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Asymmetric addition of trimethylsilylcyanide to *N*-benzylimines catalyzed by recyclable chiral dimeric V(V) salen complex

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ABSTRACT

Chiral dimeric vanadium (V) salen complex (10 mol%) derived from 5,5-Methylene di-[(*S,S*)-{*N*-(3-*tert*-butyl salicylidine)-*N*′-(3′,5′-di-*tert*-butyl salicylidene)]-1,2-cyclohexanediamine] with vanadyl suphate followed by auto oxidation was used as efficient catalyst for enantioselective Strecker reaction of *N*-benzylimines with TMSCN at −30 °C. Excellent yield (92%) of α-aminonitrile and high chiral induction was achieved (ee up to 94%) in case of 2-methoxy substituted *N*-benzylimines in 10 h. The catalytic system worked well up to four cycles with retention of enantioselectivity.

1. Introduction

The catalytic asymmetric Strecker reaction represents simple and efficient method for the synthesis of optically pure α-amino acid derivatives [1], nucleic acids [2], various nitrogen and sulfur containing heterocycles and pharmaceuticals [3]. The classical Strecker reaction reported in 1850 comprises a condensation of an aldehyde, ammonia and a cyanide source, followed by the hydrolysis of the resulting α-amino nitrile [1a]. However, the classical Strecker reaction yields racemic products, which after hydrolysis yield α-amino acids in racemic form [4]. Asymmetric version of this synthetically very useful reaction reportedly used a variety of chiral catalyst such as organocatalysts [5], Jacobsen's Schiff base complexes [6], bi-functional catalyst [7] and metal based catalysts [4,8]. Among these, Jacobsen salen-metal complexes have emerged as an efficient catalyst for the asymmetric Strecker reaction [8a]. Since chiral ligands are expensive, the recycling of chiral catalyst is of immense value. In this context, our group has reported dimeric salen complexes as recyclable chiral catalysts for various asymmetric organic transformations [9]. These dimeric complexes due to relatively high molecular weight are less soluble in solvents like hexane and hence can be easily precipitated out from the reaction mixture in a post-work up step. Previously we have reported dimeric (V) salen complex as an efficient catalyst for the cyanation of aldehydes [9a]. Herein, we are extending the application of dimeric V(V) salen complex for the asymmetric addition of TMSCN to various *N*-benzylimines.

2. Results and discussion

Chiral vanadium (V) salen complex **1** (Fig. 1) was synthesized by the reaction of ligand 5,5-methylene di-[(*S,S*)-{*N*-(3-*tert*-butyl salicylidine)-*N*′-(3′,5′-di-*tert*-butyl salicylidene)]-1,2-cyclohexanediamine] with vanadyl sulfate by the reported method [9a]. Our systemic study for the optimization of the reaction condition for the Strecker reaction (Fig. 2) was initiated by the use of 2-methoxy imine as a model substrate with TMSCN as a source of cyanide using chiral dimeric V(V) salen complex **1** as a recyclable catalyst. As the temperature plays a crucial role to achieve high chiral induction in asymmetric catalysis, we first varied the reaction temperature in a stepwise manner from room temperature (RT) to −40 °C (Table 1, entries 1–5). On decreasing the temperature from RT to −30 °C (entries 1–5), the yield of α-aminonitrile remained nearly same, however there was an increase in reaction time and improvement in enantioselectivity. A further decrease in the reaction temperature from –30 to –40 °C adversely affects the reactivity and enantioselectivity (entry 6). Hence, −30 °C was taken as optimum reaction temperature for the present protocol for the synthesis of α-aminonitrile. Next, to find out the optimum catalyst loading, we carried out the Strecker reaction with 5, 10 and 20 mol% of the catalyst (Table 1, entries 4, 6, and 7) at −30 °C. In the case of 5 mol% catalyst loading 89% yield with 82% ee was achieved within 10 h. When we increase the catalyst loading from

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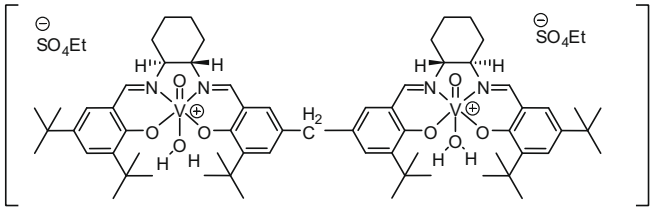


Fig. 1. Structure of catalyst **1**.

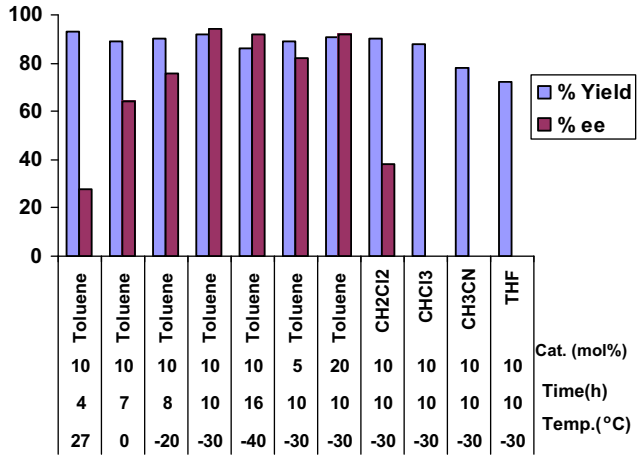


Fig. 2. Optimization of the reaction conditions for Strecker reaction of *N*-benzylimines with TMSCN.

5 to 10 mol% there was significant improvement in the yield (92%) and ee (94%) of the product, however a further increase in the catalyst loading (20 mol%) was inconsequential. Having optimized the reaction temperature (−30 °C) and catalyst loading (10 mol%), next we optimized reaction medium bearing in mind that the reactivity and enantioselectivity of the Strecker reaction is strongly dependent on the nature of the solvent used [8a]. The solvents e.g., toluene, dichloromethane, chloroform, acetonitrile and THF (Table 1, entries 4, 8–11) were screened for their effect on the yield and ee of the product. A good yield (90%) with moderate ee (38%)

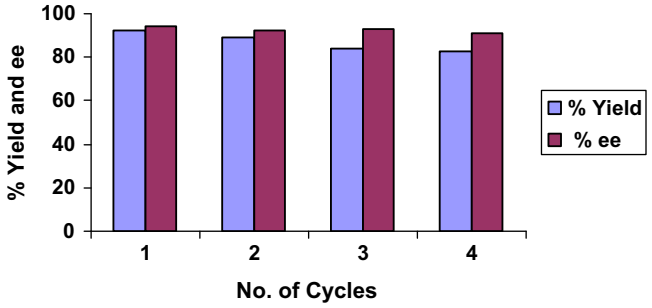
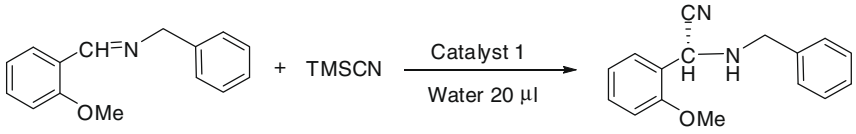


Fig. 3. Recycling of the catalyst **1**.

was obtained with dichloromethane. However, on using chloroform, acetonitrile, THF as a solvent although the product yield was 72–88% but the reaction took non chiral path. The best results in terms of yield and ee of the product for the model reaction was achieved with toluene as a solvent (Table 1, entry 4). In all catalytic runs the 1*S*, 2*S* chiral dimeric V(V) salen complex gives the *R*-form of α-aminonitrile.

After optimizing the reaction conditions (Table 1, entry 4) this catalytic protocol was implemented on various *N*-benzylimines in order to see the generality of the catalytic system and the results are summarized in Table 2. Both the electron donating and electron withdrawing substituent present on imine had some effect on the asymmetric Strecker reaction. *N*-Benzylimines with no substituent gave 89% isolated yield with 80% ee. The electron donating (–Me, –OMe) groups at 2- and 4-positions of *N*-benzylimines gave higher yields as well as ee (Table 2, entries 2, 4, 5, 7) than in the cases where these substituents were on 3-position (Table 2, entries 3, 6). Among the methyl and methoxy substituent, the methoxy substituent showed better results in terms of product yield and ee (Table 2, entries 4, 7). The presence of electron withdrawing group on the aromatic ring of imines gave moderate yield and ee (Table 2, entries 8, 9). Furthermore, on conducting the same reaction with *N*-benzylimines derived from aliphatic aldehydes and benzyl amine we could achieve a poor yield (65%) and ee (22%) in the case of crotonaldehyde (Table 2, entry 11) whereas with trimethyl acetaldehyde better yield (78%) and ee (75%) was achieved (Table 2, entry 10).

Table 1
Data for the optimization of reaction conditions.[a]



Entry	Catalyst loading (mol%)	Temp (°C)	Time (h)	Solvent	Yield[b] (%)	Ee[c] (%)
1	10	RT	4	Toluene	93	28
2	10	0	7	Toluene	89	64
3	10	−20	8	Toluene	90	76
4	10	−30	10	Toluene	92	94
5	10	−40	16	Toluene	86	92
6	5	−30	10	Toluene	89	82
7	20	−30	10	Toluene	91	92
8	10	−30	10	CH_2Cl_2	90	38
9	10	−30	10	$CHCl_3$	88	Racemic
10	10	−30	10	CH_3CN	78	Racemic
11	10	−30	10	THF	72	Racemic

[a] All reactions were carried out using 1.5 equiv of TMSCN.
[b] Isolated yield.
[c] Ee were determined using chiral OD-H column.