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Chiral complexes of Ni(II), Cu(II), and Cu(I) as reagents, catalysts and receptors for asymmetric synthesis and chiral recognition of amino acids

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Abstract: New reagents and catalysts for the asymmetric syntheses of amino acids were developed. Among the reactions which have been studied are alkylation, carbonyl and C=C bond addition reactions of a chiral 'glycine equivalent'. Chiral phase-transfer and hydrolysis catalysts, based on chiral Cu(II) complexes, have been used to promote asymmetric alkylation of an achiral 'glycine equivalent' and hydrolysis of racemic azlactones. Transition metal based new type of chiral receptors for amino acid anions was developed.

INTRODUCTION

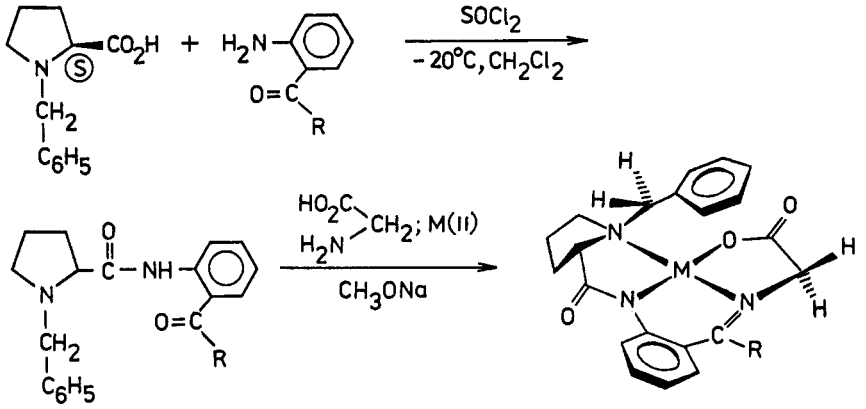
The importance of proteinogenic amino acids is well known (ref.1). Their production, usually microbiological, is a flourishing multimillion dollar business, and, in principle, the problem has been solved for all practical purposes. But isotopically labelled proteinogenic amino acids and non-proteinogenic amino acids, constituents of antibiotics, physiologically active peptides or other pharmaceuticals are important synthetic targets and search for cheap and convenient synthetic methods of their asymmetric synthesis is still going on (ref.2). At present, there are several excellent general methods of asymmetric synthesis of amino acids, based on the stoichiometric use of chiral auxiliaries and kinetic control approach (ref.2). The approach to the stoichiometric synthesis described in here differs in some respect from above mentioned ones. It relies on a very limited set of simple chemicals, ambient temperatures, and in most cases thermodynamic control of the stereoselectivity of the reactions. In addition, new types of simple chiral catalysts for asymmetric C-C bond formation via alkyl halide alkylation and Michael addition reactions of CH-acids were designed.

1. STOICHIOMETRIC ASYMMETRIC SYNTHESIS OF AMINO ACIDS VIA COMPLEXES OF Cu(II) and Ni(II)

Scheme 1 illustrates the structure and synthesis of the chiral auxiliary (BPB) we used in the reactions. Synthesis of the compound has been easily accomplished via a sequence of simple reactions, as illustrated by Scheme 1. Amino acids easily form Schiff's base complexes with BPB and transition metals Cu(II) and Ni(II) (ref.3, Scheme 1). The complexes are neutral, crystalline compounds with the charge of the central metal ion neutralized by two negative charges

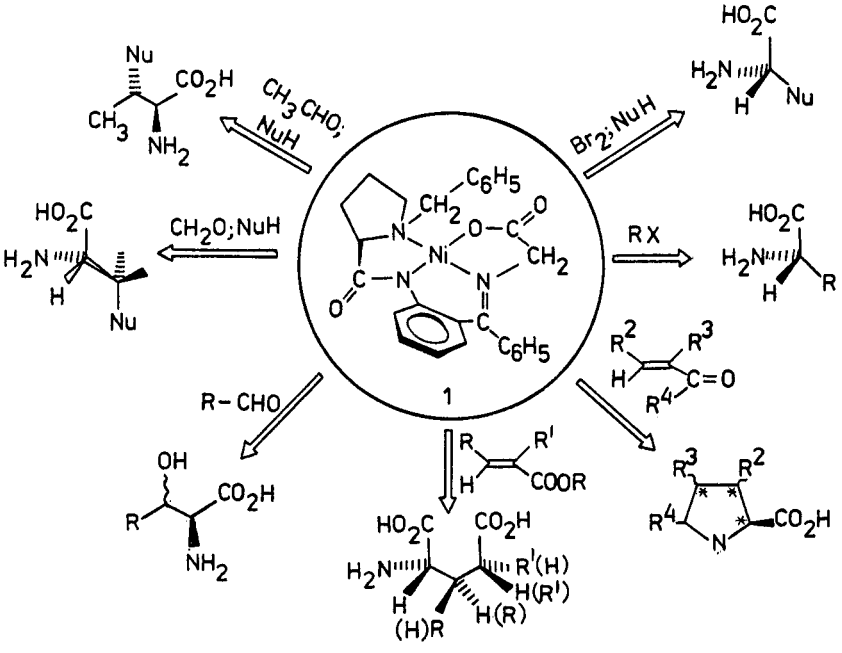
of ionized carboxyl and amide-groups. The coordination is essentially square planar with minor distortions, as was indicated by the X-ray crystal structure analysis of the complexes (ref.3a,e). Complexes of Ni(II) (Ni-BPB-AA) are much more robust than the corresponding complexes of Cu(II) and enter several reactions under which conditions Cu(II) complexes would be completely decomposed. Also Ni(II) complexes are diamagnetic and NMR-spectroscopy could be applied to the analysis of the reaction mixtures (ref.3a-g) and absolute configuration of the aminoacid side chains (ref.3a,e).

Scheme 1

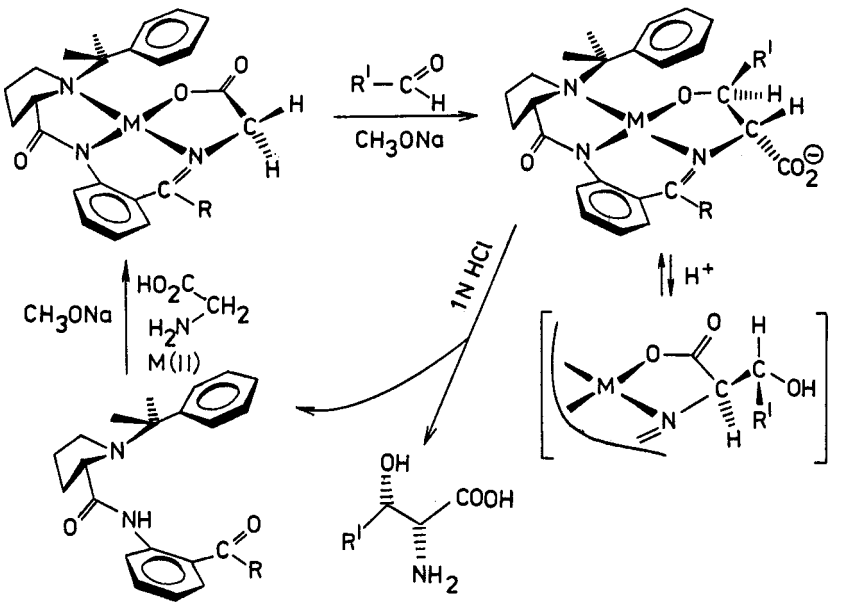


Ni-(S)-BPB-Gly or Ni-(R)-BPB-Gly ('glycine equivalent') may enter several types of reactions, including base catalyzed alkyl halide alkylations (NaOH or KOH, in DMF, ref.3f,g), Michael type additions (MeONa in MeOH, ref. 3a,b,f), condensations with aldehydes (Et_3N in MeOH, ref.4, Scheme 2). In all cases only mono-alkylated products were formed in the reactions and the equilibrium ratio of (S,S)/(S,R)-diastereoisomers [or (R,R)/(R,S)-isomers] was in the range 90/10-98/2 and it isn't influenced by the size of the amino acid side chain and solvent.

Scheme 2



Scheme 3



Other types of reactions (ref.3c,d,e) (Scheme 2), where the initial complex derived from Ni-BPB-Gly acts as an electrophile, are possible. Such complexes are easily obtained via dehydration of the intermediate complexes of Ser and Thr. The dehydroalanine and dehydroaminobutanoic acid moieties of the complexes add different nucleophiles, including amines, copper-organic compounds, thiols and alcohols. A set of radical addition reactions could be performed at the dehydroalanine moiety. A significant asymmetric induction was observed in the addition reactions. Simple base catalyzed bromination of glycine moiety of Ni-(S)-BPB-Gly produces a mono-bromoderivative, substitution of which with different nucleophiles results in a great excess of (S,S)-diastereoisomers.

The intermediate diastereoisomeric complexes might be easily decomposed with aq. mineral acids and the amino acids recovered in good chemical yields (60-90%). In all these cases complexes derived from (S)-BPB gave (S)-amino acids and (R)-BPB produced (R)-amino acids with optical purity of 80-96% (100% if the diastereoisomeric complexes were initially separated by crystallization or chromatography). Under the experimental conditions equilibration of the formed intermediate diastereoisomeric complexes [Ni-(S)-BPB-(S)-AA and Ni-(S)-BPB-(R)-AA] was always established (the only exception was the radical addition reactions) and the stereoselectivity of the reaction was of thermodynamic origin. The chiral auxiliary, BPB, could always be recovered from the reaction mixtures in very good chemical yields.

According to molecular mechanics calculations and some model studies, it is the non-bonding interaction of the phenyl group substituent at the C=N bond and the amino acid alkyl group which is the prime reason for the observed difference in energy between the diastereoisomers (ref.3e).

Unexpectedly, base catalyzed aldehyde condensation reactions of Ni-(S)-BPB-Gly or Cu-(S)-BPB-Gly, catalyzed by MeONa in MeOH at high pH of the solution, gave predominantly syn-(2R,3S)-β-hydroxy-α-amino acids (ref.4). Taking together the chemical and some additional physical data, the following mechanism of the reaction was suggested (ref. 4, Scheme 3):

1. At a low pH of the solution the condensation proceeds as usual, giving an equilibrium mixture of isomers with the predominance of Ni-(S)-BPB-(S)-Aa isomer.

2. At a high pH the hydroxyl-group becomes ionized and, being in this form more basic than the carboxyl-group, substitutes the later in the coordination plane of the complex. Those steric forces which stabilized (S)-configuration in the ordinary amino acid five-membered chelate ring, facilitate the orientation of the carboxyl group away from the phenyl ring of the N-benzyl substituent. Such an orientation is possible only in case of (R)-configuration of the amino acid moiety. Energetically favorable is trans-disposition of carboxylate- and alkyl-groups in the five-membered chelate-ring of the formed complex. It corresponds to syn or threo-configuration of the amino acid diastereoisomers.

Introduction of electronegative substituents into the alyphatic chain of the aldehyde influenced the stereoselectivity of the reaction. In fact, perfluoro-substituted aldehydes gave only (S)-syn-β-hydroxy-α-amino acids.

The chiral reagent BPB is sufficiently universal and its use is simple and forthcoming, in addition the reagent may be used several times without any deteriorating in the quality of the final product. Optically pure non-proteinogenic (S)-amino acids in 100 g-scale could be obtained by this method.

Another chiral auxiliary, (S)-2-[N-(N'-benzylprolyl)amino]-benzaldehyde (BBA) can be made in quantity by a simple synthesis (ref.5a). The chiral Ni(II) complex of a Schiff's base derived from BBA and Ala [Ni-(S)-BBA-Ala] enters alkyl halide alkylation and Michael addition furnishing a mixture of (S,S)- and (S,R)-diastereoisomers. Separation of the diastereoisomers by crystallization or chromatography followed by the decompositon of the complexes (see above) gave homochiral α-methyl-substituted amino acids (ref. 5b). The method may be developed further with almost any kind of α-methyl-substituted amino acids obtained using this approach.

2. CATALYTIC ASYMMETRIC SYNTHESIS OF AMINO ACIDS

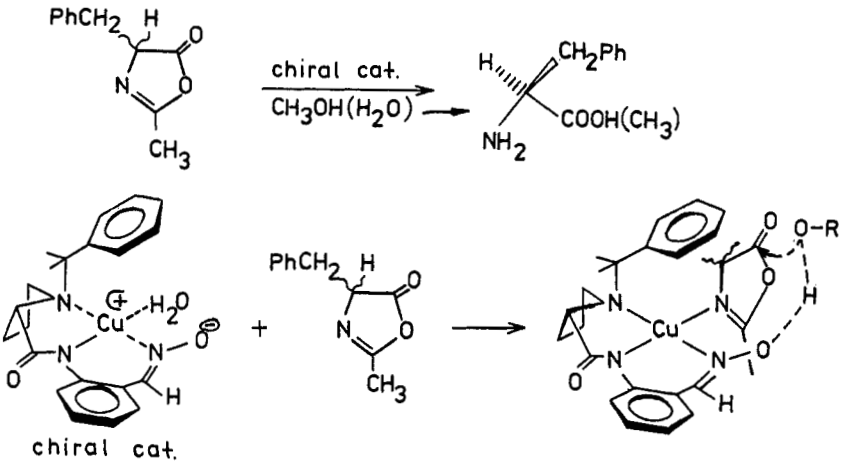
One way of developing an efficient approach to the catalytic asymmetric synthesis of amino acids would be to design a chiral catalyst of azlactone solvolysis. The azlactones are well known for their propensity to undergo racemization. If racemization of (S)- and (R)-enantiomers could be rapid enough with respect to the enantioselective hydrolysis, then when rates of the solvolysis of (S)- and (R)-enantiomers are substantially different, the solvolysis would form one isomer selectively.

The catalyst derived from (S)-[2-N-(N'-benzylprolyl)amino]-benzaldehyde, hydroxylamine and CuX_2 was found to be very efficient for the hydrolysis or methanolysis of the azlactone obtained from racemic phenylalanine (ref.6, Scheme 4).

The mechanism of the reaction includes a ternary complex formation, followed by the attack of a solvent molecule at the carbonyl group of the azlactone, facilitated by the ionized oxime group oxygen atom, acting as a general base. Although the stereoselectivity of the hydrolysis was low (11% e.e. at 25% of conversion), the enantioselectivity of methanolysis was much higher and the ratio of the rates of the enantiomer solvolysis was more than 10/1. The system may be developed further with the racemization induced by higher pH of the solution.

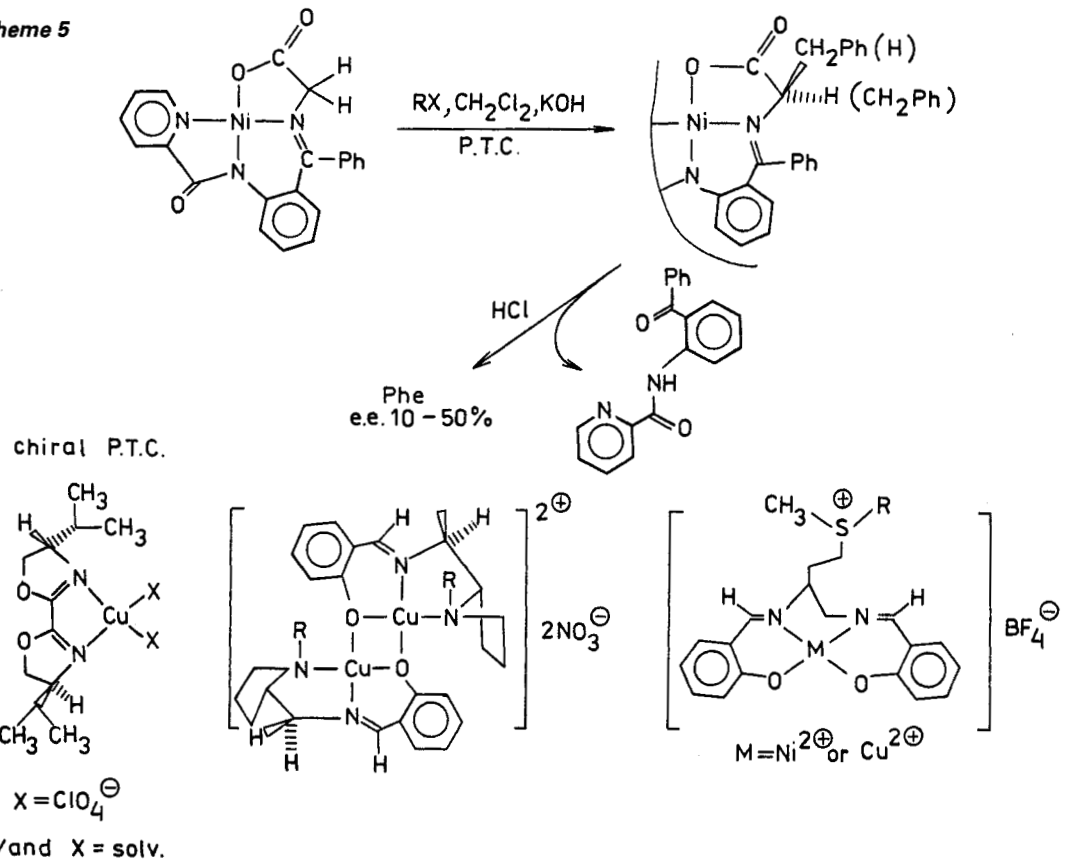
An achiral glycine equivalent', derived from [2-N-(N'-pyridine-carbonyl)amino]benzophenone, NiX_2, and glycine, enters alkylation reactions with activated alkyl halides in CH_2Cl_2 at ambient temperature in presence of KOH (Scheme 5).

Scheme 4



The reaction was catalyzed by chiral phase transfer agents, based on chiral positively charged complexes of transition metals (ref.7, Scheme 5). The best catalyst (ratio of substrate/catalyst =20/1) was found to be the chiral Cu(II) complex of a Schiff's base derived from (S)-2-aminomethylpyrrolidine and salicylaldehyde. Asymmetric induction observed in these cases was not very significant (20-40% e.e.), however, the structure of the positively charged complexes might be easily modified and, probably, the e.e. of the reaction significantly improved.

Scheme 5

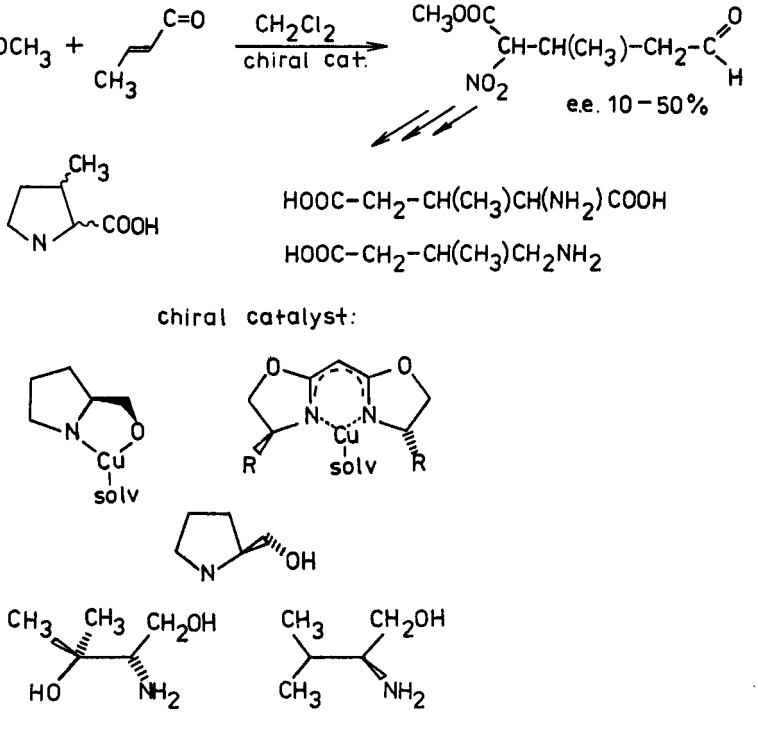


The addition reaction of a relatively strong CH-acid, nitroacetic ester, to substituted acrylic aldehydes was catalyzed (ratio of substrate/catalyst=50/1-100/1) by chiral amines and their Cu(I) complexes (Scheme 6) in aprotic solvents (C_6H_6, CH_3CN and CH_2Cl_2) at ambient temperature. The most efficient catalysts were found to be (S)-prolinol and its Cu(I) complex (ref.8, good chemical yields and e.e. up to 50%).

The mechanism of the amine-catalyzed reaction seems to include the formation of a chiral intermediate ion pair from the amine and nitroacetic ester and the whole process reminds prolinol-catalyzed asymmetric addition of thiols to activated C=C bonds (ref.9). Intriguingly, Cu(I)-prolinol complex catalyzed the addition reaction furnishing the adduct with the same sense of chirality (but lower e.e.), as the product of the free amine catalyzed reaction.

The adduct of nitroacetic ester and crotonic aldehyde could be easily converted into a substituted glutamic acid or substituted proline.

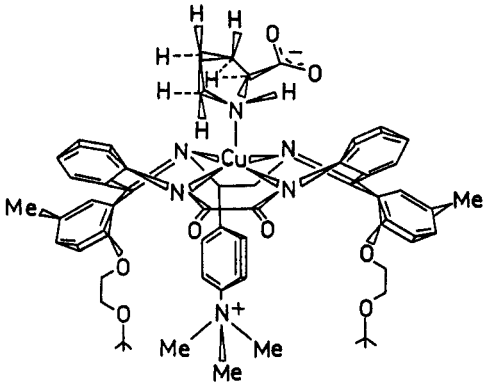
Scheme 6



3. CHIRAL ATROPOISOMERIC Cu(II) COMPLEXES AS RECEPTORS FOR AMINO ACID ANIONS

The use of macrocyclic complexes of transition metals as catalysts of oxydation and reduction of organic compounds is well known. One of many possible avenues of exploration in the field of macrocyclic complex chemistry would be the design and synthesis of transition metal complexes bearing additional donor functional side groups incapable of interaction with the central metal ion but capable to become potential hosts for organic substrates. By varying the structure of the side group one can create a receptor system 'tailored' for a particular type of substrate and even be able to bring the substrate into a catalytically effective position relative to the central metal ion (ref.10).

Scheme 7



Here we describe the synthesis and properties of some novel complexes of Ni(II) and Cu(II) with macrocyclic Schiff's bases, formed from the corresponding derivatives of N,N'-bis(2-benzoylphenyl)oxamide and 1.2-diaminoethane (ref.11). They provide a strong four-coordinate ligand, complexes of which can be very stable toward destruction by other ligands, including amino acid anions. A detailed study of proline complexation by {(R)-7,8,15,18-tetrahydro-5,10-bis(2'-methoxyethoxy-5'-methylphenyl)-7-(p-trimethylammonio-phenyl)dibenzo[e,m][1,4,8,11]-tetra-azacyclo-tetradecine-16,17-dionato- (1-) -N6N9N15N18}copper(II) chloride in D_2O, using n.m.r. relaxation techniques, was undertaken (ref.12, Scheme 7).

The results clearly indicate coordination of proline in the apical position of the complex. The complex might be used as a lipophilic carrier of amino acid anions (ref.12) and serve as a catalyst for C-alkylation of amino acids (ref.13).

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