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Enantioselective O-acetylcyanation/cyanoformylation of aldehydes using catalysts with built-in crown ether-like motif in chiral macrocyclic V(V) salen complexes

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ABSTRACT

Chiral macrocyclic V(V) salen complexes **1a**–**f** derived from macrocyclic ligands obtained by the reaction of 1*R*,2*R*-(−) diaminocyclohexane/(1*R*,2*R*)-(+)-1,2-diphenylethylenediamine with bis-aldehydes **2** and **3** were synthesized and used as efficient catalysts in asymmetric cyanation reactions. The V(V) catalysts demonstrated excellent performance (product yields and ees up to 99%) with potassium cyanide (KCN) and sodium cyanide (NaCN). The catalytic system also performed very well with a safer source of cyanide-ethyl cyanoformate to give cyanohydrin carbonates in excellent yield and ee (up to 97%). The V(V) macrocyclic salen complex **1b** retained its performance at multi-gram level and was conveniently recycled for a number of times.

1. Introduction

Asymmetric cyanation of carbonyl compounds to form cyanohydrins is one of the most important C–C bond forming reactions in organic chemistry.[1] Chiral cyanohydrins being bifunctional, can be conveniently transformed to produce a number of biologically important compounds including α-hydroxy acids, esters, α-hydroxy aldehydes, ketones, α-amino acids[2] and β-aminoalcohols.[2,3] Driven by the potential application of chiral cyanohydrins, the last couple of decades have seen spurt of excellent reports on enantioselective cyanation of carbonyl compounds. Typically for this reaction enzymes,[3,4] synthetic peptides,[3,4] organo-catalysts[3] and complexes of V, Mn, Ti, Al and lanthanide metal ions[5–22] have been used as catalysts under homogenous and heterogeneous[6] condition. As far as the source of cyanide is concerned, HCN,[2] NaCN,[21,23] KCN,[5c,7] trimethylsilyl cyanide (TMSCN),[5a,10,24] ethyl cyanoformate[5f,8a,19,25] acyl cyanide[8] and acetone cyanohydrin[13] have been frequently employed. From mechanistic studies, it has been established that for mononuclear Ti–salen complexes the key transition state is bimetallic in nature. According to this transition state both the titanium ions simultaneously activate the aldehyde and the cyanide[5,22] (Fig. 1s, Supplementary data). Similar mechanism was also visualized for mononuclear V–salen complex.[5,7] It is proposed that in solution, two mononuclear Ti/V–salen complexes form dinuclear μ-oxo species in the presence of stoichiometric amount of water by intermolecular association. In order to maximize the amount of bimetallic complex in solution, we conceptualized a macrocyclic framework having two salen units covalently linked through a flexible linker. Accordingly, in the present manuscript we are reporting the synthesis of chiral V(V) dinuclear macrocyclic salen complexes **1a**, **1b** where two salen units linked appropriately in a macrocycle whose structure is somewhat akin to Jacobsen's macrocyclic catalyst[26] and can act co-operatively[27] within an enzyme-like chiral cavity. These complexes were used as catalysts for enantioselective cyanation of aldehydes with KCN/NaCN and ethyl cyanoformate as cyanide sources. For the sake of comparison, we have also synthesized mononuclear salen complexes **1c**, **1d** in a macrocyclic framework. For linker we used polyether motif (crown ether like) with a purpose of activation of KCN and NaCN by trapping K^+ and Na^+ ions, respectively.[28] A support of this concept was provided by Evans and Truesdale[29] wherein crown ether complex of alkali metal cyanide was found to be effective catalytic agent for the cyanation reaction. Belokon et al., also demonstrated encouraging role of KCN/18-crown-6 complex as a co-catalyst in asymmetric addition of achiral cyanoformates to aldehydes.[30] While we were preparing this manuscript Ding group[21] reported exceptionally efficient Ti based chiral catalysts for the enantioselective cyanation of aldehydes with TMSCN and NaCN. Structurally

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these catalysts are open ended bimetallic Ti–salen complexes, where the two salen units were linked with various linkers. Although, full characterization data for the corresponding ligands were given, the synthesis or synthetic procedure for these ligands and their complexes was not provided.[22] Nevertheless, among all these complexes, the complex having two salen units that are orientated 180° to one another gave best catalytic performance.[22] The chiral macrocyclic V(V) catalysts synthesized for the present study have indeed demonstrated excellent performance (albeit among reported vanadium based catalysts) with KCN and ethyl cyanoformate as cyanide sources in the enantioselective cyanation of various aldehydes to give *O*-protected cyanohydrins/cyanohydrins carbonate in quantitative yields with high chiral induction. Moreover, the V(V) macrocyclic salen complex **1b** demonstrated excellent recyclability. We have also tested structurally similar but relatively rigid macrocyclic salen ligands **1e** and **1f**[31] in V(V) catalyzed asymmetric cyanation of benzaldehyde, which showed relatively inferior performance.

2. Results and discussion

Chiral macrocyclic ligands **1′a**–**f** were synthesized as depicted in Scheme 1. Dialdehydes 2 and 3, were synthesized in moderate yields by the reaction of 3-*t*-Bu-5-chloromethyl-2-hydroxy benzaldehyde with trigol and 1,3-phenylenedimethanol, respectively in dry THF containing sodium hydride. The macrocyclic chiral salen ligands 1′c, 1′d, 1′e, 1′f were synthesized by reacting stoichiometric amount of dialdehydes 2 and 3 with (1*R*,2*R*)-(−)-diaminocyclohexane 5/(1*R*,2*R*)-(+)-1,2-diphenylethylenediamine 6, respectively in methanol for 12 in quantitative yield. However, the macrocyclic dinuclear ligands 1′a and 1′b were obtained by the reaction of chiral diamines 5, 6 with dialdehydes 2, 3 in dry THF in 2 h. V(V)-complexes **1′a**–**f** were synthesized by the reaction of corresponding macrocyclic ligands 1′a–1′f with vanadyl sulfate followed by auto-oxidation (Scheme 1).

All the mononuclear and dinuclear ligands **1′a**–**f** used in the present study were isolated in pure form by column chromatography and their characterization was accomplished by elemental analysis, MALDI-TOF, ^{1}H and ^{13}C NMR. An attempt is also made to correlate catalyst structure vis-à-vis catalytic performance in view of experimental results. MS and MALDI-TOF data for ligands **1′a**–**f** gave molecular peaks that correspond to the proposed structures. In the case of dinuclear complexes, ICP analysis of V in **1b** demonstrated complete metallation of the ligand **1′b**.

MS spectral analysis of mononuclear **1′d** showed base peak at 610.2 [M+2H], which matched well with its calculated molecular weight (610.3 [M+2H]), while the base peak at 1218.1 (M+2H) (calculated molecular weight, 1218.7 [M+2H]) in MALDI-TOF spectra (Please see Supplementary data) correspond to ligand **1′b**. ^{1}H NMR spectroscopy of the ligands **1′b** and **1′d** has clearly differentiated the two ligands (Please see Supplementary data). A peak for −*H*C=N– appeared at 8.00 ppm in the case of **1′d**, whereas for ligand **1′b** it was at 8.27 ppm. However, major difference in the ^{1}H NMR spectra of **1′d** and **1′b** noticed for the protons of $-O-CH_2-CH_2-O-$ spacer groups and $-O-CH_2-$ attached with the benzene ring. While the ^{1}H NMR spectrum for **1′b** gave singlet at 4.37 ppm for $-O-CH_2$, these protons appeared as double doublet (4.17–4.47 ppm) with geminal coupling of 12 Hz. Similarly, in **1′b** protons for $-O-CH_2-CH_2-O-$ appeared as two triplets (3.54–3.55 ppm and 3.60–3.63 ppm) but these were multiplet (3.30–3.35 ppm and 3.55–3.69 ppm) in the case of **1′d**. These changes in ^{1}H NMR of the ligand **1′d** can be attributed to its rigid skeleton, which restrict flipping bonds of $-O-CH_2-$ and $-O-CH_2-CH_2-O-$, thereby making these protons chemically different, whereas the skeleton of **1′b** is flexible.

The macrocyclic salen ligands used in the present study were designed with the expectation that crown ether-like motif may attract alkali metal ions[29] and therefore can facilitate the activation of KCN in cyanation reactions. To examine the concept experimentally, cyanation of benzaldehyde was carried out in the presence and absence of dibenzo-18-crown-6 using earlier reported dinuclear V(V) salen complex[24c] (Fig. 2s, supplementary data) as catalyst and KCN as cyanide source under identical condition. However, the catalytic reaction in the presence of crown ether yielded the cyanohydrin product in a very low ee (20%) possibly due to the enhanced background reaction. This is to be noted that conducting the cyanation of benzaldehyde with dibenzo-18-crown-6 alone and in combination with ligand **1′d**/**1′b** yielded racemic benzocyanohydrin.

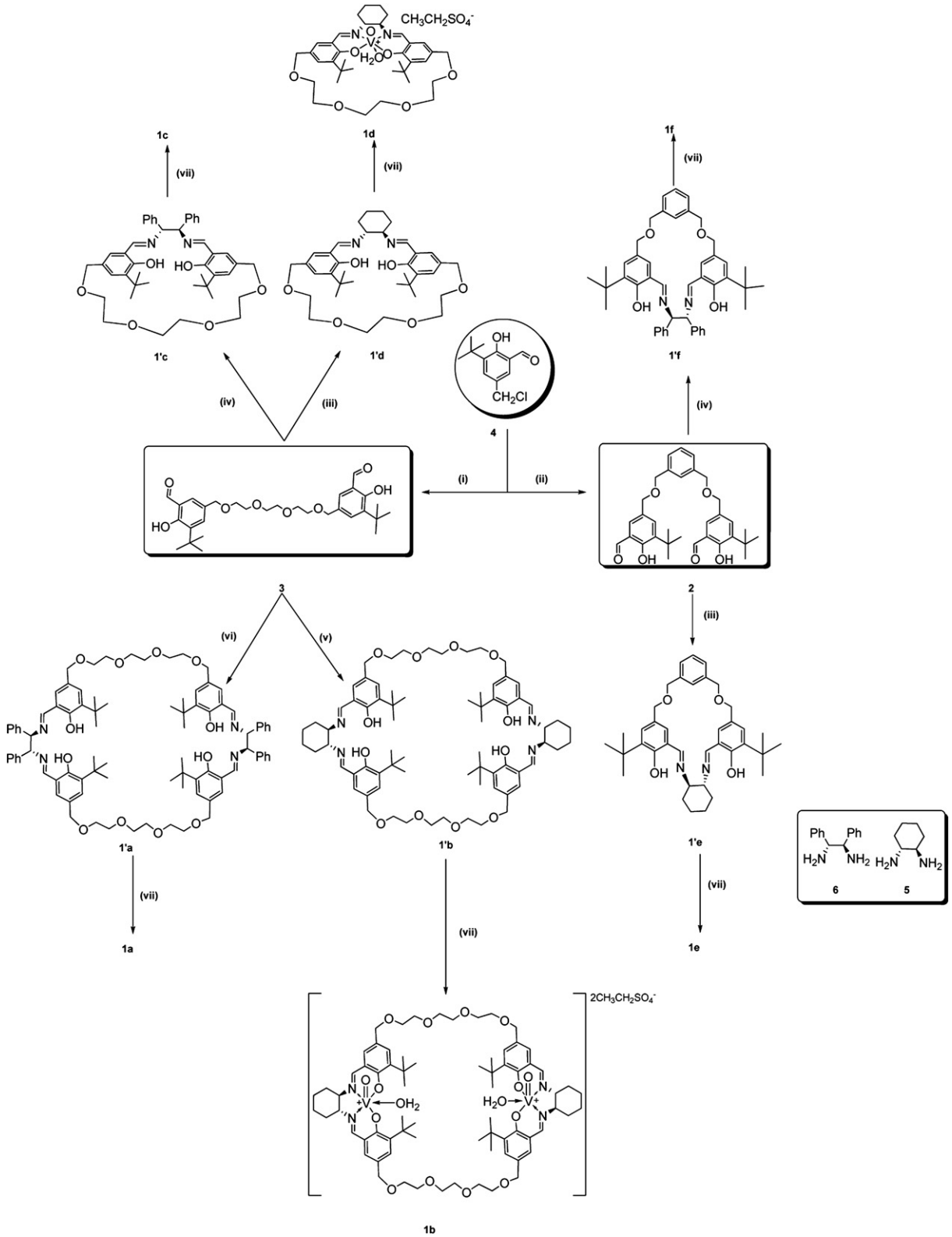
In order to understand the role of polyether functionality in catalytic reaction KCN was added to the $CDCl_3$+CD_3OD solution of **1′b**, the signals of polyether ethylene proton signals shifted downfield (ca. 35 Hz) as a result of binding of K^+ to the oxygen atoms. Similar trend was also observed in ^{13}C spectra of **1′b** with downfield shift of ca. 22 Hz for polyether ethylene carbons. All the spectra on this aspect are given in Supplementary data. These results indicate that polyether (crown ether like) functionality activate KCN/NaCN, thereby, facilitate the catalytic cyanation reaction (TOF 19.8 h^{-1} as compared to reported[5] ~9.6).

With this backdrop, our initial experiments were conducted with macrocyclic mononuclear vanadium complex **1d** and dinuclear complex **1b** to catalyze asymmetric cyanation of benzaldehyde with KCN in the presence of acetic anhydride. At first, the effect of loading of the catalysts **1d** and **1b** in CH_2Cl_2 was carried out at 25 °C (Table 1, entries 1–4 and 9–12). The data revealed that 5 mol % mononuclear complex **1d** gave best results in terms of yield (99%) and enantio-induction (ee, 45%; entry 3) for the product cyanohydrin. On the other hand, the dinuclear complex **1b** (having two salen units) with a loading of 1 mol % was found to be the best (yield, 99%; ee, 63%, entry 10). Therefore, 5 mol % of **1d** (entries 5–8) and 1 mol % of **1b** (entries 13–16) were used to optimize the reaction temperature. Accordingly, this reaction was conducted at temperatures 0, −10, −20 and −30 °C, where −20 °C was found to be most suitable reaction temperature for both the catalysts **1d** and **1b** (Table 1, entries 7, 15). We next screened the mononuclear catalysts **1c**, **1e** and **1f** (5 mol %) and dinuclear complex **1a** (1 mol %) for asymmetric cyanation of benzaldehyde as model substrate with KCN as source of cyanide in CH_2Cl_2 at −20 °C. The data clearly show that complex **1b** is better catalyst in terms of product yield and enantioselectivity (Fig. 1). For the sake of comparison the asymmetric cyanation of benzaldehyde with KCN was carried out by the catalysts **1d** and **1b** having similar metal loadings in CH_2Cl_2 at −20 °C. Accordingly, 2 mol % of **1d** (conversion, 44%; ee, 59%) and 1 mol % of **1b** (conversion, 99%; ee, 92%) were taken to catalyze this reaction under identical reaction conditions for 5 h.

These data on catalyst loading of **1d** and **1b** under similar reaction parameters strongly suggest that the two salen units in the catalysts have some cooperative role to play.[5]

In homogenous catalysis the nature of solvent plays an important role on the activity and enantioselectivity of the catalyst. It is reported in literature[5] that protic solvents play an important role in cyanation reaction. A proton source as an additive (1–2 equiv of water and *tert*-butanol with respect to catalyst) was found to have positive impact on reactivity and to some extent enantioselectivity of the catalyst with CH_2Cl_2 as main solvent. However, when the asymmetric cyanation reaction was conducted solely in protic solvents like methanol, ethanol and *tert*-butanol there was a drastic decrease in enantioselectivity though these reactions were much faster (Table 2, entries 3, 4, 9, 10).

This effect can be attributed to the release of HCN by the reaction of protic solvent with KCN, which in turn enhances the racemic background reaction. Other aprotic solvents, for example, THF, toluene and acetonitrile (in the presence of water and *tert*-

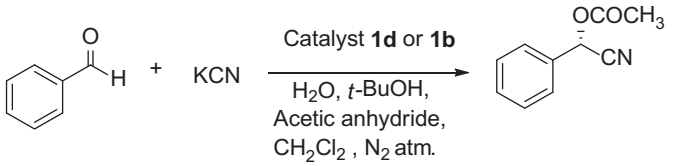


Scheme 1. Synthesis of the macrocyclic catalysts. (i) NaH, trigol, dry THF, N_2 atm rt, 6–8 h, yield 55%. (ii) NaH, 1,3-phenylenedimethanol, dry THF, N_2 atm rt, 6–8 h, yield 50%. (iii) **5**, dry methanol, rt, 12 h, yield 85–88% (iv) **6**, dry methanol, rt, 12 h, yield 85–88% (v) **5**, dry THF, rt, 2 h, yield 96% (vi) **6**, dry THF, rt, 2 h (vii) vanadyl sulfate, dry ethanol, H_2O, N_2 atm reflux 6 h, followed by auto-oxidation, yield 65–70%.

butanol as an additive) were relatively less effective than CH_2Cl_2 both in terms of yield and enantioselectivity.

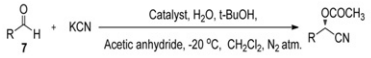
Catalysts **1d** and **1b** enabled asymmetric cyanation reaction of a variety of aromatic and aliphatic aldehydes as substrates with KCN as cyanide source (Table 3) at the best reaction conditions given in Table 2 (entries 6 and 12). In general, substrates irrespective of electron donating or withdrawing group on benzene ring attached to aldehyde functional group gave the products with very good to excellent ee in 5–6 h with the catalyst **1b** and 10–12 h with **1d**.

Table 1
Catalyst loading and temperature variations in the asymmetric O-acetylcyanation of benzaldehyde[a]



Entry	Catalyst	Temp (°C)	Catalyst loading (mol %)	Time (h)	Yield[b] (%)	ee (%)[c]
1	**1d**	25	2	7	92	40
2	**1d**	25	1	7	91	32
3	**1d**	25	5	6	99	45
4	**1d**	25	10	8	96	46
5	**1d**	0	5	12	96	68
6	**1d**	−10	5	12	96	75
7	**1d**	−20	5	12	97	83
8	**1d**	−30	5	15	96	83
9	**1b**	25	2	3	99	62
10	**1b**	25	1	4	99	63
11	**1b**	25	0.5	6	95	60
12	**1b**	25	5	3	96	62
13	**1b**	0	1	5	99	81
14	**1b**	−10	1	5	99	86
15	**1b**	−20	1	5	99	92
16	**1b**	−30	1	6	98	92
17	**1d**	−20	2	5	44	59

[a] Reaction conditions: catalyst **1d** or **1b**, benzaldehyde (1.2 mmol), KCN (2.4 mmol), H_2O (1.11 mmol), *t*-BuOH (2.09 mmol), acetic anhydride (4.8 mmol) in DCM (2 mL).
[b] Isolated yield.
[c] ees were determined by HPLC on chiral OD column. The absolute configuration (*S*) was established by comparison of the optical rotation values with that in the literature.[24]



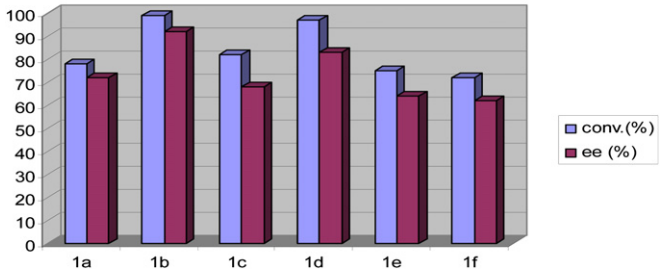


Fig. 1. Screening of catalysts activity towards asymmetric O-acetylcyanation of benzaldehyde with KCN. Reaction conditions: catalyst mononuclear (**1c**, **1d**, **1e**, **1f** 5 mol %) or dinuclear (**1a**, **1b** 1 mol %), benzaldehyde (1.2 mmol), KCN (2.4 mmol), H_2O (1.11 mmol), *t*-BuOH (2.09 mmol), acetic anhydride (4.8 mmol) in DCM (2 mL).

However, aldehyde group directly appended to an aliphatic carbon gave the products in high yield but with moderate to good ee (entries 13–15). Over all the catalyst **1b** gave better performance than catalyst **1d** in terms of product yield and ee, therefore, the catalyst **1b** was further explored for cyanation of aldehydes (**7a**–**q**) using NaCN as cyanide source at the most suitable reaction conditions as given in entry 12 of Table 3. Both the cyanide sources KCN and NaCN gave comparable results, therefore data on NaCN with catalyst **1d** were not included in Table 3.

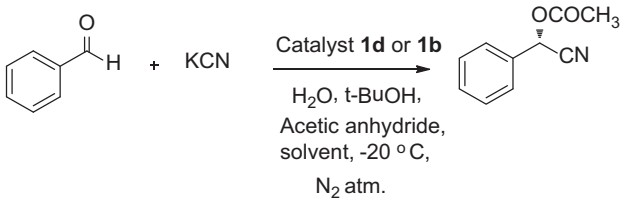
2.1. Scope of organic cyanide source

After successfully demonstrating the utility of catalysts **1d** and **1b** for the asymmetric cyanation of various aldehydes with inorganic cyanide source, we explored the usefulness of **1b** (1 mol %) with organic cyanide source ethyl cyanoformate for asymmetric cyanation of benzaldehyde as representative substrate (Table 4). It is known in the literature that a base as an additive[8,25] or a built-in basic site in the catalyst is vital to activate ethyl cyanoformate.

In view of the above we screened several organic and inorganic bases as co-catalyst (5 mol %) with **1b** for the cyanation of benzaldehyde with ethyl cyanoformate in CH_2Cl_2 (entries 1–10). Very good to excellent yield of cyanohydrins carbonate was achieved with the use of all the bases except for imidazole and 2-methyl imidazole where 50–60% yield was obtained in 48 h (entries 1 and 2). The use of triethylamine as a co-catalyst accelerated the ethyl cyanoformylation reaction tremendously (the reaction was over in 4 h) giving the product in >99% yield however, the reaction took non-enantioselective route (ee, 10%; entry 4). Among all the co-catalysts used in the present study, 2,6-lutidine gave 97% product yield with moderate ee (64%).

Therefore, our subsequent studies for asymmetric ethyl cyanoformylation were carried out with chiral V(V) macrocyclic salen complex **1b** as catalyst and 2,6-lutidine as a co-catalyst. Further, in order to get the optimal reaction condition we carried out asymmetric ethyl cyanoformylation of benzaldehyde at different temperatures, catalyst loading and co-catalyst loading and the results are summarized in Table 5. At first, the catalyst loading was varied over a range of 0.25–2.5 mol % keeping the co-catalyst loading at 5–10 mol % at 25 °C to −40 °C (Table 5). It is evident from the results that only 0.5 mol % catalyst loading and 5 mol % co-catalyst is optimum (entry 7) at −20 °C. Further, it is observed for most enantioselective reactions that on decreasing the reaction temperature there is an improvement in enantioselectivity. Therefore, we carried out cyanoformylation reaction at −40 °C as well, which showed no improvement in the enantioselectivity moreover, there was concomitant decrease in the yield of the product (entry 8). On the other hand, raising the temperature from −20 °C to 0 °C the ee of cyanohydrins carbonate was dropped significantly (entry 6).

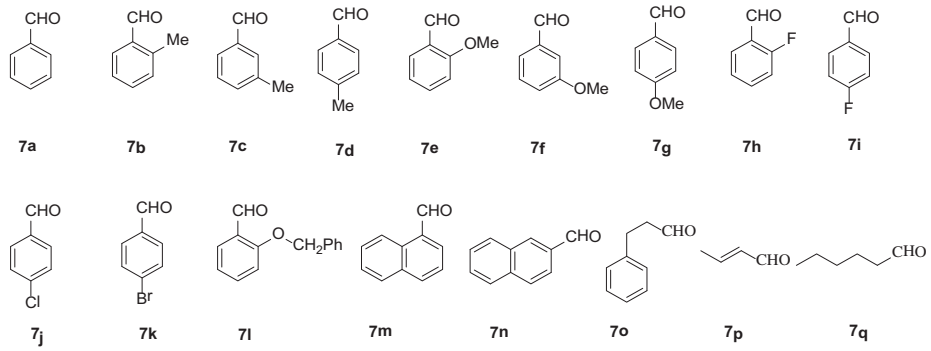
Table 2
Screening of the solvents in the asymmetric O-acetylcyanation of benzaldehyde[a]

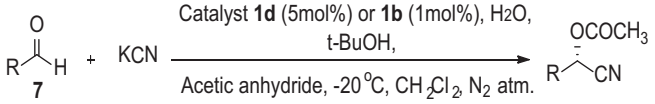


Entry	Catalyst	Solvent (2 mL)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1d**	THF	16	63	51
2	**1d**	Toluene	12	85	58
3	**1d**	MeOH	6	90	40
4	**1d**	*t*-BuOH	6	90	45
5	**1d**	Acetonitrile	12	58	49
6	**1d**	Dichloromethane	12	97	83
7	**1b**	THF	16	62	59
8	**1b**	Toluene	12	82	65
9	**1b**	MeOH	5	92	45
10	**1b**	*t*-BuOH	5	90	50
11	**1b**	Acetonitrile	12	62	50
12	**1b**	Dichloromethane	5	99	92

[a] Reaction conditions: catalyst **1d** (5 mol %) or **1b** (1 mol %), benzaldehyde (1.2 mmol), KCN (2.4 mmol), H_2O (1.11 mmol), *t*-BuOH (2.09 mmol), acetic anhydride (4.8 mmol) at −20 °C.
[b] Isolated yield.
[c] ees were determined by HPLC on chiral OD column. The absolute configuration (*S*) was established by comparison of the optical rotation values with that in the literature.[24]

Table 3
Substrate scope of catalytic asymmetric O-acetylcyanation of aldehydes[a]

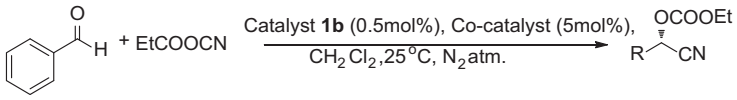




Entry	Substrate	Catalyst **1d**		Catalyst **1b**	
		Yield[b] (%)	ee[c] (%)	Yield[b] (%)	ee[c] (%)
1	**7a**	97	83	99 (98)	92 (90)
2	**7b**	98	89	98 (99)	>99 (96)
3	**7c**	97	82	95 (95)	91 (88)
4	**7d**	95	81	95 (93)	90 (89)
5	**7e**	96	86	95 (96)	97 (95)
6	**7f**	95	84	99 (99)	96 (95)
7	**7g**	94	82	97 (94)	96 (94)
8	**7h**	99	87	97 (96)	>99 (97)
9	**7j**	98	84	97 (94)	92 (90)
10	**7l**	98	78	97 (96)	89 (85)
11	**7m**	99	85	99 (99)	>99 (97)
12	**7n**	99	89	99 (99)	>99 (98)
13	**7o**	98	65	96 (95)	78 (76)
14	**7p**	98	82	98 (98)	89 (85)
15	**7q**	98	53[d]	99 (97)	73[d] (72)

[a] Reaction conditions: catalyst **1d** (5 mol %) or **1b** (1 mol %), dichloromethane (2 mL), aldehyde (1.2 mmol), KCN (2.4 mmol), H_2O (1.11 mmol), *t*-BuOH (2.09 mmol), acetic anhydride (4.8 mmol) at −20 °C in 5–6 h.
[b] Isolated yield. Data in the parentheses are with NaCN as a cyanide source.
[c] ees were determined by HPLC on chiral OD or AD column. The absolute configuration (*S*) was established by comparison of the optical rotation values with that in the literature.[24]
[d] ee was determined by GC on chiral GTA column.

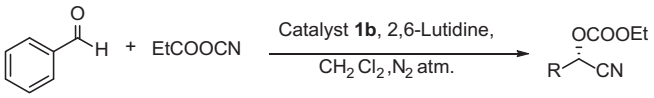
Table 4
Catalyst loading and temperature variations in the synthesis of asymmetric cyanohydrins carbonates of benzaldehyde[a]



Entry	Co-catalyst	Time (h)	Yield[b] (%)	ee[c] (%)
1	Imidazole	48	50	30
2	*N*-Methylimidazole	48	60	33
3	*N*,*N*-Diisopropyl amine	18	97	55
4	Triethylamine	4	>99	10
5	Pyridine	16	92	45
6	2,6-Lutidine	8	97	64
7	Al_2O_3	48	84	35
8	Hydrotalcite	48	82	30
9	DMAP	12	95	32
10	DBU	16	88	50

[a] Reaction conditions: catalyst **1b** (0.5 mol %), benzaldehyde (1.2 mmol), EtCOOCN (1.8 mmol), additive (5 mol %) in 0.8 mL DCM (0.8 mL) at rt.
[b] Isolated yield.
[c] ees were determined by HPLC on chiral OD column. The absolute configuration (*S*) was established by comparison of the optical rotation values with that in the literature.[25]

Table 5
Catalyst loading and temperature variations in the synthesis of asymmetric cyanohydrins carbonates[a] of benzaldehyde



Entry	Catalyst loading (mol %)	Co-catalyst loading (mol %)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	2.5	5	25	8	97	64
2	1	5	25	8	97	64
3	0.5	5	25	8	97	67
4	0.25	5	25	14	93	60
5	0.5	10	25	6	98	58
6	0.5	5	0	10	96	87
7	0.5	5	−20	12	96	95
8	0.5	5	−40	18	90	95

[a] Reaction conditions: chiral ligand **1b** (0.5 mol %), benzaldehyde (1.2 mmol), 2,6-lutidine (0.13 mmol), ethyl cyanoformate (1.8 mmol) in 0.8 mL DCM.
[b] Isolated yield.
[c] ees were determined by HPLC on chiral OD column.

Therefore, for the rest of the catalytic experiments −20 °C was taken as optimum temperature.

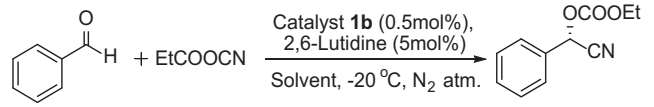
To explore the effect of solvent on the activity and enantioselectivity, ethyl cyanoformylation of benzaldehyde was carried out in various solvents e.g., toluene, toluene+isopropylalcohol, dichloromethane (DCM), dichloromethane+isopropylalcohol and tetrahydrofuran using the V(V) salen complex **1b** (data given in Table 6). Out of all the solvents used, dichloromethane was found to be the best solvent for this reaction (Table 6, entry 3).

Under the optimized reaction conditions the scope of this protocol for the ethyl cyanoformylation reaction was further extended to a variety of aromatic and aliphatic aldehydes using chiral V(V) salen complex as catalyst in the presence of 2,6-lutidine as co-catalyst in dichloromethane at −20 °C. Data in Table 7 shows overall good to excellent isolated yields (90–97%) and ee (85–97%). In the case of hexanal as representative aliphatic aldehyde, the product ethyl cyanohydrin carbonate was obtained in 81% ee and 88% isolated yield in 15 h (entry 11).

2.2. Reuse of complex 1b

Cyanide sources KCN and ethyl cyanoformate were used with catalyst **1b** for reuse experiments[6,24] by using benzaldehyde (3.06 mmol) as model substrate in the manner described earlier

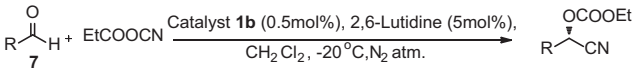
Table 6
Screening of solvents for the synthesis of asymmetric cyanohydrins carbonate of benzaldehyde[a] with catalyst in **1b**



Entry	Solvent	Time (h)	Yield[c] (%)	ee[d] (%)
1	Toluene	18	90	85
2	Toluene+isopropyl alcohol[b]	12	92	82
3	Dichloromethane	12	96	95
4	Dichloromethane+isopropyl alcohol[b]	10	98	80
5	THF	30	80	65

[a] Reaction conditions: chiral ligand **1b** (0.5 mol %), benzaldehyde (1.2 mmol), 2,6-lutidine (0.13 mmol), ethyl cyanoformate (1.8 mmol) at −20 °C.
[b] Toluene or dichloromethane 0.5 mL and isopropyl alcohol 0.3 mL.
[c] Isolated yield.
[d] ees were determined by HPLC on chiral OD column.

Table 7
Substrate scope of catalytic asymmetric cyanohydrin carbonates[a] of aldehydes with **1b** under optimum reaction conditions

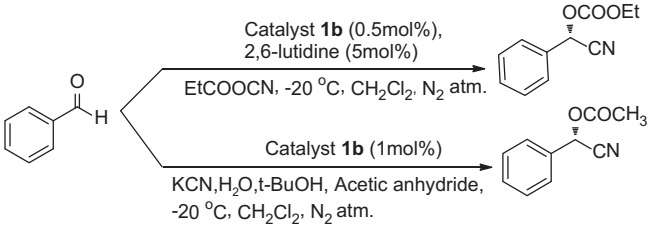


Entry	Substrate	Time (h)	Yield[b] (%)	ee[c] (%)
1	**7a**	12	96	95
2	**7b**	12	97	93
3	**7c**	15	94	85
4	**7d**	12	97	96
5	**7e**	16	95	92
6	**7f**	18	90	87
7	**7g**	12	96	97
8	**7i**	16	95	93
9	**7k**	18	93	91
10	**7n**	12	95	95
11	**7q**	15	88	81[d]

[a] Reaction conditions: chiral ligand **1b** (0.5 mol %), benzaldehyde (1.2 mmol), ethyl cyanoformate (1.8 mmol), 2,6-lutidine (5 mol %) at −20 °C in 0.8 mL DCM.
[b] Isolated yield.
[c] ees were determined by HPLC on chiral OD, OD-H columns.
[d] ee was determined by chiral GC using chiral GTA column.

(see Experimental section). In both the cases after completion of the catalytic reaction, the catalysts were retrieved quantitatively and reused five times with retention of its activity and enantioselectivity. However, during catalyst recovery process there was some physical loss of the catalyst. Since in each reuse experiment, the amount of substrate was kept constant, there was a change in substrate to catalyst ratio, which was responsible for longer reaction time in subsequent catalytic runs (Table 8). As there were no changes in the ee of the product up to the five recycle experiments conducted, it can be safely presumed that the catalyst structure remained unchanged. This was further substantiated by the FTIR of the recovered catalyst **1b**, which matched well with the fresh catalyst (IR spectra given in Supplementary data).

Table 8
Reuse of catalysts **1b** for O-acetylcyanation[a] and synthesis of asymmetric cyanohydrin carbonate[b] of benzaldehyde



Run[e]	1	2	3	4	5	6
Yield[c] (%)	95 (99)	95 (99)	94 (98)	94 (97)	93 (97)	92 (96)
ee[d] (%)	95 (92)	95 (92)	95 (92)	95 (92)	95 (92)	95 (92)

[a] Reaction conditions: chiral catalyst **1b** (0.5 mol %), benzaldehyde (3.06 mmol), 2,6-lutidine (5 mol %) ethyl cyanoformate (4.59 mmol) at −20 °C in DCM (0.8 mL).
[b] Catalyst **1b** (1 mol %), benzaldehyde (3.06 mmol), KCN (6.12 mmol), H_2O (2.22 mmol), *t*-BuOH (4.18 mmol), acetic anhydride (12.24 mmol) at −20 °C in DCM (2 mL).
[c] Isolated yield.
[d] The ees were determined by using chiralpak HPLC OD column.
[e] Data in parenthesis correspond to KCN as cyanide source.

3. Conclusions

This work has revealed a new class of chiral macrocyclic V(V) salen complexes as efficient, recyclable and scalable catalysts for asymmetric addition of KCN/NaCN and ethyl cyanoformate to aldehydes. Particularly, catalyst **1b** with flexible polyether linkage

(a crown ether-like motif) work in cooperation to afford corresponding enantio-enriched cyanohydrin derivatives (yields up to 99%) at −20 °C. Synthetic procedure for the preparation of pre-catalysts (corresponding macrocyclic ligands) once established was very convenient and reproducible to get desired mononuclear and dinuclear ligands in reasonably high yield. Multi-gram level catalytic runs demonstrated no change in the performance of these catalysts suggest that the present protocol for asymmetric cyanation reaction is scalable.

4. Experimental methods

4.1. General

Vanadyl sulfate hydrate (Loba chemie, India), KCN (Merck), NaCN (Merck), ethyl cyanoformate, benzaldehyde, 2-methoxy benzaldehyde, 3-methoxy benzaldehyde, 4-methoxy benzaldehyde, 4-chlorobenzaldehyde, 4-flurobenzaldehyde, 2-flurobenzaldehyde, 4-bromobenzaldehyde, 2-naphthaldehyde, 1-naphthaldehyde, 2-benzyloxy benzaldehyde, hydrocinnamaldehyde, hexanal and crotonaldehyde were purchased from Aldrich Chemicals, whereas 2-methyl benzaldehyde, 3-methyl benzaldehyde and 4-methyl benzaldehyde were purchased from Merck and were used as received. All the solvents were dried by standard procedures, distilled and stored under nitrogen.

4.2. General procedure for 1a–f catalyzed asymmetric O-acetylcyanation of aldehyde

Caution! KCN/NaCN must be used carefully in well-ventilated hood due to its high toxicity. Catalyst (0.012 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and the solution was cooled to −20 °C. *t*-BuOH (2.09 mmol), H_2O (1.11 mmol), aldehyde (1.2 mmol) and Ac_2O (4.8 mmol) and CH_2Cl_2 (0.5 mL) were added to the solution in that order. The addition of KCN or NaCN (2.4 mmol), taken in a Schlenk tube, was done slowly during 2 h, followed by addition of CH_2Cl_2 (0.5 mL). After the reaction was completed, the reaction mass was filtered by passing through a pad of Celite and washed with water (3×15 mL) followed by brine and the organic layer was separated and dried with anhydrous Na_2SO_4. The solution was filtered, evaporated under reduced pressure at ambient temperature and the *O*-acetylcyanohydrin product was purified by flash column chromatography on silica gel (eluted with hexane/ethyl-acetate=95:5). The ee of *O*-acetylcyanohydrin was determined by HPLC and GC analysis.

4.3. Large scale asymmetric O-acetylcyanation of benzaldehyde with KCN catalyzed by 1b

The O-acetylcyanation of benzaldehyde at relatively higher scale (50 mmol) was conducted in exactly same manner as described in Section 4.1 except that the quantities of other ingredients were scaled for 50 mmol of benzaldehyde in 15 mL DCM.

4.4. Reuse of catalyst 1b in asymmetric O-acetylcyanation of benzaldehyde with KCN

For catalyst recycle experiments the general procedure for O-acetylcyanation of benzaldehyde with KCN as described in Section 4.1 was followed at ca. three time scale. After the reaction was completed, the reaction mass was filtered by passing through a pad of Celite and washed with water (3×30 mL) followed by brine and the organic layer was separated and dried over anhydrous Na_2SO_4. The solution was filtered, evaporated under reduced pressure at ambient temperature. The catalyst was extracted with hexane to isolate the product. The remaining solid was further washed with hexane (5 mL), dried under reduced pressure for 1–2 h and was used as recovered catalyst **1b** for recycle experiments.

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Supplementary data

Experimental procedure for the synthesis and characterization of the chiral macrocyclic ligands, complexes and *O*-acetylcyanohydrin products, including ^1H, ^{13}C NMR, MALDI-TOF, TOF-MS data, HPLC and GC conditions, etc. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.07.005.

References and notes

1. North, M.; Usanov, D. L.; Young, C. *Chem. Rev.* **2008**, *108*, 5146.
2. (a) Fechter, M. H.; Griengl, H. In *Enzyme Catalysis in Organic Synthesis*, 2nd ed; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, 2002; Vol. 2, pp 974–989; (b) North, M. In *Science of Synthesis*; Murahashi, S.-I., Ed.; Georg Thieme: Stuttgart, 2004; Vol. 19, pp 235–284; (c) Ramalingam, B.; Seayad, A. M.; Chuanzhao, L.; Garland, M.; Yoshinaga, K.; Wadamoto, M.; Nagata, T.; Chai, C. L. L. *Adv. Synth. Catal.* **2010**, *352*, 2153.
3. (a) Breuer, M.; Habicher, T.; Ditrich, K.; Hauer, B.; Keβeler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788; (b) Holt, J.; Hanefeld, U. *Curr. Org. Synth.* **2009**, *6*, 15; (c) Oku, J.-I.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1981**, 229; (d) Mori, A.; Ikeda, Y.; Kinoshita, K.; Inoue, S. *Chem. Lett.* **1989**, 2119; (e) Brunel, J. M.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2752; (f) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.
4. (a) Hayashi, M.; Miyamoto, Y.; Inoue, T.; Oguni, N. *J. Org. Chem.* **1993**, *58*, 1515; (b) Zhou, X.-G.; Huang, J.-S.; Ko, P.-H.; Cheng, K.-K.; Che, C.-M. *J. Chem. Soc., Dalton Trans.* **1999**, 3303.
5. (a) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S. V.; Khrustalev, N. V.; Larichev, S. M.; Moskalenko, A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968; (b) Belokon, Y. N.; Gutnov, A. V.; Moskalenko, M. A.; Yashkina, L. V.; Lesovoy, D. E.; Ikonnikov, N. S.; Larichev, V. S.; North, M. *Chem. Commun.* **2002**, 244; (c) Belokon, Y. N.; Carta, P.; Gutnov, A. V.; Maleev, V.; Moskalenko, M. A.; Yashkina, L. V.; Ikonnikov, N. S.; Voskoboev, N. V.; Khrustalev, V. N.; North, M. *Helv. Chim. Acta* **2002**, *85*, 3301; (d) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; North, M.; Parsons, T.; Tararov, V. I. *Tetrahedron* **2001**, *57*, 771; (e) Belokon, Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433; (f) Belokon, Y. N.; Blacker, A. J.; Clutterbuck, L. A.; North, M. *Org. Lett.* **2003**, *5*, 45805; (g) Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; Larichev, V. S.; Lokshin, B. V.; Moskalenko, M. A.; North, M.; Orizu, C.; Peregudov, A. S.; Timofeeva, G. I. *Eur. J. Org. Chem.* **2000**, 2655.
6. (a) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Green Chem.* **2002**, *4*, 272; (b) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* **2003**, *44*, 6813; (c) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *J. Catal.* **2003**, *215*, 199; (d) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *J. Catal.* **2004**, *221*, 77; (e) Kim, J.-H.; Kim, G.-J. *Catal. Lett.* **2004**, *92*, 123; (f) Huang, W.; Song, Y.; Bai, C.; Cao, G.; Zheng, Z. *Tetrahedron Lett.* **2004**, *45*, 4763; (g) Huang, W.; Song, Y.; Wang, J.; Cao, G.; Zheng, Z. *Tetrahedron* **2004**, *60*, 10469; (h) Lundgren, S.; Lutsenko, S.; Jolnsson, C.; Moberg, C. *Org. Lett.* **2003**, 3663.
7. (a) Watanabe, A.; Matsumoto, K.; Shimada, Y.; Katsuki, T. *Tetrahedron Lett.* **2004**, *45*, 6229; (b) Takaki, J.; Egami, H.; Matsumoto, K.; Saito, B.; Katsuki, T. *Chem. Lett.* **2008**, *37*, 502.
8. (a) Lundgren, S.; Wingstrand, E.; Penhoat, M.; Moberg, C. *J. Am. Chem. Soc.* **2005**, *127*, 11592; (b) Homberg, A.; Lundgren, S.; Wingstrand, E.; Moberg, C.; Hault, K. *Chem.—Eur. J.* **2007**, *13*, 4334; (c) Casa, J.; Baeza, A.; Sansano, J. M.; Nájera, C.; Saá, J. M. *Tetrahedron: Asymmetry* **2003**, *14*, 197; (d) Baeza, A.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Tetrahedron: Asymmetry* **2005**, *16*, 2385.
9. Brunel, J. M.; Legrand, O.; Buono, G. *Tetrahedron: Asymmetry* **1999**, *10*, 1979.
10. Sellner, H.; Faber, C.; Rheiner, P. B.; Seebach, D. *Chem. —Eur. J.* **2000**, *6*, 3692.
11. Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636.
12. (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989; (b) Hamashima, Y.; Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1999**, *121*, 2641; (c) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805.
13. Sakai, Y.; Mitote, J.; Matsumoto, K.; Katsuki, T. *Chem. Commun.* **2010**, 5787.
14. Casas, J.; Nájera, C.; Sansano, J. M.; Saá, J. M. *Org. Lett.* **2002**, *4*, 2589.
15. Qian, C.; Zhu, C.; Huang, T. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2131.
16. Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, *41*, 7453.
17. Ooi, T.; Miura, T.; Takaya, K.; Ichikawa, H.; Maruoka, K. *Tetrahedron* **2001**, *57*, 867.

18. (a) Minamikawa, H.; Hayakawa, S.; Yamada, T.; Iwasawa, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379; (b) Narasaka, K.; Yamada, T.; Minamikawa, H. *Chem. Lett.* **1987**, 2073.
19. (a) Li, Y.; He, B.; Qin, B.; Feng, X.; Zhang, G. *J. Org. Chem.* **2004**, *69*, 7910; (b) Gou, S.; Chen, Y.; Xiong, X.; Feng, X. *J. Org. Chem.* **2006**, *71*, 5732; (c) Wang, J.; Li, W.; Liu, Y.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *Org. Lett.* **2010**, *12*, 1280.
20. Gama, Á; Flores-López, L.; Aguirre, Z. G.; Parra-Hake, M.; Somanathan, R.; Cole, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1167.
21. Zhang, Z.; Wang, Z.; Zhang, R.; Ding, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6746.
22. North, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8079.
23. Qu, Y.; Jing, L.; Wu, Z.; Wu, D.; Zhou, X. *Tetrahedron: Asymmetry* **2010**, *21*, 187.
24. (a) Khan, N. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Mayani, V. J.; Jasra, R. V. *Tetrahedron: Asymmetry* **2006**, *17*, 2659; (b) Khan, N. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Mayani, V. J.; Jasra, R. V. *J. Mol. Catal. A: Chem.* **2007**, *264*, 140; (c) Khan, N. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Mayani, V. J.; Jasra, R. V. *Eur. J. Org. Chem.* **2006**, 3175; (d) Khan, N. H.; Kureshy, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. *Coord. Chem. Rev.* **2008**, *252*, 593; (e) Kureshy, R. I.; Khan, N. H.; Abdi, S. H. R.; Patel, S. T.; Jasra, R. V. *Tetrahedron Lett.* **2001**, *42*, 2915.
25. (a) Khan, N. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Prathap, K. J.; Jasra, R. V. *Eur. J. Org. Chem.* **2008**, 4511; (b) Khan, N. H.; Agrawal, S.; Kureshy, R. I.; Abdi, S. H. R.; Pathak, K.; Jasra, R. V. *Chirality* **2010**, *22*, 153.
26. (a) Ready, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 2687; (b) Ready, J. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 1374; (c) Ready, J. M.; Jacobsen, E. N. *Angew. Chem.* **2002**, *114*, 1432.
27. (a) Haak, R. M.; Wezenberg, S. J.; Kleij, A. W. *Chem. Commun.* **2010**, 2713; (b) Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4760.
28. Liu, H.; Shau, X.-B.; Jia, M.-X.; Jiang, X.-K.; Li, Z.-T.; Chen, G.-J. *Tetrahedron* **2005**, *61*, 8095.
29. Evans, D. A.; Truesdale, L. K. *Tetrahedron Lett.* **1973**, *49*, 4929.
30. Belokon, Y. N.; Ishibashi, E.; Nomura, H.; North, M. *Chem. Commun.* **2006**, 1775.
31. Maity, N. C.; Abdi, S. H. R.; Kureshy, R. I.; Khan, N. H.; Suresh, E.; Dangi, G. P.; Bajaj, H. C. *J. Catal.* **2010**, *277*, 123.