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New heterogeneous catalysts for the synthesis of chiral amino acids: Functionalization of organic resins with chiral salen complexes

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ABSTRACT

Four new heterogeneous catalysts were synthesized by covalent attachment of vanadium(V) and aluminum(III) salen complexes to polystyrene polymers, namely, Merrifield and JandaJel resins. The solid catalysts were characterized by analytical and spectroscopic techniques and tested in the asymmetric addition of hydrogen cyanide (generated *in situ* from TMSCN) to *N*-benzyl benzylimine (Strecker type reaction). Heterogeneous vanadium(V) catalysts are more efficient than the Al(III) catalysts, as expected from comparison with the corresponding homogeneous systems. The activity of the vanadium(V) heterogeneous catalysts is similar to the homogenous counterpart (after 4 h of reaction at −40 °C using 10 mol% of catalysts), while the enantiomeric excess was slightly inferior to the one obtained with the corresponding homogeneous catalysts. The **Janda-V(V)** heterogeneous catalyst can be reused by simple filtration up to three times without significative loss of conversion and enantioselectivity. This is the first study dedicated to the synthesis of asymmetric amino acids through the Strecker reaction using heterogeneous salen catalysts.

1. Introduction

Interest in synthetic routes to chiral amino acids can be traced to the presence of these building blocks in a variety of biologically interesting natural products [1]. The addition of cyanide to imines (the Strecker reaction) using a chiral catalyst constitutes one of the most direct and viable strategies for the asymmetric synthesis of chiral α-amino acids [2]. In the literature there are many homogeneous catalysts for this reaction with high enantiomeric excess, from organic catalysts to metallic complexes [3].

Salen complexes is one of the most versatile family of metallic complexes for catalyzed enantioselective reactions [4]. In fact, an aluminum(III)–salen complex was the first chiral complex used in a Strecker type reaction, obtaining good yields and excellent enantioselectivities [5]. More recently, chiral vanadium(V)–salen complexes proved to be very effective in the asymmetric addition of hydrogen cyanide (generated *in situ* from TMSCN) to imines [6]. Others examples of pioneering studies of catalyzed enantioselective Strecker type reaction using chiral metal complexes were a tripeptide salicylimine Schiff base titanium complex [7], a zirconium binuclear complex based in binaphthol ligands [8], and bifunctional Lewis acid–base chiral aluminum binaphthol complex [9].

In spite of the good results achieved with the homogeneous catalysts (excellent enantioselectivities conjugated with high yields), their use brings difficulties at experimental, environmental and economic level. The separation of the catalysts from the reaction media is a laborious process, with the production of a high quantity of wastes, which also makes hard the recuperation of the catalyst and their reutilization. The transformation of these catalysts into heterogeneous systems will lead to environmental and experimental advantages, since the catalyst will be separated by simple filtration, avoiding the production of wastes, and also economic benefits, due to their re-use [10]. Different systems could be used to develop a heterogeneous catalyst from a homogeneous one. Polymers and inorganic solids (e.g. silicas, zeolites, mesoporous solids), biphasic catalysts, carbon materials or metal organic frameworks could be used to heterogenize the homogeneous catalysts, and especially salen complexes [11].

Herein we present the first study dedicated to the synthesis of chiral amino acids through the Strecker reaction conditions using heterogeneous salen catalysts. Vanadium(V) and aluminum(III) salen complexes were anchored following different strategies to Merrifield and JandaJel polystyrene resins and the obtained heterogeneous catalysts were tested in the asymmetric addition of hydrogen cyanide to *N*-benzyl benzylimine.

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2. Experimental

2.1. Materials and instrumentation

All reagents and solvents were of the purest grade available and were purchased from Aldrich. Whenever necessary, the solvents were dried according to standard methods [12]. Jandajel-OH (100–200 mesh, 2% cross-linked, 1.0 mmol OH/g) and 4-nitrophenyl carbonate Merrifield resin (100–200 mesh, 2% cross-linked, 0.8 mmol N/g) were purchased from Aldrich. 4-Nitrophenyl carbonate JandaJel resin was synthesized, from JandaJel-OH according to published procedures [13]. Homogeneous aluminum(III)–salen complex (**Homo-Al(III)**), (1R,2R)-(−)-[1,2-cyclohexanodiamino-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)]aluminum(III) chloride was purchased from Strem Chemicals. (1R,2R)-*N*-(3,5-di-*tert*-butyl-2-hydroxybenzylidene)-*N*′-(3-*tert*-butyl-2,5-di-hydroxybenzylidene)-1,2-cyclohexyl-diamine (**1**) was obtained from (R,R)-1,2-diaminocyclohexane mono hydrochloride, 3,5-di-*tert*-butylsalicylaldehyde and 3-*tert*-butyl-2,5-di-hidroxybenzaldehyde in an one-pot synthesis [14]. Homogeneous vanadium(V)-salen (**Homo-V(V)**) complex was synthesized according to published procedures [15].

Melting points were determined in a Reichert Thermovar apparatus and are uncorrected. IR spectra were obtained in a JASCO FT/IR 4100 spectrometer or in a Perkin-Elmer Spectrum BX v5.3.1 spectrometer. NMR spectra were run on a BRUKER AVANCE 400 MHz Ultra Shield spectrometer at Faculty of Sciences of Lisbon University. ICP-OES analyses were performed on a Perkin Elmer Optima 4300 DV at CACTI of Vigo University. GC analyses were performed on a Agilent Technologies 6890N gas chromatograph equipped with a Astec Chiraldex G-TA 30 m × 0.25 mm × 0.12 μm column.

2.2. General procedure for the immobilization of salen ligand **1** to 4-nitrophenyl carbonate resins

A suspension of 4-nitrophenyl carbonate JandaJel or Merrifield resin (0.20 g, 0.2 mmol N), salen ligand **1** (152 mg, 0.3 mmol), 4-dimethylaminopyridine (DMAP, 25 mg, 0.2 mmol), *N*,*N*-diisopropylethylamine (DIPEA, 68 μL, 0.4 mmol) in dry DMF (4 mL) was stirred for 1.5 h at ambient temperature under N_2 atmosphere. The mixture was filtered and the resin was sequentially washed with DMF, distilled water, methanol and dichloromethane and dried in vacuum to yield the product as yellow beads.

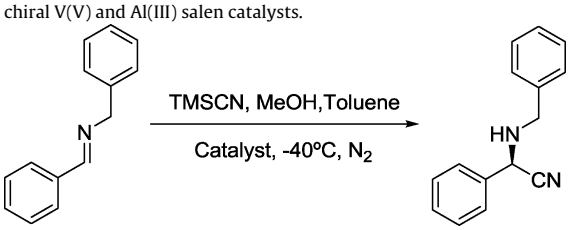
2.3. General procedure for the synthesis of vanadium(V) heterogeneous catalysts

The salen ligand functionalized (Merrifield or JandaJel) resin (0.5 g) was added to a warm solution (60 °C) of vanadyl sulphate hydrate (1.2 equiv. of active groups in the resin) in ethanol/THF (1.6/1, 20 mL) and the suspension was stirred overnight under reflux in air. The mixture was filtered and the solid washed with distilled water, methanol, dichloromethane and finally dried in vacuum. The loading of complex in the heterogeneous catalyst was calculated from the amount of vanadium determined by ICP-OES analysis.

2.4. Synthesis of (1R,2R)-N-(3,5-di-tert-butyl-2-hydroxybenzylidene)-N′-(3-tert-butyl-2,5-di-hydroxybenzylidene)-1,2-cyclohexyl-di-amine aluminum(III) chloride **2**

To a solution of salen ligand **1** (0.3 g, 0.59 mmol), in dry dichloromethane (4 mL) under nitrogen atmosphere, the diethylaluminium chloride (1.8 M in toluene, 0.33 mL, 0.59 mmol) was slowly added and the resulting mixture was stirred for 3 h at ambient temperature. The mixture was concentrated in vacuum and the yellow solid that precipitated was filtered, washed with hexane and dried in vacuum (0.26 g, 76%). m.p. = 310 °C (dec.). FTIR (KBr, υ, cm^{-1}): 3334, 2957, 2867, 1634, 1620, 1559, 1350, 846. ^{1}H RMN (DMSO, δ, ppm): 8.64 (s, 1H), 8.32 (s, 1H), 8.18 (s, 1H), 7.39 (s, 1H), 7.34 (s, 1H), 6.93 (d, J = 4.0 Hz, 1H), 6.72 (d, J = 4.0 Hz, 1H), 2.57–2.51 (m, 2H), 1.94–1.99 (m, 2H), 1.51 (s, 9H), 1.49 (s, 9H), 1.48–1.29 (m, 6H), 1.28 (s, 9H).

Table 1
Results of the catalytic addition of TMSCN to *N*-benzyl benzylimine catalyzed by chiral V(V) and Al(III) salen catalysts.



Entry	Catalyst	Metal loading (mmol/g)	mol%	Conversion (%)[a]	TON	e.e. (%)[b]
1	**Homo-V(V)**	–	10	96	10	69
2	**Janda-V(V)**	0.201	5	77	15	55
3			10	84	8	50
4	**Merr-V(V)**	0.331	7	80	11	47
5			10	96	10	50
6	**Homo-Al(III)**	–	10	82	8	34
7	**Janda-Al(III)**	0.304	10	24	2	0
8	**Merr-Al(III)**	0.246	10	85	9	8

[a] 4 h reaction, and no additional products were found.
[b] e.e. determined by ^{1}H NMR with (1*R*)-(−)-camphorsulfonic acid [16].

2.5. General procedure for the synthesis of aluminum(III) heterogeneous catalysts

A suspension of 4-nitrophenyl carbonate Merrifield or JandaJel resin (0.20 g, 0.16–0.2 mmol N), Al salen complex **2** (170 mg, 0.3 mmol), DMAP (25 mg, 0.2 mmol), DIPEA (68 μL, 0.4 mmol) in dry DMF (5 mL) was stirred for 1.5 h at room temperature under N_2 atmosphere. The mixture was filtered and the resin was sequentially washed with DMF, distilled water, methanol and dichloromethane and dried in vacuum to yield the product as yellow beads. The loading of complex in the heterogeneous catalysts was calculated from the amount of aluminum determined by ICP-OES analysis.

2.6. General procedure for the asymmetric addition of cyanide to N-benzyl benzylimine

A Schlenk tube was charged with dry toluene (1 mL), methanol (1.2 equiv., 50 μL) and trimethylsilyl cyanide (TMSCN, 1.2 equiv., 80 μL). The resulting mixture was stirred at 0 °C under nitrogen atmosphere for 1 h. Then, homogeneous (0.1 equiv.) or heterogeneous (Table 1) catalyst in dry toluene (2 mL) and *N*-benzyl benzylimine (0.5 mmol, 93 μL) were added. The resulting mixture was stirred at −40 °C under nitrogen atmosphere for 4 h. Then, the reaction mixture was filtered (heterogeneous catalyst) or passed through a plug of silica gel with elution of hexane/ethyl acetate (9/1, 300 mL) (homogeneous catalysts) and the solvent evaporated in vacuum. The residue obtained was analyzed without further purification by ^{1}H RMN for the determination of the enantioselectivity using (1*R*)-(−)-camphorsulfonic acid as resolving agent [16]. A part of the residue was derivatized with trifluoroacetic anhydride for GC determination of conversion.