Metal-dependent stereochemistry of C—C bond formation under the asymmetric phase transfer catalysis by chiral salen complexes

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The effect of the nature of the central metal atom in chiral salen type complexes on the stereodifferentiating capacity of these complexes as catalysts in phase transfer asymmetric alkylation of Schiff´s base derived from alanine isopropyl ester and benzaldehyde by benzyl bromide. The nature of the central metal atom in the complex has a pronounced influence on the stereochemistry of alkylation; copper(II) complexes exhibit the highest activity combined with a high stereoselectivity.

Key words: asymmetric phase transfer catalysis, salen type chiral complexes of transition metals, chiral phase transfer catalysts.

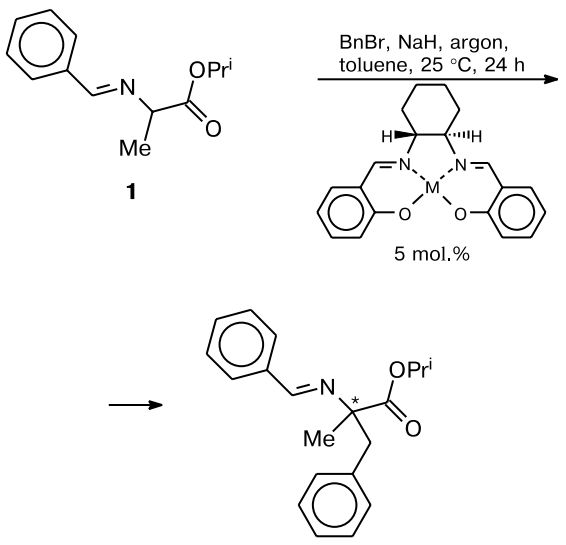
At present, asymmetric synthesis is a vigorously developing branch of organic chemistry, the most interesting results being obtained in asymmetric catalysis.[1] The asymmetric phase transfer catalysis stands out against this background; after the fundamental publication by O´Donnell,[2] rather moderate results were obtained along this line, and the asymmetric induction rarely exceeded 40%. It was not until recently that, by using chiral phase transfer catalysts, stably high entantiomeric yields were attained in the asymmetric formation of a C—C bond.[3—11]

The capacity of chiral Cu^{II} salen complexes for catalyzing the asymmetric phase transfer alkylation of the Schiff´s bases of amino acid esters, found in our studies,[12,13] is a very interesting phenomenon calling for detailed investigation. Some features of the process mechanism have been established previously; however, many aspects still remain obscure. In particular, it is unknown whether it is possible to increase the efficiency and the stereodifferentiating capacity of the catalysts by replacing the central metal ion (Cu^{II}) by other metal ions.

In this work, we studied the influence of the nature of the central metal ion in chiral salen type complexes on their ability to catalyze the asymmetric alkylation and on the stereochemical outcome of the alkylation.

As a model reaction (Scheme 1), we used benzyl bromide alkylation of Schiff´s base derived from benzaldehyde and the isopropyl ester of racemic alanine **1**. The preparation of the Schiff´s base from benzaldehyde and the amino acid ester was described previously.[12,13]

Scheme 1



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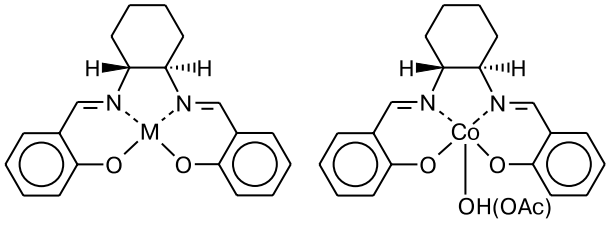
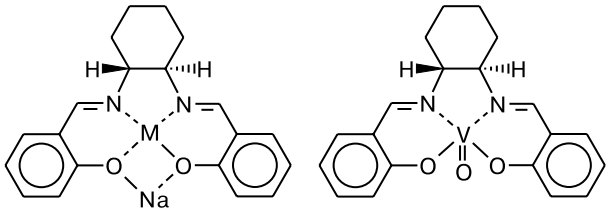
The alkylation takes place under phase transfer conditions because NaH used as the base is a solid insoluble in toluene in which the reaction is carried out. The reaction takes place only when all the components (a base, a catalyst, an alkylating agent, and azomethine **1**) are present. The catalysts we used in this work were complexes of Schiff´s bases derived from salicylaldehyde and (*R,R*)-cyclohexane-1,2-diamine (**2**) with a broad range of transition metals (**3—9**).



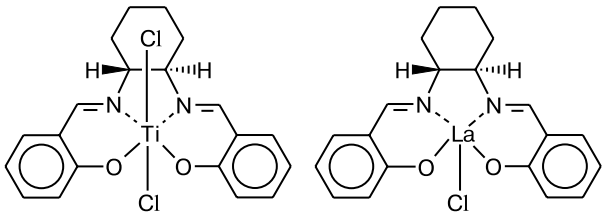
3 **4**

M = Mn, Fe, Co, Ni, Cu, Pd, Sn, Zn

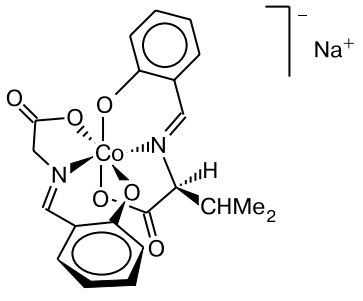


5 **6**

M = Cu^{I}, Ag^{I}



7 **8**



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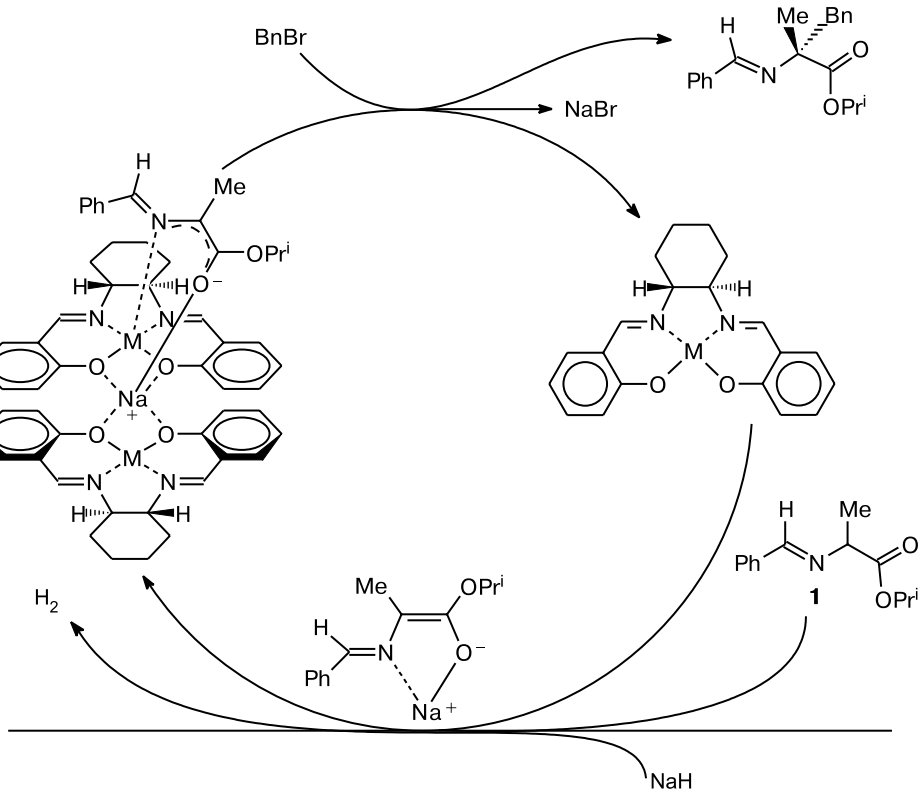
Complexes **3—8** were synthesized by a standard procedure[13] described for the Cu^{II} complex. In some experiments, the catalysts were prepared *in situ* under the reaction conditions; preliminary experiments (for Cu^{II} complexes) showed that in these cases, both the chemical yield and the asymmetric induction coincide with those attained with the use of pure pre-synthesized catalysts.

The previous study showed that the *ee* value of the final product follows a nonlinear dependence on the catalyst *ee*,[13] specifically, a positive nonlinear effect is observed. This, in turn, indicates that the stereodifferentiating step of the process involves, at least, two catalyst molecules and alkylation mainly proceeds *via* a homochiral ion pair.[14] At the given stage of mechanistic studies, the reaction pattern shown in Scheme 2 appears most likely. In the transition state, the molecules of the chiral complex catalyst solvate the Na^+ ion, which is the counter-ion for the carbanion formed from azomethine **1** at the interphase (in this particular case, on the solid NaH surface). As a consequence, the ion pair becomes sufficiently lipophilic to pass into the solution where the alkylation takes place. A similar situation is also observed in reactions catalyzed by quaternary ammonium salts due to the formation of a lipophilic ion pair comprising a carbanion and an ammonium cation.

In this work, we studied complexes **3** formed by various metals with the same ligand environment. The comparison was made for complexes that have different capacities for apical coordination. Thus in the case of square-planar complexes, coordination of apical ligands is typical of Cu^{II} and atypical of Pd^{II}, while Ni^{II} complexes occupy an intermediate position. A Sn^{II} complex that tends to form a trigonal bipyramid and a number of octahedral complexes (Mn^{II}, Co^{II}, Fe^{II}, and Zn^{II}) differing in the conformational stability and in the efficiency of binding of apical ligands were also included in the consideration.

The obtained data summarized in Table 1 provide the following conclusions. The use of charged complexes (see Table 1, runs *11—13*) results in rather efficient alkylation, which, however, yields a racemic product. The stereodifferentiating capacity was found for coordination-labile and coordinatively unsaturated complexes. To verify this assumption, an inert coordinatively saturated charged complex, Δ-[*N*-salicylideneglycinato-*N*-salicylidene-(*S*)-valinato]cobalt(III) (**9**), was specially synthesized, and the alkylation catalyzed by this complex was carried out. The reaction product, which was the racemic compound formed in 8% chemical yield, fully confirms our conclusions. A similar outcome was obtained in the case of chiral Co^{III} complex **4** (see Table 1, run *11*). With noncharged Pd^{II} or Sn^{II} complexes, which are not prone to coordinate additional ligands, both the chemical yield and the product *ee* were relatively low (runs *4* and *5*, respectively). Vanadyl and Ni^{II} complexes show similar results, which are somewhat inferior to the results attained with isostructural Cu^{II} complexes. Complexes

Scheme 2



having a substantial Lewis acidity, for example, complex **7** (see Table 1, run *9*), are relatively inefficient in this reaction.

The results obtained in this study and presented in Table 1 still do not suffice for drawing general conclusions, but it is evident that Cu^{II} complexes stand out of the other catalysts, as they ensure high chemical yields and asymmetric induction. In all probability, this is related to the structure of the outer electron shell of the metal ($3d^9$), due to which Cu^{II} tends to form complexes with pyramidal geometry (square pyramid) with a remote apical ligand. This ligand is sufficiently labile and can be easily replaced. In our case, competitive chelation to the apical position in the complex can be accomplished by substrate **1**. This appears to be responsible for the high efficiency of the stereoselective catalysis of alkylation.

Experimental

^{1}H NMR spectra were recorded on Bruker 200 and Bruker 400 spectrometers in $CDCl_3$. Optical rotation was measured on a Perkin—Elmer 241 polarimeter. Enantiomeric GLC analysis of amino acids as *N*-trifluoroacetyl derivatives of their *n*-propyl esters was performed using a Chirasil-L-Val type chiral phase on quartz capillary columns (40 m × 0.23 mm) with 0.12 μm film thickness at a column temperature of 125 °C, using helium as a carrier gas. Aldrich commercial reagents were used. (1*R*,2*R*)-[*N*,*N*´-Bis(2´-hydroxybenzylidene)]-1,2-diaminocyclohexane (**2**) was synthesized by a previously described procedure.[15]

Schiff´s base 1 was prepared in 71% yield as a colorless oil from the racemic amino acid using a previously described procedure,[13] b.p. 120—121 °C (2 Torr), n_D^{15} 1.5168. ^{1}H NMR, δ: 1.23 (d, 3 H, Me, J = 6.2 Hz); 1.27 (d, 3 H, Me, J = 6.2 Hz); 1.51 (d, 3 H, Me, J = 7.1 Hz); 4.09 (q, 1 H, CH, J = 7.1 Hz); 5.05 (m, 1 H, OCH); 6.30—7.30 (m, 5 H, Ph); 8.29 (s, 1 H, CH=N). IR, ν/cm^{-1}: 1644, 1735.

Complexes **3** and complex **6** were prepared by standard procedures.[12,16]

Complex 3 (M = Cu^{II}). M.p. 315—319 °C (dec.), $[\alpha]_D^{25}$ –917 (*s*, 0.048, $CHCl_3$). Found (%): C, 62.97; H, 5.43; N, 7.47. $C_{20}H_{20}N_2O_2Cu$. Calculated (%): C, 62.57; H, 5.25; N, 7.30.

Complex 3 (M = Ni^{II}). M.p. >345 °C (dec.), $[\alpha]_D^{25}$ –610 (*s*, 0.04, $CHCl_3$). ^{1}H NMR, δ: 1.31—2.39 (m, 8 H, $(CH_2)_4$); 3.29 (m, 2 H, CHN=); 6.47—7.19 (m, 8 H, Ph); 7.24 (s, 2 H, PhCH=N). Found (%): C, 62.50; H, 5.36; N, 6.99. $C_{20}H_{20}N_2O_2Ni \cdot 1/3\ H_2O$. Calculated (%): C, 62.38; H, 5.41; N, 7.27.

Complex 3 (M = Pd^{II}). M.p. 320 °C (dec.), $[\alpha]_D^{25}$ –369 (*s*, 0.054, $CHCl_3$). ^{1}H NMR, δ: 1.45, 1.57, 1.96, 2.49 (all m, 8 H, $(CH_2)_4$); 3.70 (m, 2 H, CHN=); 6.49, 6.91, 7.10, 7.30 (all m, 8 H, Ph); 7.40 (s, 2 H, PhCH=N). Found (%): C, 56.20; H, 4.67; N, 6.36. $C_{20}H_{20}N_2O_2Pd$. Calculated (%): C, 56.28; H, 4.72; N, 6.56.

Complex 3 (M = Mn^{II}). M.p. 324—325 °C (dec.), $[\alpha]_D^{25}$ –1597 (*s*, 0.021, $CHCl_3$). Found (%): C, 57.83; H, 4.52;

Table 1. Efficiency of catalysts based on various metal ions[a]

Run	Complex type	M	Amino acid	
			Yield (%)	*ee*[b] (%)
1	**3** (**5**)	Cu^{II} (Cu^{I})[c]	>95	90
2	**3**	Ni^{II}	36	31
3	**3**	Zn^{II}	62	20
4	**3**	Pd^{II}	50	5
5	**3**	Sn^{II}	35	6[d]
6	**3**	Fe^{II}	38	17
7	**3**	Co^{II}	84	15
8	**3**	Mn^{II}	28	3
9	**7**	Ti^{IV}	0	—
10	**6**	V^{IV}	60	31
11	**4**	Co^{III}	21	0
12	**5**	Ag^{I}	>95	0
13	**8**	La^{III}	>95	0

[a] **Reaction conditions**: 1 equiv. of Schiff´s base **1**, 1.5 equiv. of BnBr, 5 mol.% of the catalyst, 2.2 equiv. of NaH. The change in the amount of the chiral catalyst from 0.5 to 10 mol.% does not change the chemical yield or the stereochemical outcome of the reaction. When comparing the efficiency of various chiral salen complexes in alkylation, 5 mol.% of the catalyst was always used.
[b] Determined by chiral GLC.
[c] During alkylation, the catalyst is rapidly (over ~20 min) oxidized to give a Cu^{II} complex, which can be easily detected by a typical coloring.
[d] The reaction catalyzed by the Sn^{II} complex with (*R*,*R*)-cyclohexane-1,2-diamine afforded (*S*)-α-methylphenylalanine, whereas catalysis by complexes of other metals with the same diamine gave rise to (*R*)-amino acid.

N, 6.59. $C_{20}H_{20}N_2O_2Mn \cdot 0.4\ CHCl_3$. Calculated (%): C, 57.91; H, 4.86; N, 6.62.

Complex 6. M.p. 345—346 °C (dec.), $[\alpha]_D^{25}$ −816 (*s*, 0.024, $CHCl_3$). Found (%): C, 60.12; H, 5.21; N, 6.98. $C_{20}H_{20}N_2O_3V \cdot 2/3\ H_2O$. Calculated (%): C, 60.15; H, 5.38; N, 7.01.

Alkylation catalyzed by complexes **3** (M = Co^{II}, Fe^{II}, Sn^{II}, Zn^{II}), **5** (M = Cu^{I}, Ag^{I}), and **8** was preceded by preparation of the catalysts *in situ* under argon from $Co(OAc)_2 \cdot 4\ H_2O$, $FeCl_2$, $SnCl_2 \cdot 2\ H_2O$, $Zn(OAc)_2$, $CuBr \cdot MeCN$, $AgNO_3$, and $LaCl_3$, respectively.

Complex **4** was prepared *in situ* similarly to complex **3** (M = Co^{II}) but with bubbling air through the reaction mixture.

Complexes **7** and **9** used in the work were prepared previously.[17,18]

Catalytic asymmetric alkylation (general procedure). Catalyst (0.0228 mmol) was placed in a round-bottom two-necked flask filled with argon, the flask was evacuated three times and filled with argon with heating by a torch flame. The flask was cooled in an argon flow, and a solution of compound **1** (100 mg, 0.457 mmol) and BnBr (0.1 mL) in 2 mL of anhydrous toluene was added, followed by the addition of NaH (40 mg, 1 mmol). The reaction mixture was stirred for 24 h under argon. After completion of the reaction, the precipitate was filtered off; the amino acid was isolated by workup of the filtrate according to a previously described procedure.[13] The optical purity of the isolated amino acid was determined by enantiomeric GLC analysis.

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