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Asymmetric addition of trimethylsilyl cyanide to aldehydes promoted by chiral polymeric vanadium(V) salen complex as an efficient and recyclable catalyst

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Abstract—The asymmetric addition of trimethylsilyl cyanide to various aldehydes catalyzed by efficient new vanadyl polymeric salen complexes having 12 repeating salen units was investigated at room temperature. An excellent yield of the trimethylsilylether of cyanohydrins (up to 98%) with high chiral induction (96%) in case of 2-methylbenzaldehyde was achieved in 18 h. The catalyst recovered four times with retention of its performance.

1. Introduction

Chiral cyanohydrins are highly versatile intermediates, which can easily be converted into a wide range of valuable classes of chiral compounds, such as α-amino acids, α-hydroxy acids, β-amino alcohols, vicinal diols, α-hydroxy ketones.[1,2] They also play an important role for the preparation of a wide range of pharmaceuticals, agrochemicals and insecticides.[3] Substantial progress has been made towards the development of efficient methods for the preparation of these compounds, with a growing emphasis on the identification of enantioselective catalytic approaches with practical potential.[4,5] Several useful cyanation reagents have been reported in the literature.[6] Among them trimethylsilylcyanide (TMSCN) seems to be one of the most effective and safe cyanation sources for nucleophilic addition to carbonyl compounds in the presence of a chiral catalyst.[7–10]

Although impressive enantio-induction have been obtained in many cases, issues such as moderate temperature, reaction conditions and recycling of the expensive chiral catalyst need to be addressed for their practical application. Recently, much effort has been made to develop recyclable metal complexes involving multi-step surface modification of the support and its binding with a catalytically active complex using organic or inorganic supports[11] and ionic liquids[12] as reaction media. Our groups have been involved in developing recyclable polymeric and dimeric salen complexes for various asymmetric organic transformations.[13] Herein, we extend the application of a polymeric salen ligand[13c] by synthesizing its vanadium(V) salen complexes **1** and **2** for the asymmetric addition of TMSCN to various aldehydes at room temperature. An excellent yield (98%) of trimethylsilylether of cyanohydrin derivatives with high chiral induction (ee, up to 96%) was achieved in the case of 2-methylbenzaldehyde with catalyst **1**. In all catalytic runs, the (*R*)-form of polymeric V(V) salen complexes converted all aldehydes into (*S*)-cyanohydrins. To the best of our knowledge, V(V) polymeric salen complex **1** is a more efficient, recyclable catalyst for cyanosilylation reaction than the complex **2** and chiral monomeric V(V) salen system.[7b]

2. Results and discussion

Synthesis of polymeric V(V) salen complexes **1** and **2** was carried out by the condensation of the mono tartrate salt of (1*R*,2*R*)-(−)-diaminocyclohexane with 5,5-methylene-di-3-*tert*-butyl salicylaldehyde/5,5-methylene-di-3-methyl

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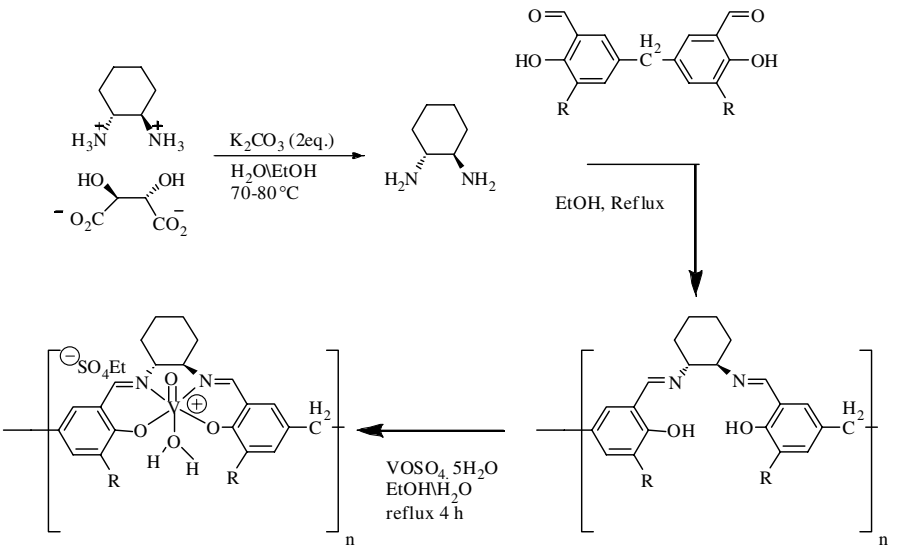
salicylaldehyde in (1:1) molar ratio in methanol followed by insertion of vanadium (Scheme 1). The number of repeating units and the average molecular weight of the polymeric ligands, as measured by vapour pressure osmometry, was ~5400 and ~4300 ($n = 12$), respectively. ^{1}H NMR and IR spectra showed the absence of an aldehyde group in ligands **1′** and **2′** Scheme 1. The complexes **1** and **2** were characterized by ^{1}H NMR, IR, UV–vis spectroscopy and microanalysis (data given in Experimental section).

The catalytic asymmetric addition of trimethylsilyl cyanide to benzaldehyde **3a**, 4-fluorobenzaldehyde **3b**, 2-methylbenzaldehyde **3c** and 2-methoxybenzaldehyde **3d** as representative substrates was carried out at room temperature using complexes **1** and **2** (data given in Table 1). ^{1}H and ^{13}C NMR data showed the exclusive formation of products **4a–d** with no formation of the enolizable product (data given in Experimental section). The data shown in Table 1 revealed that the present catalytic protocol is quite general for the range of substrates studied in the present study. Good to excellent conversions were achieved with all substrates for both the catalysts (entries 1–8) with high enantiomeric excess for the substrate **3c** (entries 5 and 6) in 18 h as shown by their turn over frequency (TOF) values. The overall performance of complex **1** is better than complex **2**. Complex **1** was explored further for the catalytic asymmetric addition of trimethylsilyl cyanide to different aromatic aldehydes viz. 4-methoxybenzaldehyde **3e**, 3-methoxybenzaldehyde **3f**, 4-chlorobenzaldehyde **3g**, 4-bromobenzaldehyde **3h**, 4-methylbenzaldehyde **3i** in order to examine the effect of the substituents and their position on the ring on the enantioselectivity at room temperature whereby the trimethylsilylether derivatives of the corresponding cyanohydrins **4e–i** are formed as shown in Table 1.

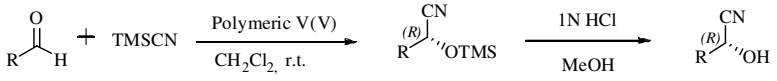
Electron withdrawing substituents such as F, Cl, Br, on the aromatic ring gave moderate enantioselectivity (Table 1, entries 3, 11 and 12) while electron donating groups, such as MeO and Me, favours the enantioselectivity (Table 1, entries 5, 7, 9, 10 and 13). Additionally, *o*-substituted benzaldehydes (Me, MeO) gave higher enantiomeric excesses (Table 1, entries 5–7) than those of *p*-substituted benzaldehydes (Table 1, entries 9 and 13). This finding indicates that not only electronic effects but also the position of substituents play a decisive role on the enantioselectivity of the reaction. The best enantio-induction (ee, 96%) was obtained with *o*-methylbenzaldehyde (Table 1, entry 5). The overall performance of this catalyst is at par in terms of reactivity and enantioselectivity with that of dimeric a V(V) complex (5 mol %) using KCN/NaCN[13b] as a cyanide source where the reaction was carried out at −20 °C. When carrying out the cyanation reaction with aliphatic aldehydes, viz. *n*-butylaldehyde **3j**, *tert*-butylaldehyde **3k**, *iso*-butylaldehyde **3l** in presence of trimethylsilyl cyanide (Table 1, entries 14–16) at room temperature, 94–99% conversion with 81–85% ee of the cyanosilylether was achieved in the case of *n*-butylaldehyde and *tert*-butylaldehyde (Table 1, entries 14 and 15) respectively in 18 h. A moderate conversion (76%) and ee (79%) was obtained with *iso*-butylaldehyde (entry 16). In all catalytic runs the (*R*)-form of the polymeric V(V) salen complexes converted aldehydes into the (*S*)-cyanohydrins. These results are in consonance with earlier reports in the literature.[14]

The reactivity and enantioselectivity of the cyanation reaction is strongly dependent upon the nature of the solvent used.[8d] Therefore, catalytic enantioselective cyanation reactions were conducted in different solvents, such as dichloromethane, 1,2-dichloroethane, toluene and THF using benzaldehyde as a representative substrate with cata-



Scheme 1. Synthesis of the complexes **1** and **2**.

Table 1. Enantioselective addition of trimethylsilyl cyanide to various aldehydes catalyzed by polymeric V(V) complexes



3a-l **4a-l** **5a-l**

3a; R = phenyl **3b**; R = 4-fluorophenyl **3c**; R = 2-methylphenyl
3d; R = 2-methoxyphenyl **3e**; R = 4-methoxyphenyl **3f**; R = 3-methoxyphenyl
3g; R = 4-chlorophenyl **3h**; R = 4-bromophenyl **3i**; R = 4-methylphenyl
3j; R = n-butyl **3k**; R = *t*-butyl **3l**; R = *iso*-butyl

Entry	Substrate	Time (h)	Conversion[a] (%)	ee[b] (%)	TOF (h^{-1})[c]
1 (2)[d]	**3a**	18	97 (80)	94 (58)	5.38 (4.44)
3 (4)	**3b**	18	85 (70)	80 (48)	4.72 (3.88)
5 (6)	**3c**	18	98 (92)	96 (89)	5.44 (5.11)
7 (8)	**3d**	18	93 (88)	89 (35)	5.16 (4.88)
9	**3e**	18	85	86	4.72
10	**3f**	18	89	82	4.94
11	**3g**	18	86	77	4.77
12	**3h**	18	88	79	4.88
13	**3i**	18	94	92	5.22
14	**3j**	18	99	85	5.50
15	**3k**	18	94	81	5.22
16	**3l**	18	76	79	4.22

All reactions carried out at room temperature.
[a] The conversion of the cyanosilylether was determined based on the GC integral area.
[b] The ee was determined by using a Chiralpak HPLC OD and AD column, after conversion to the corresponding acetate.
[c] TOF = [Product]/[Catalyst] × time (h).
[d] Results in parenthesis are for catalyst **2**.

lyst **1** under identical reaction conditions. A good conversion (88%) with good enantioselectivity was obtained with 1,2 dichloroethane (Table 2, entry 18) but on using THF and toluene as a solvent the conversion was (78–65%) with ee (65–70%) (Table 2, entries 19 and 20). The best results of the model reaction were achieved with dichloromethane (Table 2, entry 17).

Table 2. Data for the effect of solvents on conversion and ee of enantioselective addition of trimethylsilyl cyanide to benzaldehydes, catalyzed by recovered polymeric chiral V(V) complex **1**

Entry	Solvent	Conversion[a] (%)	ee[b] (%)
17	Dichloromethane	97	94
18	1,2-Dichloroethane	88	79
19	Toluene	65	70
20	THF	78	65

All reactions carried out at room temperature.
[a] The conversion of the cyanosilylether was determined based on the GC integral area.
[b] The ee was determined by using a Chiralpak HPLC OD column, after conversion to the corresponding acetate.

It has been reported in the literature that the use of an additive greatly influences the reactivity and enantioselectivity of the asymmetric cyanation reaction.[15a–g] We tested triphenylphosphine, triphenylphosphine-oxide, triethylamine, pyridine, pyridine-*N*-oxide and 4-phenylpyridine-*N*-oxide (5 mol %) for this purpose using benzaldehyde as a representative substrate with catalyst **1** with data are given in Table 3. The use of *O* coordinating additives gave a better outcome in terms of reaction time with little improvement in conversion and retention of enantioselectivity (Table 3, entries 22–24) compared to other additives such as triphenylphosphine, triethylamine and pyridine (Table 3, entries 21, 25 and 26). The additive quantity was also varied using 4-phenylpyridine-*N*-oxide (1–10

Table 3. Data for the effect of additives on conversion and ee of enantioselective addition of trimethylsilyl cyanide to benzaldehydes, catalyzed by polymeric chiral V(V) complex **1**

Entry	Additives	Mol %	Time (h)	Conversion[a] (%)	ee[b] (%)
21	Triphenylphosphine	5	12	90	69
22	Triphenylphosphine-oxide	5	12	99	94
23	Pyridine-*N*-oxide	5	12	99	94
24	4-Phenyl pyridine-*N*-oxide	5	12	99	94
25	Pyridine	5	12	75	78
26	Triethylamine	5	12	85	36
27	4-Phenyl pyridine-*N*-oxide	10	6	99	95
28	4-Phenyl pyridine-*N*-oxide	2.5	17	96	94
29	4-Phenyl pyridine-*N*-oxide	1	18	96	94

All reaction carried out at room temperature.
[a] The conversion of the cyanosilylether was determined based on the GC integral area.
[b] The ee was determined by using a Chiralpak HPLC OD column, after conversion to the corresponding acetate.

mol %) as the representative additive with benzaldehyde as the substrate under identical conditions and data are given in Table 3. When using 4-phenylpyridine-*N*-oxide (10 mol %) the catalytic reaction was completed in 6 h with a slight improvement in ee (entry 27). On the contrary, decreasing the amount of additive from 2.5 to 1 mol % there is no improvement in conversion and ee of trimethylsilylether derivative of cyanohydrin (Table 3, entries 28 and 29). Thus, the use of 5 mol % additive is proved to be optimal (Table 3, entry 24).

The reaction temperature and catalyst loading were also found to be an essential factor for the enantioselective cyanation reaction. When carrying out the cyanation reaction with 5 mol % catalyst at rt, using benzaldehyde as the representative substrate, the same conversion (97%) with 94% ee of trimethylsilylether (Table 4, entry 30) was obtained with 1 mol % catalyst loading (Table 4, entry 33). Lowering the temperature from rt to −20 °C, greatly increases the reaction time with a lower yield (71%) (Table 4, entry 31) but there is an increase in ee (95%). An increase in reaction temperature to 45 °C resulted in a detrimental effect on the reaction due to the instability of the adduct trimethylsilylether (Table 4, entry 32). Attempts to reduce the catalyst loading from 1 to 0.1 mol % (entries 33 and 34) using benzaldehyde as a representative substrate gave 89% conversion of trimethylsilylether with 88% ee (Table 4, entry 34).

Table 4. Data for the effect of catalyst loading and temperature on conversion and ee of the trimethylsilylether derivative of cyanohydrin using benzaldehyde as a representative substrate with catalyst **1**

Entry	Catalyst loading (mol %)	Temperature (°C)	Conversion[a] (%)	ee[b] (%)
30	5	rt	97	94
31	5	−20	71	95
32	1	45	58	63
33	1	rt	97	94
34	0.1	rt	89	88

All reactions carried out at room temperature.

[a] The conversion of the cyanosilylether was determined based on a GC integral area.

[b] The ee was determined by using a Chiralpak HPLC OD column, after conversion to the corresponding acetate.

2.1. Kinetic studies

Kinetic experiments were performed with benzaldehyde as a representative substrate as a function of the concentrations of catalyst **1**, benzaldehyde and TMSCN. A representative kinetic profile as a function of catalyst concentration is given in Figure 1. It was generally observed from the kinetic profiles, that the formation of products increased linearly up to 5 min, after which a significant increase is not observed. Therefore, the initial rate constants k_{obs} were determined from the data in this time range.

2.2. Dependence of the rate on catalyst concentration

The cyanation reaction of benzaldehyde as representative substrate was studied at room temperature by conducting the kinetic experiments at different concentration of the catalyst **1** [1.5×10^{-3} M–12.2×10^{-3} M] at a constant concentration of benzaldehyde [399.3×10^{-3} M] and TMSCN [1118.3×10^{-3} M]. From the kinetic data, a linear plot of K_{obs} of the cyanosilylether formation versus log[catalyst] with unit slopes ($d\log K_{obs}/d\log[\text{catalyst}] = 1$) was obtained, which passes through the origin, indicating that the cyanation of benzaldehyde is first order with respect to the concentration of the catalyst (Fig. 2).

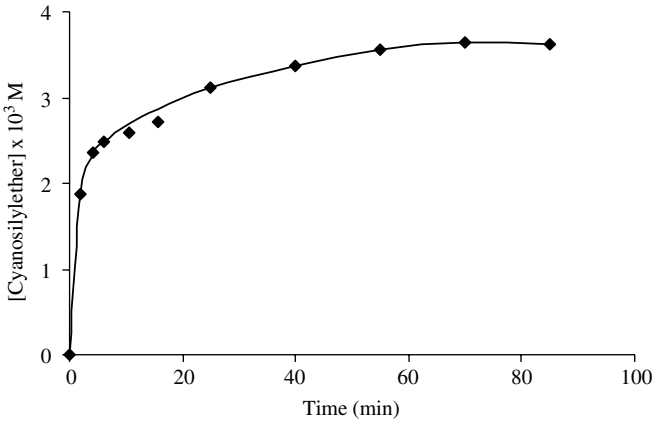


Figure 1. Time dependent plot of the formation of trimethylsilylether at room temperature, [catalyst **1**] = 3.0×10^{-3} M, [benzaldehyde] = 399.3×10^{-3} M, [TMSCN] = 1118.3×10^{-3} M.

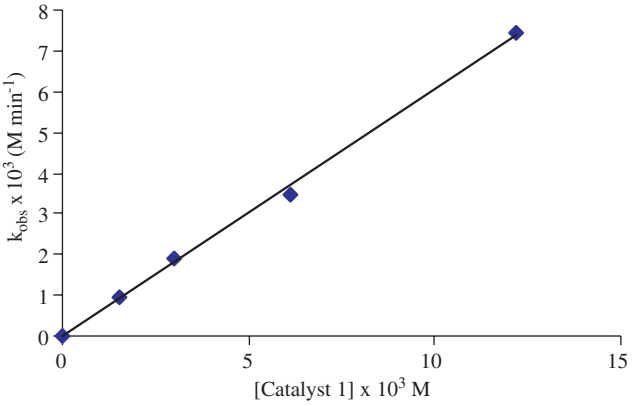


Figure 2. Plot of catalyst **1** versus K_{obs} at rt, [benzaldehyde] = 399.3×10^{-3} M and [TMSCN] = 1118.3×10^{-3} M.

2.3. Dependence of the rate on benzaldehyde concentration

Kinetic experiments were carried out at different initial concentrations of benzaldehyde ranging from (198.1×10^{-3} M–1597.4×10^{-3} M) by keeping the concentration of other reactants and physical conditions constant from which the rate was calculated and the plot of rate constant (K_{obs}) versus the concentration of benzaldehyde ($d\log K_{obs}/d\log[\text{benzaldehyde}] \sim 1$) also showed the first dependence of the reaction on the substrate concentration (Fig. 3).

2.4. Dependence of the rate on TMSCN concentration

The effect of concentration of the TMSCN over the range of (557.7×10^{-3} M–4475.3×10^{-3} M) on the rate of the

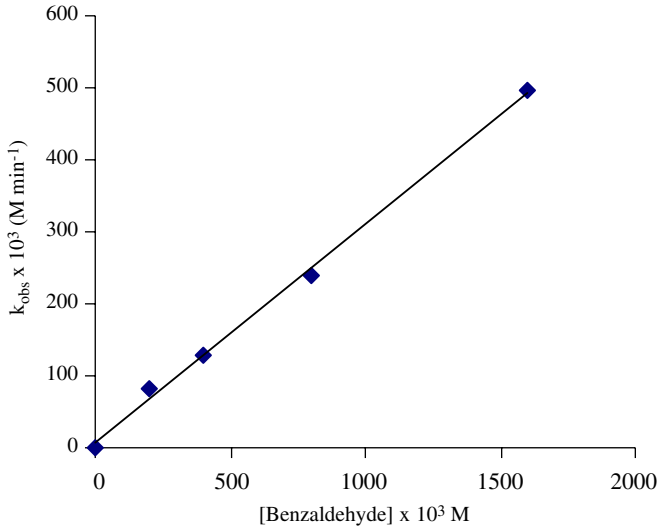


Figure 3. Plot of Benzaldehyde versus K_{obs} at rt, [catalyst **1**] = 3.0×10^{-3} M and [TMSCN] = 1118.3×10^{-3} M.

cyanation of benzaldehyde were studied, keeping the catalyst [3.0×10^{-3} M] and benzaldehyde [399.3×10^{-3} M] concentration as constant, which indicated a zero order dependence in terms of the concentrations of TMSCN. The tendency of following zero order kinetics during cyanosilylation in term of concentration of TMSCN has also been observed earlier[16] (Fig. 4).

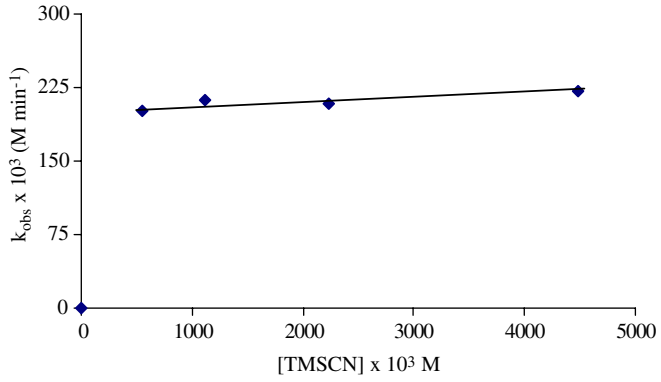


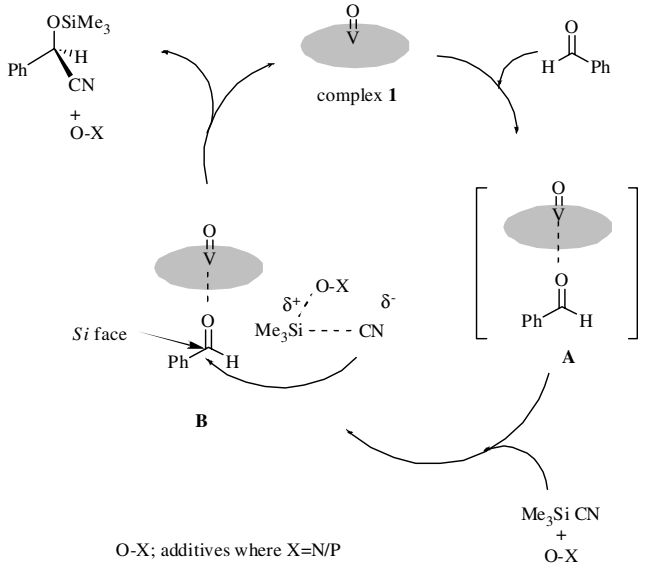
Figure 4. Plot of TMSCN versus K_{obs} at rt, [catalyst **1**] = 3.0×10^{-3} M and [benzaldehyde] = 399.3×10^{-3} M.

The kinetic data for TMSCN dependence for cyanation of benzaldehyde are given in Table 5.

On the basis of the kinetic data, it is evident that the reaction is first order with respect to complex and the substrate, benzaldehyde and zero order with respect to TMSCN. A probable mechanism is shown in Scheme 2 where, in presence of an acidic complex the activation of the substrate, benzaldehyde, takes place to form an intermediate **A** in the rate determination step. This intermediate reacted in a fast step with polarized TMSCN guided by the chiral environment of the catalyst **1** to produce trimethylsilylether of the respective cyanohydrin.

Table 5. Concentration dependent kinetics data for the cyanation of benzaldehyde at rt

Reactants	[Concentration] $\times 10^3$ M	$k_{obs} \times 10^3$ M min^{-1}
Catalyst	1.5	0.95
	3.0	1.89
	6.1	3.47
	12.2	7.44
Benzaldehyde	198.1	81
	399.3	127
	798.7	239
	1597.4	495
TMSCN	557.7	201
	1118.3	212
	2237.6	208
	4475.3	222



Scheme 2. Probable mechanism for the catalytic cynosilylation.

The interesting feature of this novel polymeric V(V) salen complex is its inherent tendency to be precipitated out in nonpolar solvent such as hexane due to its higher molecular weight and lower solubility in reaction medium. After one catalytic cycle, the polymeric catalyst was recovered and re-used for the subsequent runs of cyanosilylation of 2-methyl benzaldehyde as representative substrate by adding fresh reactants. From the data in Table 6 it is evident

Table 6. Enantioselective addition of trimethylsilyl cyanide to 2-methylbenzaldehyde catalyzed by a polymeric chiral V(V) complex

Run	1	2	3	4
Time (h)	18	20	20	20
Conversion[a] (%)	98	98	96	94
ee[b] (%)	96	96	96	96

All reactions carried out at room temperature.

[a] The conversion of the cyanosilylether was determined based on a GC integral area.

[b] The ee was determined by using a Chiralpak HPLC OD column, after conversion to the corresponding acetate.

that catalyst **1** worked well for up to four cycles with a small decrease in reactivity due to some physical loss during the post work up process with retained enantioselectivity of trimethylsilylether of cyanohydrin.

3. Conclusions

Chiral recyclable polymeric vanadium(V) salen complexes **1** and **2** with 12 repeating salen units were synthesized and used for the asymmetric addition of trimethylsilyl cyanide to various aldehydes at room temperature. The catalyst **1** performed very well with 2-methyl benzaldehyde by giving an excellent yield of trimethylsilylether of cyanohydrins up to (98%) with high chiral induction (96%) in 18 h with the added advantage of four times recyclability.

4. Experimental

Vanadyl sulfate hydrate (Loba Chemie, India), benzaldehyde, 4-methoxybenzaldehyde, 3-methoxybenzaldehyde, 2-methoxybenzaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, 4-fluorobenzaldehyde, *n*-butylaldehyde, *iso*-butylaldehyde, 3-methylbutarldehyde, 4-phenyl pyridine-*N*-oxide, triphenylphosphine-oxide (Aldrich), 2-methylbenzaldehyde, 4-methylbenzaldehyde, triphenylphosphine (Merck Chemicals), trimethysilylcyanide (Acros), pyridine-*N*-oxide (Fluka), triethylamine (S. D. Fine-Chem, India), pyridine (Qualigens Fine Chem, India) were purchased and used as received. Polymeric chiral salen ligand **1′** and **2′** was synthesized by a previously reported method.[13c]

All the solvents were dried using standard procedures,[17] distilled and stored under nitrogen. The synthesis and characterization of poly-[(*R*,*R*)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine} cyclohexane-1,2-diamine] **1′** and its precursors was carried out as described.[13c]

4.1. Synthesis of polymeric vanadium(V) complex 1

Ligand **1′** (0.799 g, 1.79 mmol) was dissolved in the mixed solvent ethanol/CH_2Cl_2 (3:2, 15 ml) to which an aqueous solution of vanadyl sulfate hydrate (0.453 g, 1.79 mmol in 2 ml water) was added dropwise under an inert atmosphere at rt. The resulting solution was refluxed for 4 h and then cooled to room temperature with extended stirring for 12 h while opening the side arm of the reaction flask. The solvent was completely evaporated and the residue dissolved in CH_2Cl_2 (10 ml), washed with water (3×5 ml) and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give the polymeric V(V) complex. Yield, 0.680 g, 73.9%; mp: 204–210 °C; IR: (KBr): $\bar{\nu} = 3473$, 2957, 2867, 1612, 1536, 1466, 1387, 1345, 1315, 216, 1177, 1030, 987, 887, 821, 789, 748, 714, 662, 567 cm^{-1}; $[\alpha]_D^{27} = -204.6$ (*c* 0.05, CH_2Cl_2); λ_{max} (ε): 236 (45,090), 404 (11,680), 630 (2620); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 7.2$, 3H), 1.30 (s, 18H), 1.51–1.88 (m, 8H), 3.31 (q, $J = 7.2$, 2H), 3.39 (br s, 2H), 3.81 (m, 2H), 4.26 (m, 2H), 6.89–7.24 (m, 4H), 8.26 (br s, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.4$, 23.4, 26.2, 28.9, 30.0, 40.8, 63.6, 121.3, 126.4, 128.2, 132.0, 135.6, 160.6, 168.3. Anal. Calcd for $C_{31}H_{43}N_2O_8SV^{\cdot+}$: C, 56.88, H, 6.57, N, 4.28. Found: C, 56. 92, H, 6.58, N, 4.30.

4.2. Synthesis of polymeric vanadium(V) complex 2

Ligand **2′** (0.160 g, 0 .45 mmol) was dissolved in the mixed solvent ethanol/CH_2Cl_2 (3:2, 10 ml) to which an aqueous solution of vanadyl sulfate hydrate (0.115 g, 0.45 mmol in 2 ml water) was added dropwise under an inert atmosphere at rt. The resulting solution was refluxed for 4 h and then cooled to room temperature with an extended stirring for 12 h while opening the side arm of the reaction flask. The solvent was completely evaporated and the residue dissolved in CH_2Cl_2 (10 ml), washed with water (3×5 ml) and finally with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give polymeric V(V) complex **2**. Yield, 0.180 g, 69.5%; mp: 198–205 °C; IR: (KBr): $\bar{\nu} = 3398$, 2924, 2853, 1617, 1561, 1466, 1381, 1312, 1262, 1163, 1031, 973, 934, 839, 746, 709, 626, 568, 462 cm^{-1}; $[\alpha]_D^{27} = -591$ (*c* 0.05, CH_2Cl_2); λ_{max} (ε): 248 (31,512), 358 (10,375), 650 (1138); ^1H NMR (200 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.3$, 3H), 1.25 (s, 6H), 1.60–1.85 (m, 8H), 3.30 (q, $J = 7.1$, 2H), 3.42 (m, 2H), 3.77 (br s, 2H), 4.26 (m, 2H), 6.76–7.24 (m, 4H), 8.22 (br s, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.7$, 24.8, 34.1, 28.9, 30.0, 40.8, 73.6, 118.8, 129.1, 132.3, 133.8, 135.5, 158.2, 165.1. Anal. Calcd for $C_{25}H_{31}N_2O_8SV^{\cdot+}$: C, 52.63, H, 5.48, N, 4.91. Found: C, 52.60, H, 5.51, N, 4.89.

4.3. Procedure for vanadium(V) polymeric salen-catalyzed asymmetric addition of trimethylsilyl cyanide to aldehydes

V(V) salen catalyst **1** (0.006 g, 0.0125 mmol) was dissolved in dry CH_2Cl_2 (3 ml) and the solution stirred at room temperature under a nitrogen atmosphere. To this solution, benzaldehyde (0.12 ml, 1.25 mmol) was added, followed by the dropwise addition of TMSCN (0.33 ml, 2.50 mmol). After the reaction was completed (as shown by TLC) the mixture was concentrated and the compound purified by flash column chromatography on silica gel (eluted with hexane/ethylacetate = 95:5). The corresponding trimethylsilylether derivative of cyanohydrin was dissolved in MeOH (3 ml) and then 1 N HCl (3 ml) was dropped to the mixture. The mixture was stirred vigorously at room temperature for 4 h. The aqueous solution was then extracted with CH_2Cl_2, and the combined organic layer dried with anhydrous sodium sulfate. After evaporating the solvent, the corresponding cyanohydrin was obtained. The ee was determined by using Chiralpak HPLC OD and AD column, after conversion to the corresponding acetate.

4.3.1. (*S*)-2-*O*-Acetyl-2-phenyl acetonitrile (derived from 5a). ^1H NMR (200 MHz, $CDCl_3$): $\delta = 2.11$ (s, 3H), 6.38 (s, 1H), 7.40–7.52 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.8$, 63.3, 116.7, 128.3, 129.7, 130.8, 132.3, 169.4; $[\alpha]_D^{27} = -31.5$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 160.2 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, $t_{R1} =$ 19.61 min (minor), $t_{R2} = 21.88$ min (major).

4.3.2. (*S*)-2-*O*-Acetyl-2-(4-flourophenyl) acetonitrile (derived from 5b). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.16$ (s, 3H), 6.39 (s, 1H), 7.09–7.18 (m, 2H), 7.49–7.55 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.0$, 68.8, 116.7, 117.2, 129.4, 130.6, 160.9, 169.5; $[\alpha]_D^{27} = -20.2$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 195.19 (M+H); HPLC analysis: Chiralpak AD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, $t_{R1} = 19.68$ min (minor), $t_{R2} = 21.44$ min (major).

4.3.3. (*S*)-2-*O*-Acetyl-2-(2-methylphenyl) acetonitrile (derived from 5c). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.17$ (s, 3H), 2.43 (s, 3H), 6.51 (s, 1H), 7.23–7.58 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 19.6$, 21.0, 61.7, 113.2, 127.5, 129.2, 130.8, 131.2, 132.0, 138.2, 169.0; $[\alpha]_D^{27} = -26.2$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 191.03 $(M+H)^+$; HPLC analysis: Chiralpak AD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, $t_{R1} = 17.48$ min (major), $t_{R2} = 22.13$ min (minor).

4.3.4. (*S*)-2-*O*-Acetyl-2-(2-methoxyphenyl) acetonitrile (derived from 5d). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.13$ (s, 3H), 3.85 (s, 3H), 6.68 (s, 1H), 6.91–7.57 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.8$, 56.2, 68.6, 111.7, 116.8, 121.2, 129.2, 132.3, 157.3, 169.3; $[\alpha]_D^{27} = -25.6$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 207.14 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, $t_{R1} = 19.90$ min (major), $t_{R2} = 22.41$ min (minor).

4.3.5. (*S*)-2-*O*-Acetyl-2-(4-methoxyphenyl) acetonitrile (derived from 5e). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.14$ (s, 3H), 3.83 (s, 3H), 6.35 (s, 1H), 6.94 (d, $J = 8.75$, 2H), 7.44 (d, $J = 8.90$, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.5$, 56.1, 63.3, 115.1, 115.3, 130.3, 132.6, 161.9, 169.7; $[\alpha]_D^{27} = -24.4$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 207.18 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min: $t_{R1} = 28.41$ min (minor), $t_{R2} = 32.71$ min (major).

4.3.6. (*S*)-2-*O*-Acetyl-2-(3-methoxyphenyl) acetonitrile (derived from 5f). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.16$ (s, 3H), 3.83 (s, 3H), 6.37 (s, 1H), 6.96–7.39 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.0$, 56.1, 63.3, 113.9, 116.6, 120.5, 130.9, 133.7, 160.8, 169.5; $[\alpha]_D^{27} = -23.1$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 207.38 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min: $t_{R1} = 27.38$ min (minor), $t_{R2} = 35.05$ min (major).

4.3.7. (*S*)-2-*O*-Acetyl-2-(4-chlorophenyl) acetonitrile (derived from 5g). ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.15 (s, 3H), 6.25 (s, 1H), 7.39 (d, $J = 8.70$, 2H), 7.46 (d, $J = 8.56$, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 20.8$, 62.6, 116.7, 129.7, 129.9, 130.9, 132.9, 169.2; $[\alpha]_D^{27} = -10.2$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 211.20 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, $t_{R1} = 27.41$ min (minor), $t_{R2} = 31.91$ min (major).

4.3.8. (*S*)-2-*O*-Acetyl-2-(4-bromophenyl) acetonitrile (derived from 5h). ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.16$ (s, 3H), 6.36 (s, 1H), 7.36 (d, $J = 8.52$, 2H), 7.58 (d, $J = 8.38$, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 21.0$, 62.8, 116.3, 125.5, 129.4, 131.0, 133.1, 169.3; $[\alpha]_D^{27} = -11.6$ (*c* 1, CH_2Cl_2); TOF-MS (ESI+): *m*/*z* 153.10 $(M+H)^+$; HPLC analysis: Chiralpak OD column, hexane/isopropanol = 99:1, Flow rate 0.8 ml/min, $t_{R1} = 31.33$ min (minor), $t_{R2} = 37.01$ min (major).

4.4. Recycling of the catalyst

At the end of the catalytic run (checked on TLC), the solvent was completely removed under a reduced pressure. The residue was extracted with hexane to remove the reactants. The remaining solid was further washed with hexane (10 ml), dried under a reduced pressure at 50 °C for 1–2 h and then used as the recovered catalyst for recycle experiments of the cyanation of 2-methyl benzaldehyde.

4.5. Cyanation reaction for kinetic measurement

Catalyst **1** (1.5×10^{-3} M–12.2×10^{-3} M) was dissolved in 3 ml of CH_2Cl_2 and then benzaldehyde (198.1×10^{-3} M–1597.4×10^{-3} M) added. The stirred solution was then reacted with TMSCN (198.1×10^{-3} M–1597.4×10^{-3} M) at rt with constant stirring. To determine the rates of cyanation reaction, aliquots at an interval of 2 min were drawn from the reaction mixture, quenched with anhydrous Na_2SO_4 and analyzed on a GC.

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