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Chiral Salen-Metal Complexes as Novel Catalysts for Asymmetric Phase Transfer Alkylations

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Abstract: Chiral, salen-metal complexes have been tested as catalysts for the *C*-alkylation of aldimine Schiff's bases of alanine esters with alkyl bromides under phase-transfer conditions (solid sodium hydroxide, toluene, ambient temperature, 1-10% of the catalyst). The best catalyst, which was derived from a Cu(II) complex of (1*R*,2*R* or 1*S*,2*S*)-[*N*,*N*'-bis(2'-hydroxybenzylidene)]-1,2-diaminocyclohexane, gave α-methyl-α-amino acids with enantiomeric excesses of 70-96%.

Keywords: Phase transfer; catalysis; copper; asymmetric synthesis; amino acid.

Asymmetric catalysis is rapidly becoming an important tool for both small scale laboratory syntheses[1] and large scale industrial production of enantiomerically enriched compounds.[1a,b] Amongst the many chiral catalysts, metal complexes feature prominently. This is partly due to their unique ability to fix the mutual orientation of chiral ligands and substrates in the coordination sphere of the complex and thus provide the necessary chiral template for chiral recognition in the transition state of the reaction.[1a,b] Another industrially important reaction, asymmetric phase-transfer-catalysis (PTC) of CH-acid alkylation, proceeds *via* ion-pair formation and usually relies on the use of chiral quaternary ammonium salts to promote the enantioselective version of the reactions.[2] The ion-pair interactions inside the loose ion pairs, formed by the carbanions and quaternary ammonium ions, are usually not strong enough to provide effective control of the stereochemistry of the alkylation. In spite of recent progress in the field,[3] it is still not possible to predict in advance which reaction conditions will give good enantioselectivity in a particular reaction.

Recently, we reported the use of TADDOL [(*4S,5S*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxalane-4,5-dimethanol] to promote the asymmetric PTC *C*-alkylation of Schiff's bases of alanine esters with enantiomeric excesses as high as 82%.[4] In this reaction, TADDOL functioned as a chelating agent for the alkali ions and thus made the ion-pair (formed by the corresponding carbanion and alkali ions) soluble in organic solvents. This modification combined the synthetic simplicity of the PTC approach with the advantages of catalysis by metal complexes. We expected that other types of preformed chiral metal complexes might function in the same way: activating the ion-pair by complexation of an alkali ion and/or forming a complex with the carbanion itself. Our earlier attempts to realize this principle met with only limited success.[5] In this manuscript, we report the use of chiral salen-metal complexes **1-6** as phase transfer catalysts. These compounds were chosen since they are known to be able to chelate additional metal ions.[6]

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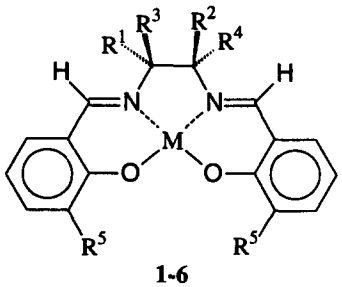
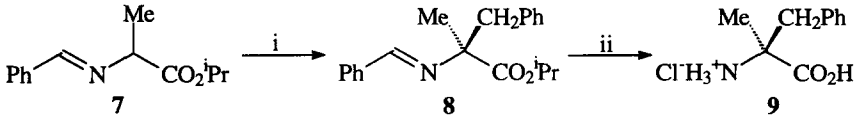


1-6

1 $R^1 = CH_2CH_2S^+Me_2$; $R^2 = R^3 = R^4 = R^5 = H$; M = Ni(II)
2 $R^1 = CH_2CH_2SMe$; $R^2 = R^3 = R^4 = R^5 = H$; M = Ni(II)
3 R^1-$R^2 = (CH_2)_4$; $R^3 = R^4 = R^5 = H$; M = Ni(II)
4 R^1-$R^2 = (CH_2)_4$; $R^3 = R^4 = R^5 = H$; M = Cu(II)
5 R^1-$R^2 = (CH_2)_4$; $R^3 = R^4 = H$; R^5 = t-Bu; M = Ni(II)
6 $R^1 = R^2 = H$; R^3-$R^4 = (CH_2)_4$; $R^5 = H$; M = Cu(II)

As a model reaction, the alkylation of Schiff's base **7** (derived from benzaldehyde and *R,S*-alanine isopropyl ester) with benzyl bromide under PTC conditions (solid NaOH / toluene) was chosen (**Scheme 1**). The advantages of using this substrate were the stability to racemization of product **8** and the importance of amino acids containing quaternary α-carbon atoms.[7] The reaction was conducted in toluene at ambient temperature, using solid MOH (or NaH) to activate the substrate (usually 0.2 g in 4 ml of solvent) and chiral salen-metal complexes (**1-6**) as promoters of the reaction (substrate / catalyst ratio from 10 / 1 to 100 / 1). After 5-12 hours, the reaction was quenched with dilute hydrochloric acid and the liberated amino acid ester was hydrolysed. The enantiomeric excess of the resulting amino acid **9** was established by chiral GLC, and the experimental results are summarized in **Table 1**.



7 **8** **9**

Scheme 1: *Reagents; i, $PhCH_2Br$ / **1-6** / $PhCH_3$ / solid NaOH; ii, HCl (aqueous)*

Analysis of the results indicated that, in the absence of a transition metal, the salen ligands did not produce any asymmetric induction in the product (**Table 1**, run 1). In other words, the disodium salt of the ligand, which would form under the PTC conditions, was not an efficient asymmetric catalyst of the alkylation reaction under the reaction conditions. Catalyst **1**, derived from Ni(II) and a positively charged Schiff's base was also quite inefficient (**Table 1**, run 2), which may be due to the poor solubility of **1** in toluene. The removal of one methyl group from the $(Me)_2S^+$- moiety of **1** to give ligand **2**, improved the performance of the catalyst (**Table 1**, run 3), bringing the enantiomeric excess of the product to 31% at a ratio of substrate / catalyst of 10 / 1. Complex **3**, the Ni(II) complex of a Schiff's base derived from (1*R*,2*R*)-[*N*,*N*'-bis(2'-hydroxybenzylidene)]-1,2-diaminocyclohexane, was also catalytically active, giving the same level of asymmetric induction at the same concentration of the catalyst (**Table 1**, run 4). The performance of the catalyst was greatly improved when the Ni(II) ion in **3** was substituted by a Cu(II) ion to give complex **4**, with the enantiomeric excess of the final product reaching 85% (**Table 1**, run 5). The introduction of *t*-butyl groups into the 3'-position of the salen moiety of the catalyst to give complex **5** was counterproductive, with the enantiomeric excess of the product dropping to 6% (**Table 1**, run 6). In other cases of catalysis using salen ligands, the introduction of substituents at the 3'-position greatly improved the enantioselectivity of the catalyst.[8] The reaction could be scaled up to 5 g of substrate **7**, employing **4** as a catalyst without any significant decrease in the enantiomeric excess of the reaction (**Table 1**, run 7).

If the ratio of sodium hydroxide / substrate was chosen in the range of 1.2-2.0, the chemical yield of the product was low (20-50%, **Table 1**, runs 1-7). One reason for this might be consumption of sodium hydroxide in a side reaction

Table 1. Asymmetric alkylation of Schiff's base **7** by benzyl bromide mediated by complexes **1-6**[a].

run	catalyst	mol % of catalyst	Base, equiv.	e.e. % (conf.), [b]	yield % [b]
1	ligand	10	NaOH, 1.2	0.5	50
2	1	10	NaOH, 1.5	1 (*S*)	50
3	2	10	NaOH, 1.5	31 (*R*)	44
4	3	10	NaOH, 1.2	30 (*R*)	34
5	4	10	NaOH, 1.2	85 (*R*)	40
6	5	10	NaOH, 1.2	6 (*R*)	47
7 [c]	4	10	NaOH, 1.2	80 (*R*) [d]	20
8 [e]	6	2	NaOH, 2.0	80 (*R*)	4
9[f]	4	10	NaOH, 1.2	46 (*R*)	91
10	4	10	NaH, 1.2	89 (*R*)	82
11 [c]	6	1	NaOH, 3.0	92 (*S*) [d]	71
12	6	2	NaOH, 3.5	88 (*S*)	91
13	4	2	NaOH, 4.0	76 (*R*)	99
14 [g]	6	2	NaOH, 3.0	53 (*S*)	95
15	6	2	LiOH, 2.0	0	7
16	6	2	KOH, 2.0	63 (*S*)	87
17 [h]	6	2	NaOH, 1.2	90 (*S*)	48

[a] The concentration of the substrate was 0.2-0.3 M [usually 0.110 g (0.5 mmol) of substrate in 4 ml of the solvent, unless indicated otherwise]. The reaction was conducted for 5-12 hours under an argon atmosphere, solid MOH was used as base unless indicated otherwise, and the ratio of benzyl bromide to **7** was 1.2-2. [b] The enantiomeric excess of α–methylphenylalanine was determined by GLC of the *N*-trifluoroacetyl derivative of its propyl-ester, and the chemical yield was determined by ^{1}H NMR spectroscopy using leucine as an internal standard. [c] The experiment was scaled up to 5 g of **7** in 100 ml of toluene. [d] The enantiomeric excess of α-methylphenylalanine was increased to 98% after crystallization. [e] Aqueous NaOH (50%) was used as a base. [f] The substrate was derived from the *t*-Bu ester of *R,S*-alanine. [g] The experiment was conducted in an open vessel without an Ar atmosphere. [h] The catalyst recovered from the previous experiments was used.

such as hydrolysis of the substrate. This was corroborated by a drop in the chemical yield to 4% if aqueous sodium hydroxide was used (**Table 1**, run 8). An almost quantitative chemical yield could be achieved using *t*-butyl *N*-benzylidene-alaninate as a hydrolytically stable substrate (**Table 1**, run 9). Alternatively, use of 1.2 equivalents of sodium hydride gave a good chemical yield and satisfactory enantiomeric excess (**Table 1**, run 10). Finally, increasing the amount of solid sodium hydroxide to 3.5 equivalents improved the chemical yield without compromising the enantiomeric excess of the product (**Table 1**, runs 11, 12) even if the amount of the catalyst was decreased to 1% (**Table 1**, run 11). Further increases in the amount of sodium hydroxide to 4.0 equivalents decreased the enantiomeric excess of the product from 88% to 76% (**Table 1**, run 13). It was necessary to carry out these reactions under an inert atmosphere, as an attempt to conduct the reaction in an open vessel resulted in a low enantiomeric excess of the product (**Table 1**, run 14). Sodium hydroxide was found to be the base of choice since lithium hydroxide was inefficient (**Table 1**, run 15) and

use of potassium hydroxide gave a low enantiomeric excess (**Table 1**, run 16). Catalysts **6** or **4** could be recovered and successfully reused in the reaction (**Table 1**, run 17).

Finally, the use of other alkyl halides was investigated. Thus, using 10 mol% of catalyst **4** and 1.2 equivalents of sodium hydroxide, reaction of imine **8** with allyl bromide followed by acidic hydrolysis gave α-allyl-alanine in 56% chemical yield and with 96% enantiomeric excess. Under the same conditions, *para*-fluorobenzyl chloride gave α-methyl-*para*-fluorophenylalanine in 60% yield and with 70% enantiomeric excess.

In conclusion, a new type of PTC catalyst derived from neutral chiral salen-metal complexes has been developed and used to prepare α-methyl-α-amino acids with up to 96% enantiomeric excess. Although the mechanism of this reaction and the origin of the asymmetric induction is currently unknown, there seems to be a clear prospect of employing these catalysts in a host of reactions concerned with the *C*-alkylation of the CH-acids.

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