Chiral Resolution

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A Practical Approach to the Resolution of Racemic *N*-Benzyl α-Amino Acids by Liquid–Liquid Extraction with a Lipophilic Chiral Salen–Cobalt(III) Complex**

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The development of chiral hosts for the enantioselective recognition and separation of α-amino acids and their derivatives represents an open challenge as a method for the production of enantiopure compounds. A simultaneous binding of both the amino and the carboxylic group is usually required to achieve chiral discrimination,[1] which makes metal ions modified with a chiral ligand ideal species for such selection. In fact, transition-metal complexes have been used in several such molecular-recognition studies,[2] including the selective crystallization from a racemic mixture of a complex of one enantiomer bound to the chiral selector.[3] Molecular recognition involving chiral transition-metal complexes has also been demonstrated in various practical methods for the separation of enantiomers including chiral HPLC,[4] transport across a liquid membrane,[5] micelle-enhanced ultrafiltration,[6] and co-micellar systems with two aqueous phases.[7]

In the cases described above the complexes were usually based on the coordination of ligands derived from amino acids or amines to Cu^{II} ions,[3–7] although enantioselective complexes of other metal ions, such as Co^{II} and Ni^{II}, have also

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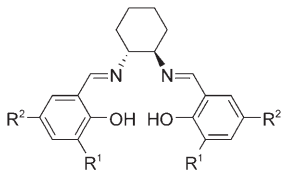
been reported.[2,3a] In one notable case, a chiral cobalt(II) complex derived from ligand **1** (Scheme 1), namely [Co^{II}(**1**)], was used in an enantioselective resolution of *N*-benzylalanine (*N*-Bn-Ala).[8] Treating [Co^{II}(**1**)] with two equivalents of



(*R*,*R*)-**1** $R^1 = R^2 = H$
(*R*,*R*)-**2** $R^1 = CH_3$, $R^2 = H$
(*R*,*R*)-**3** $R^1 = R^2 = t$Bu

Scheme 1. Chiral salen ligands.

racemic *N*-Bn-Ala in MeOH/H_2O (5:1), followed by extraction with $CHCl_3$/H_2O led to enantiomeric excesses of 94% (*R*) and 93% (*S*) for the complexed ([Co^{III}(**1**)(*N*-Bn-Ala)]) and the uncomplexed amino acid, respectively.[9] The major drawback of this approach resided in the necessity to use rather harsh conditions (reduction with $NaBH_4$) to release the complexed amino acid.

A promising methodology is the enantiomeric separation of racemic mixtures of hydrophilic substrates by liquid–liquid extraction.[10] This method involves the extraction of one enantiomer into an organic phase by selective coordination to a hydrophobic selector (for example, a chiral metal complex) to leave the uncomplexed enantiomer in an aqueous phase. The attraction of this method is that it circumvents the use of excessive handling of solids, which is associated with classical resolution by crystallization of diastereomeric salts; on a production scale this is often the slowest step in the process.

Herein we report a novel approach to the resolution of racemic *N*-benzyl α-amino acids by liquid–liquid extraction, using the lipophilic chiral salen–cobalt(III) complex [Co^{III}(**3**)(OAc)] (Scheme 2), in excellent yield and enantioselectivity. As a result of the resolution by extraction, one enantiomer of the *N*-benzyl amino acid predominates in the aqueous phase, while the other enantiomer is driven into the organic phase by complexation to the cobalt center. The complexed amino acid can then be released by a reductive (Co^{III}→Co^{II}) counter-extraction into an aqueous phase. The original chiral Co^{III} complex can be regenerated and reused with essentially no loss of reactivity or selectivity. Enantiomerically pure *N*-benzyl α-amino acids have found various important synthetic applications,[11] and can be easily transformed into α-amino acids by hydrogenolysis.[12]

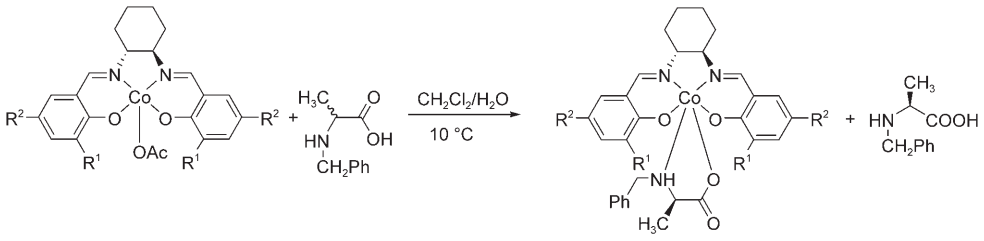
As a preliminary investigation, we dissolved [Co^{II}(**1**)] (1 equiv) in dichloromethane and stirred this phase with an aqueous solution of racemic *N*-benzylalanine (2 equiv). As expected, the interaction of [Co^{II}(**1**)] with *N*-benzylalanine induced the air oxidation of the metal ion to cobalt(III) with concurrent formation of the cobalt(III) complex [Co^{III}(**1**)(*N*-Bn-Ala)]. This complex was isolated in nearly quantitative yield (99%) and was characterized by HRMS (ESI) as well as IR, ^{1}H and ^{13}C NMR spectroscopy. The absolute configuration (*S*) and the *ee* value of uncomplexed *N*-Bn-Ala (55.8% *ee*) were determined by HPLC analysis of the aqueous phase (Table 1, entry 1);[13] reduction of the Co^{III} complex with $NaBH_4$ led to the recovery of (*R*)-*N*-Bn-Ala with a consistent *ee* value. An extraction using the methyl-substituted analogue [Co^{II}(**2**)] under the same conditions again led to the formation of a cobalt(III) species, [Co^{III}(**2**)(*N*-Bn-Ala)], through air oxidation of the metal. In this case *N*-benzylalanine was also extracted in high yield (96%), however decreased enantioselectivity (38.9% *ee*) was observed in the unbound *N*-benzylalanine (Table 1, entry 2). The possibility of releasing the coordinated amino acid by using different reductive (Na_2SO_3, $Na_2S_2O_4$, $Na_2S_2O_3$, Na_2S, $NaBH_4$) or hydrolytic (HCl, CF_3COOH, CF_3SO_3H) methods was investigated; in general, no reaction occurred except by the above-mentioned reduction with $NaBH_4$.

Table 1: Extraction of racemic *N*-Bn-Ala using chiral salen–cobalt(II) and –cobalt(III) complexes at 10°C.

Entry	Host complex	Product	Equiv extracted	*ee* [%][a]
1	(*R*,*R*)-[Co^{II}(**1**)]	[Co^{III}(**1**)(*N*-Bn-Ala)]	0.99[b]	55.8[c]
2	(*R*,*R*)-[Co^{II}(**2**)]	[Co^{III}(**2**)(*N*-Bn-Ala)]	0.96[b]	38.9
3	(*R*,*R*)-[Co^{II}(**3**)]		0[b]	
4	(*R*,*R*)-[Co^{III}(**1**)(OAc)]	[Co^{III}(**1**)(*N*-Bn-Ala)]	0.92	54.8
5	(*R*,*R*)-[Co^{III}(**2**)(OAc)]	[Co^{III}(**2**)(*N*-Bn-Ala)]	0.99[d]	53.6
6	(*R*,*R*)-[Co^{III}(**3**)(OAc)]	[Co^{III}(**3**)(*N*-Bn-Ala)]	**0.99**	**93.0**
7	(*R*,*R*)-[Co^{III}(**3**)(OAc)][e]	[Co^{III}(**3**)(*N*-Bn-Ala)]	**0.98**	**93.0**
8	(*R*,*R*)-[Co^{III}(**3**)(OTf)]	[Co^{III}(**3**)(*N*-Bn-Ala)]	0.92	85.5
9	(*R*,*R*)-[Co^{III}(**3**)(PF_6)]	[Co^{III}(**3**)(*N*-Bn-Ala)]	0.92	87.8

[a] Determined on uncomplexed (*S*)-*N*-Bn-Ala by chiral HPLC analysis of the aqueous phase (see the Supporting Information). [b] Extractions were run at room temperature. [c] For a comment, see Ref. [13]. [d] Extraction time of 48 h was necessary, compared to 24 h in all other cases. [e] Second cycle: (*R*,*R*)-[Co^{III}(**3**)(OAc)] was obtained from [Co^{III}(**3**)-(*N*-Bn-Ala)] after reductive cleavage and reoxidation (see text and the Supporting Information).

Chiral ligand **3** is known for its selectivity in several asymmetric processes such as epoxidation, epoxide opening, and kinetic resolution.[14] It



[Co^{III}(**1**)(OAc)] $R^1 = R^2 = H$
[Co^{III}(**2**)(OAc)] $R^1 = CH_3$, $R^2 = H$
[Co^{III}(**3**)(OAc)] $R^1 = R^2 = t$Bu

[Co^{III}(**1**)(*N*-Bn-Ala)]
[Co^{III}(**2**)(*N*-Bn-Ala)]
[Co^{III}(**3**)(*N*-Bn-Ala)]

Scheme 2. Resolution of a racemic mixture of *N*-benzylalanine by liquid–liquid extraction using salen–cobalt(III) complexes.

can be easily prepared by a high-yielding one-pot method,[15] or is commercially available on a large scale along with its cobalt(II) complex [Co^{II}(**3**)]. However, disappointing results were obtained when complex [Co^{II}(**3**)] was employed in the extraction of *N*-benzylalanine by using our procedure: no oxidation of cobalt occurred, and no extraction of *N*-benzylalanine into the organic phase was observed.

These results indicated that formation of a cobalt(III) complex was necessary for obtaining both a high yield *and* enantioselectivity in the extraction. The increased stability of [Co^{II}(**3**)] towards oxidation led us to believe that a ternary complex [Co^{III}(**3**)(*N*-Bn-AA)] (AA = α-amino acid) might have an increased susceptibility towards reduction back to cobalt(II), thus facilitating an extraction/counterextraction cycle. With this in mind, salen–cobalt(III) acetate complexes [Co^{III}(**1**–**3**)(OAc)] (Scheme 2) were tested in our extraction procedure. These complexes were readily prepared from complexes [Co^{II}(**1**–**3**)], by oxidation with air in the presence of acetic acid.[16] It became apparent during the course of our investigation that there was a significant correlation between temperature and enantioselectivity, with extractions performed at 10 °C giving the optimal results.[17,18] The results of extractions using one equivalent of complexes [Co^{III}(**1**–**3**)(OAc)] with two equivalents of racemic *N*-benzylalanine under thermostated conditions at 10 °C are summarized in Table 1. In all cases, extraction of *N*-benzylalanine was very efficient and the cobalt(III)/amino acid complexes were isolated from the organic phase in near-quantitative yields. Enantioselectivities were moderate to high, with the *tert*-butyl-substituted ligand **3** giving the best results (93.0% *ee*, Table 1, entry 6). In addition, similar results were obtained when extractions were conducted with cobalt(III) complexes [Co^{III}(**3**)(X)] bearing alternative counterions (X = OTf, PF_6; Table 1, entries 8, 9).

The significance of the substituents on the salen ligand became further apparent when the counterextraction of complexed *N*-benzylalanine from ternary complex [Co^{III}(**3**)(*N*-Bn-Ala)] was investigated. We found that by vigorously mixing a solution of the complex in dichloromethane with an aqueous solution containing excess sodium dithionite (10 equiv),[19] the bound *N*-benzylalanine was cleaved from the complex and recovered in the aqueous phase in quantitative yield (Scheme 3). The *ee* value of this counterextracted *N*-benzylalanine was consistent with the expected value based on the *ee* value of the *N*-benzylalanine which remained in the aqueous phase after the initial extraction step. Furthermore, cobalt(III) was reduced back to cobalt(II) during the cleavage of complex [Co^{III}(**3**)(*N*-Bn-Ala)]; after separation, the pure [Co^{II}(**3**)] complex could be isolated from the organic phase by simple evaporation of dichloromethane, trituration in methanol, and filtration (78% recovered yield).[20] In contrast, complexes [Co^{III}(**1**)(*N*-Bn-Ala)] and [Co^{III}(**2**)(*N*-Bn-Ala)] were not reduced under these conditions.

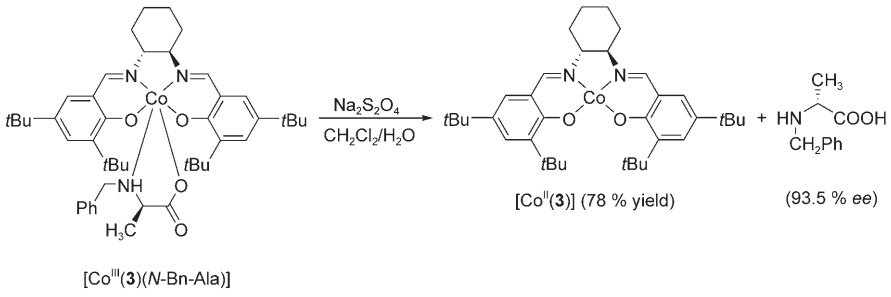
The recovered [Co^{II}(**3**)] was then reoxidized with air in the presence of acetic acid, and the cobalt(III) acetate thus formed was reused in a second extraction with no loss of activity or enantioselectivity (Table 1, entry 7). It should be noted that in the case of [Co^{III}(**3**)(*N*-Bn-Ala)], the amino acid release/cobalt(II) complex recovery was not successful by using the previously reported[8] $NaBH_4$-reduction method.[21]

Preliminary studies into the scope of this methodology have been conducted with particular interest in adapting the procedure to substrates of varying hydrophilicity relative to *N*-benzylalanine. The results of extractions of a range of racemic *N*-benzyl amino acids using complex [Co^{III}(**3**)(OAc)] are summarized in Table 2. The extraction of water-soluble *N*-benzylthreonine proceeded in near quantitative yield (94%) and with high *ee* values (96.3%), thus leaving uncomplexed (*S*)-*N*-benzylthreonine in the aqueous phase (Table 2, entry 1). Extractions of racemic mixtures of *N*-benzylvaline, *N*-benzylleucine, and *N*-benzylphenylalanine were also investigated (Table 2, entries 2–4). These substrates, with increased lipophilicity compared to *N*-benzylalanine, are essentially insoluble in both neutral water and dichloromethane. In the cases of *N*-benzylvaline and *N*-benzylleucine, however, all of the substrate was drawn into solution to form

Table 2: Resolution of racemic *N*-Bn-amino acids using (*R*,*R*)-[Co^{III}(**3**)(OAc)] at 10 °C.

Entry	Substrate	Meth.[a]	Product	Equiv extracted	*ee* [%][b]
1	*N*-Bn-Thr	A	[Co^{III}(**3**)(*N*-Bn-Thr)]	0.94	96.3[c]
2	*N*-Bn-Val	A	[Co^{III}(**3**)(*N*-Bn-Val)]	0.98	90.1
3	*N*-Bn-Leu	A	[Co^{III}(**3**)(*N*-Bn-Leu)]	0.99	99.0
4	*N*-Bn-Phe	B	[Co^{III}(**3**)(*N*-Bn-Phe)]	0.99	93.3
5	*N*-Bn-Val	C	[Co^{III}(**3**)(*N*-Bn-Val)]	0.99	94.2
6	*N*-Bn-Phe	C	[Co^{III}(**3**)(*N*-Bn-Phe)]	0.98	92.7
7	*N*-Bn-Ala	C	[Co^{III}(**3**)(*N*-Bn-Ala)]	0.98	16.3
8	*N*-Bn-Ala	C	[Co^{III}(**3**)(*N*-Bn-Ala)]	0.98[d]	65.8

[a] Method A: biphasic water/dichloromethane extraction; method B: biphasic water/dichloromethane treatment and recovery of the uncomplexed amino acid by filtration; method C: stirring a suspension of the racemic *N*-Bn-amino acid with a solution of (*R*,*R*)-[Co^{III}(**3**)(OAc)] in dichloromethane and recovery of the uncomplexed amino acid by filtration. [b] Determined on the uncomplexed (*S*)-*N*-Bn-amino acid by chiral HPLC analysis. [c] Determined by chiral HPLC analysis on (*R*)-*N*-Bn-Thr, following treatment of [Co^{III}(**3**)(*N*-Bn-Thr)] with aqueous sodium dithionite. [d] Performed at −10 °C; a reaction time of 72 h was necessary, compared to 24 h in all other cases.



Scheme 3. Reductive cleavage of the cobalt(III) complex [Co^{III}(**3**)(*N*-Bn-Ala)].

two clear phases over the course of the extraction. One equivalent was extracted into the dichloromethane phase to form the complexes [Co^{III}(**3**)(*N*-Bn-AA)], while the second equivalent was dissolved in the aqueous phase where the *ee* values were found to be 90.1 and 99.0% in favor of (*S*)-*N*-benzylvaline and (*S*)-*N*-benzylleucine, respectively (Table 2, entries 2, 3). The extraction of *N*-benzylphenylalanine under the same conditions also proceeded in high yield with one equivalent of substrate extracted into the organic phase through formation of [Co^{III}(**3**)(*N*-Bn-Phe)] (Table 2, entry 4). The unbound substrate, (*S*)-*N*-benzylphenylalanine remained as a suspension and could be isolated by filtration or dissolved into the aqueous phase by treatment with NaOH. Again, a high *ee* value was observed (93.3% *ee*). Treatment of the complexes [Co^{III}(**3**)(*N*-Bn-AA)] with aqueous sodium dithionite released the opposite enantiomer in quantitative yield and with consistent *ee* values (see the Supporting Information).

Resolution of racemic *N*-benzyl amino acids using only dichloromethane and no water was also attempted (Table 2, entries 5–8, method C). In all cases, one equivalent of the substrate was complexed by [Co^{III}(**3**)(OAc)] and dissolved into the dichloromethane phase, while the uncomplexed solid material could be isolated simply by filtration. Enantioselectivities of 94.2 and 92.7% *ee* were observed for the recovered *N*-benzylvaline and *N*-benzylphenylalanine, respectively (Table 2, entries 5, 6). Thus, method C represents a more practical procedure for less hydrophilic amino acids with no loss of enantioselectivity. Conversely, and surprisingly, *N*-benzylalanine showed only poor enantioselectivity by this method (Table 2, entry 7), which could be somewhat improved by lowering the temperature, with 65.8% *ee* obtained at −10°C (Table 2, entry 8).

In conclusion, we have developed a novel approach to the resolution of racemic *N*-benzyl α-amino acids in excellent yields and enantiomeric excesses by using the lipophilic chiral salen–cobalt(III) complex [Co^{III}(**3**)(OAc)]. The complexed amino acid can then be released by a reductive ($Co^{III}\rightarrow Co^{II}$) counterextraction with aqueous sodium dithionite. The original chiral cobalt(III) complex can be regenerated and reused with essentially no loss of reactivity and selectivity. We are actively investigating the scope of this methodology using different substrates as well as its large-scale application in an industrial environment.

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