed, and 4.5 mL of toluene and the catalyst were added. Then PhCHO (0.1 mL, 0.1044 g, 0.984 mmol) and Ac_2O (0.2 mL, 0.217 g, 2.13 mmol) were successively introduced with stirring. The reaction mixture was stirred for 2.5 h and filtered through a silica gel layer, the product being washed out with an AcOEt—hexane mixture (1 : 5).

The reactant addition and the experimental procedure for the reaction in toluene are similar to those described above for the toluene—water system except that a suspension of finely ground KCN in toluene was used.

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