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Coordination Chemistry Reviews 252 (2008) 593–623
COORDINATION CHEMISTRY REVIEWS
www.elsevier.com/locate/ccr

Review

Metal catalyzed asymmetric cyanation reactions

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Received 28 June 2007; accepted 14 September 2007
Available online 20 September 2007

Contents

Abstract

Chiral cyanohydrins are versatile building blocks for pharmaceuticals, agrochemicals and specialty materials. A number of efficient and successful synthetic methods have been developed however, the chiral catalytic method is one of the most attractive strategies where asymmetric addition of different source of cyanide to the carbonyl group of aldehydes and ketones was affected with the help of a chiral metal complex. This review would discuss the various methods for catalytic asymmetric synthesis of cyanohydrins derived from both aldehydes and ketones using different source of cyanide. The emphasis would be given to chiral Lewis acid metal complexes as efficient catalysts for cyanation reaction with the probable mechanism, wherever necessary.

Keywords: Enantioselective cyanation reaction; Lewis acid metal complexes; Carbonyl compounds; Chiral cyanohydrins; Cyanide

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doi:10.1016/j.ccr.2007.09.010

1. Introduction

Chiral cyanohydrins are well-known natural products and versatile synthetic intermediates for pharmaceuticals and agrochemicals. They are present in over 3000 plants, bacteria, fungi, and many insects as antifeedants forming part of the self-defense system [1–3]. Cyanohydrins also serve as source of nitrogen for the biosynthesis of amino acids [4]. For the synthetic organic chemists, chiral cyanohydrins offer an immense opportunity for synthesizing various chiral compounds. Different enantiomers of chiral compounds have different *in vivo* activity spectrum and metabolic transformations and/or degradation as the molecule-binding sites are chiral in nature. Therefore, chiral compounds for biological applications are required to be synthesized in all possible stereo-isomers in their high chiral purity. The development of straightforward synthetic procedures for such compounds, which also result in a high degree of stereoselectivity, therefore, has prime importance. To this effect chiral cyanohydrins may serve as stereochemically pure starting materials [5–11]. They can easily be prepared by the addition of cyanide to a carbonyl compound in the presence of a synthetic chiral catalyst or an enzyme. The resulting cyanohydrins are readily transformed into a variety of compounds such as α-hydroxyacids [12], α-aminoacids [13–22], α-hydroxyaldehydes, α-hydroxyketones [23,24], β-aminoalcohols, among others [25–37] (Fig. 1). Despite immense synthetic potential offered by chiral cyanohydrins in the synthesis of bio-active molecules, it is surprising that intensive research on this topic has started only relatively recently.

Among the various methods, catalytic enantioselective cyanation of aldehydes and ketones by new generation of catalysts is increasingly finding application in the syntheses of bio-active natural and synthetic compounds. Although, many methods of asymmetric cyanohydrin synthesis using enzyme and peptide that give high yield are well known [38–46], many synthetic chemists are apprehensive about using enzymatic procedures as they require the use of totally different laboratory set-up and reagents for which they are normally trained. Moreover, the flexibility of enzymatic process in term of accommodating different substrates and scale-up of the process to the economically viable scale are also limiting factors. Hence, recent advances in the field of metal complexes catalyzed asymmetric cyanation are about to deliver the much desired breakthrough for process scale synthesis of chiral cyanohydrins in high yields and excellent enantioselectivity [16].

This review covers the recent developments in metal catalyzed asymmetric synthesis of cyanohydrins derived from both aldehydes and ketones using different sources of cyanide. We

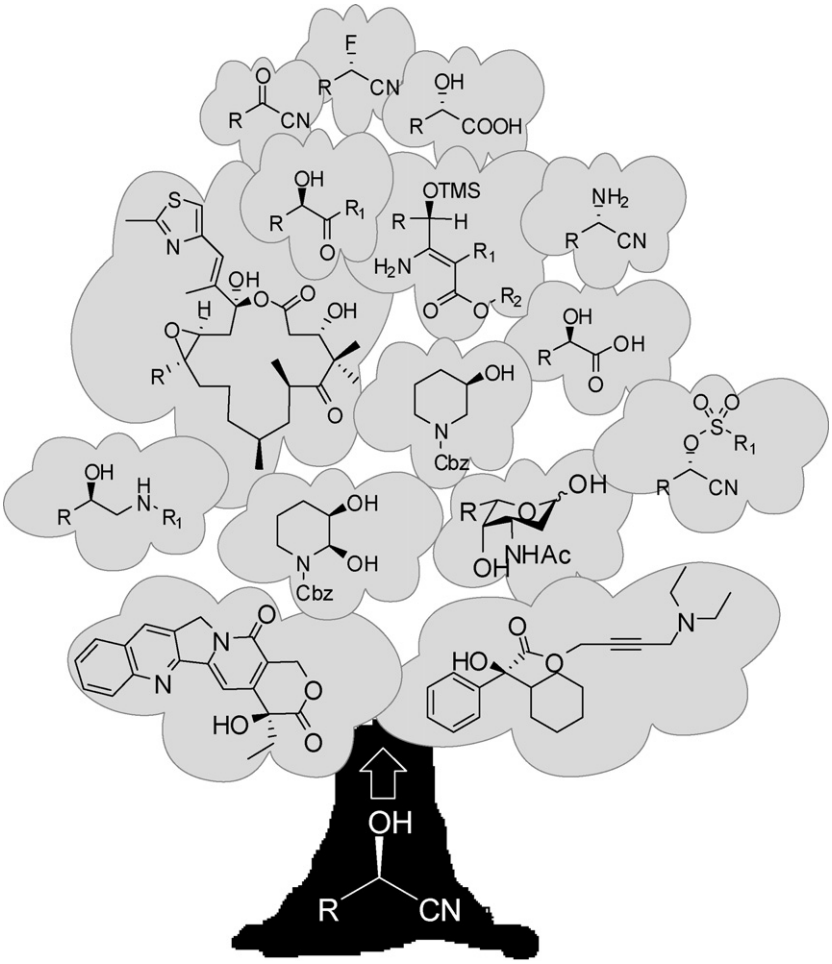


Fig. 1. Synthetic transformations of cyanohydrins.

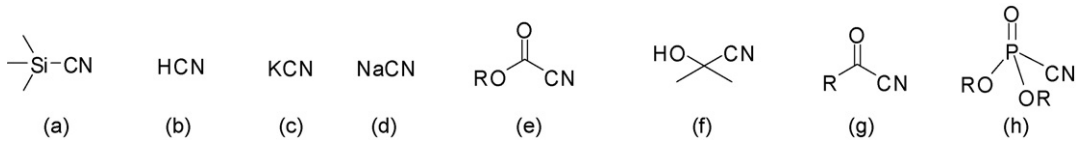


Fig. 2. Examples of cyanide sources.

expect that this review would provide timely update to previous major reviews [5,16,17,47–49]. The present review would deal with three major components of the metal catalyzed asymmetric cyanation, viz., source of cyanide, substrate and catalyst. The other important aspects such as reaction conditions that include temperature, solvent and role of additive and reaction mechanism would also be dealt with respective catalyst system.

2. Sources of cyanide

The preparation of cyanohydrins reviewed here has utilized a source of cyanide which in most cases is trimethylsilylcyanide (TMSCN). Although TMSCN is associated with several disadvantages, it is the most commonly used cyanide source in enantioselective cyanation of carbonyl compounds because it directly provides the TMS-protected cyanohydrin. The protecting group prevents racemization by checking the reverse reaction to occur. However, TMSCN is prohibitive for large-scale production due to its high cost. For that reason, inexpensive hydrogen cyanide (HCN) is often used on large-scale production of enantioenriched compounds, e.g., mandelonitrile derivatives using enzyme catalysis [50]. However, both TMSCN and HCN are extremely toxic. Therefore, efforts are being made to look for cyanation reaction using inexpensive and less toxic cyanide source that can easily be handled for the production of protected cyanohydrins. The Fig. 2 shows other cyanide sources viz., alkyl cyanoformates (**e**), acetone cyanohydrin (**f**), acetyl cyanide (**g**) and alkyl cyanophosphorylates (**h**) besides, most frequently used TMSCN (**a**) HCN, (**b**) potassium cyanide, (**c**) and sodium cyanide (**d**).

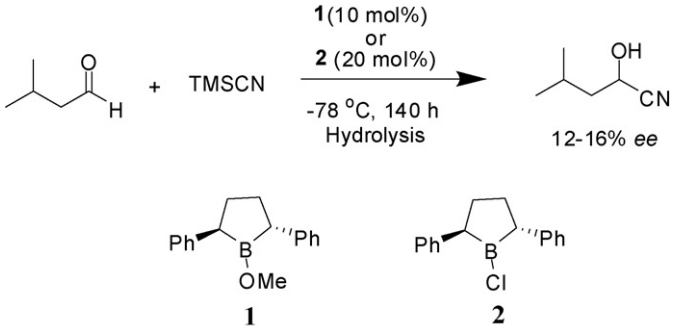
3. Use of TMSCN in metal catalyzed asymmetric cyanation of carbonyl compounds

Under this section, we would present the literature highlights for the cyanosilylation of aldehydes using various chiral coordination compounds as catalysts.

3.1. Cyanosilylation of aldehydes

3.1.1. Catalysts for the cyanation of aldehydes

Historically, trimethylsilyl cyanide (TMSCN) in the presence of certain catalysts, such as $TiCl_4$ [51], KCN/18-crown-6 [52], ZnI_2 [52,53], Me_3SiOTf [54] were reported to react with ketones to afford, after aqueous work-up a cyanohydrin. In 1986, Reetz et al. reported [55] the first enantioselective addition of TMSCN to an aldehyde (isobutanal) catalyzed by boron-based optically active Lewis acid. Although, only moderate yields (45–55%) and poor enantioselectivity (12–16% ee) could be



Scheme 1. Boron-based catalysts for asymmetric cyanosilylation reaction.

achieved at a very low temperature with prolonged period of time, (Scheme 1), this report effectively demonstrated the potential of Lewis acid catalyst systems in asymmetric cyanohydrin synthesis.It is surprising that after the first example for the use of chiral boron-based catalyst, another boron-based chiral catalyst was reported only after two decades by Corey et al. [56] where cyanosilylation of a variety of aliphatic and aromatic aldehydes was carried out in the presence of various phosphine oxides as a base additive at −20 °C in toluene as a solvent (Fig. 3). Best results in terms of yield (97%) and ee (97%) were obtained with triphenylphosphine oxide (0.2 equiv.) in 40–144 h. Another highlight of the system was the recovery of chiral catalyst after the completion of the catalytic reaction.

3.1.2. C_2 and C_1 symmetric chiral Schiff bases and related ligands

C_2 and C_1 symmetric chiral Schiff bases derived from the condensation of salicylaldehydes with suitable chiral amines are among the most successful types of ligands used in the enantioselective addition of cyanide to ketones and aldehydes. They are easy to synthesize and alter for their electronic and steric features as per the specific needs of the reaction (Scheme 2).

Schiff base ligands became one of the most frequently employed structural entities after Inoue et al. [19,57] used it

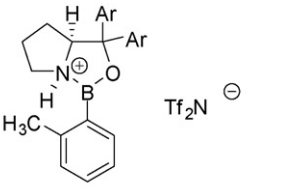


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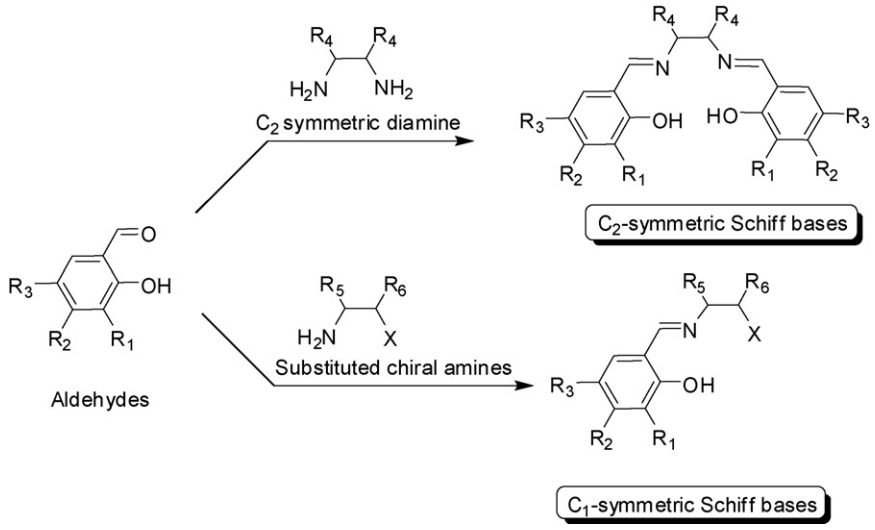
Fig. 3. Structure of chiral boron derived catalysts for the asymmetric cyanation reaction.



Scheme 2. Synthesis of C_2 and C_1 symmetric Schiff bases.

for the first time for the enantioselective addition of TMSCN to aldehydes. Table 1 summarizes the application of C_2 and C_1 symmetric Schiff base ligands with titanium metal as catalyst for the preparation of enantiomerically enriched trimethylsilyl ether of cyanohydrins using TMSCN as a source of cyanide. Reactions are catalytic with respect to the titanium complex. A close look into the Table 1 suggests that among the C_2 and C_1 symmetric chiral salen ligand, C_2 symmetric salen ligands with cyclohexane collar and *t*-butyl group on three and five positions of the salicylaldehyde (entry 5, structure **8**) is by far the best in Ti-catalyzed asymmetric addition of TMSCN to aldehydes.

The explanation for the high catalytic activity and enantioselectivity for the C_2-symmetric chiral salen ligand with titanium metal ion was investigated by Belokon et al. [64]. Based on single crystal X-ray studies, they have suggested that in the presence of water the titanium complex of salen ligand is converted into a O-bridged dimeric complex **10** as shown in Scheme 3. This dimeric complex generates a species **10a** in presence of excess of TMSCN which was well characterized by infrared, CD and NMR studies. Based on these structural information and product distribution of a catalytic run, a possible mechanism was proposed (Scheme 3) [77]. Accordingly, the dicyanide complex **10b** was obtained from **10a** which interacts with mononuclear benzaldehyde adduct **10c** to generate the key intermediate binuclear complex **10d**. Complex **10d** contains both an activated aldehyde and a titanium cyanide bond. Intramolecular transfer of cyanide within complex **10d** generates complex **10e** containing a titanium bound cyanohydrin. Consequently, trimethylsilylation of complex **10e** gives the product and dicyanide complex **10f**. Displacement of one of the weakly bound cyanide ligands of complex **10f** by benzaldehyde would regenerate complex **10d**. The catalytic cycle also correctly predicts the sense of asymmetric induction through a transition state (**10g**). Thus coordination of the aldehyde so as to minimize interactions between the aldehyde substituent and the cyclohexane ring of the ligand results in an orientation in which the *re*-face of the aldehyde is exposed to intramolecular attack by the coordinated cyanide leading to the (*S*) enantiomer of cyanohydrin trimethylsilyl ether.

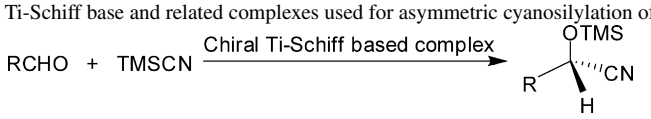
Entry 11 of the Table 1 comprises a C_2-symmetric ligand which is not a Schiff base but has been included here as this type of ligand would otherwise be an isolated structural entity as far as the asymmetric cyanation reaction is concerned. This structure motif was designed for its close resemblance to many effective chiral ligands reported in the literature [69,72–74,76] having free hydroxyl groups or amino groups that coordinated with a metal ion (mostly titanium) to produce catalytically active Lewis acid center.

(**d**) Various authors have used **14** with $Ti(O^iPr)_4$ as a catalyst for the cyanosilylation of benzaldehyde in various solvents at different catalyst loading and temperature. The optimum yield and enantioselectivity (86%, 59% ee) were achieved in CH_2Cl_2 at a catalyst loading of 5 mol% at −78 °C in 4 h. These optimized conditions were then used for the cyanosilylation of various substituted benzaldehydes where the highest enantioinduction (ee, 98%) was achieved with 2-methylbenzaldehyde.

C_1 symmetric chiral Schiff base ligands used for the cyanosilylation of aldehydes were mostly prepared by the reaction of a salicylaldehyde with a chiral aminoalcohol. Catalysts prepared from this ligand system could lead to enantioselectivities up to 92% for addition of TMSCN to aldehydes (Table 1, entries 12–19). Oguni and co-workers [69] suggested a mechanism for such a high enantioselection based on the structural features of the catalyst where shielding of one face of the activated aldehyde occurred by the substituents on the ligand (Scheme 4).

Feng et al. reported a series of titanium complexes **17** derived from hydrogenated C_1-symmetric Schiff bases as ligand (entry 14, Table 1). These complexes were used as catalysts for the cyanosilylation of various aliphatic, aromatic conjugated and heteroaromatic aldehydes to give the corresponding trimethylsilyl ethers of cyanohydrins in excellent yields (90–99%) with ee up to 94% under mild reaction conditions [71]. In view of the high chiral induction achieved by changing the substituents with different electronic and steric features, the authors proposed a

Table 1
Ti-Schiff base and related complexes used for asymmetric cyanosilylation of aldehydes



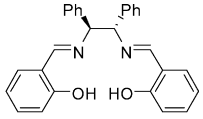
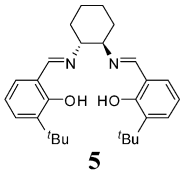
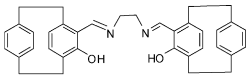
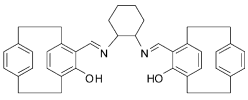
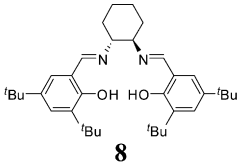
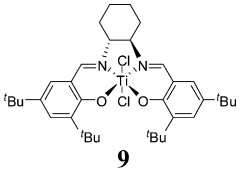
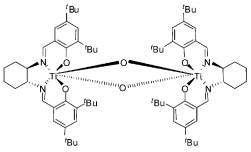
Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
C_2 symmetric Ti-Schiff base and related complexes					
1	 **4** 11 mol% with 10 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 24–36 h	58–72	22–87	[58,59]
2	 **5** 26 mol% with 20 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 24–120 h	55–70	62–77	[60]
3	 **6** 5-10 mol% with Ti(O^{i}Pr)$_4$ The catalyst is recoverable	Solvent = CH_2Cl_2; temperature = −78 °C (−5 to 25 °C); time = 24–120 h (72–4 h)	80–90; 80	82–84 (22–48)	[61]
4	 **7** 5-10 mol% with Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 24–120 h	90	35–48	[61]
5	 **8** 22 mol% with 20 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = −80 °C; time = 24–100 h	40–100	10–88	[62,63]
6	 **9** 0.1 mol%	Solvent = CH_2Cl_2; temperature = RT; time = 24 h	100	86	[64]
7	 **10** 0.1 mol% with trace of water	Solvent = CH_2Cl_2; temperature = RT; time = 1 h	100	52–92	[64]

Table 1 (*Continued*)

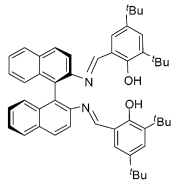
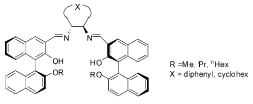
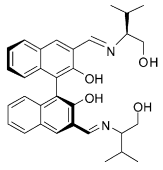
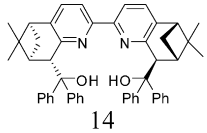
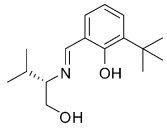
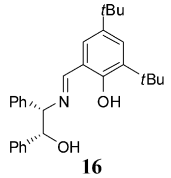
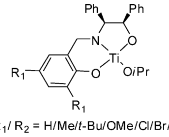
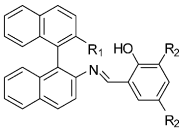
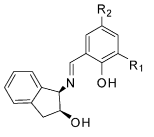
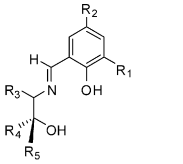
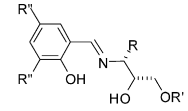
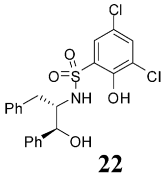
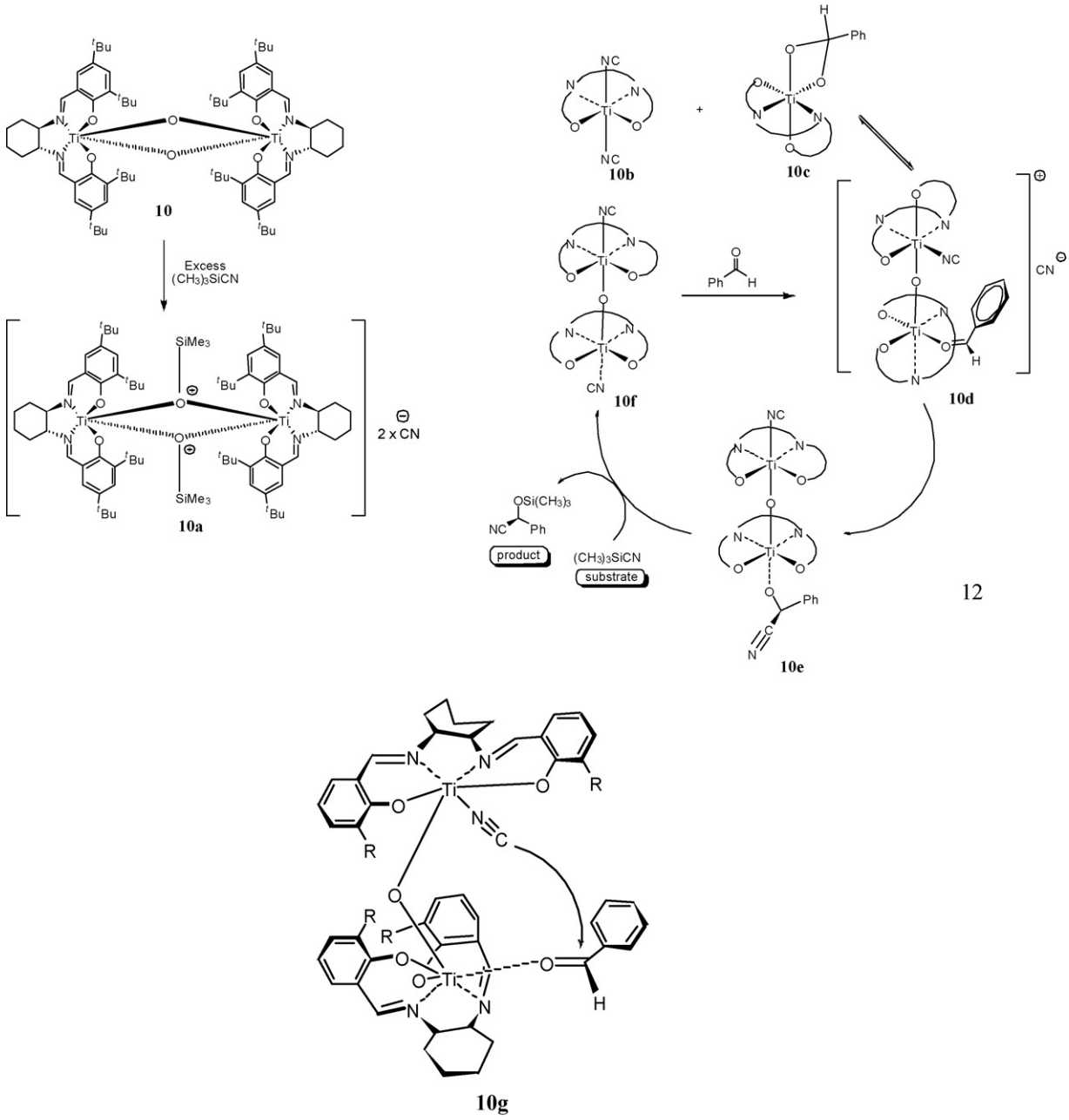
Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
8	 **11** 22 mol% with 20 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 120 h	63–92	42–96	[65]
9	 R =Me, Pr, ^{i}Hex X = diphenyl, cyclohex **12** 10-25 mol% with 8-20 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = RT; time = 2.5–18 h	64–78	55–85	[66]
10	 **13** 10 mol% with 20 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = 6 °C; time = 4 h	100	86	[67]
11	 14 5-10 mol% with 1.5-10 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2 (optimized); temperature = −78 °C (optimized); time = 4 h	11–86	2–98	[68]
C_1 symmetric Ti-Schiff base complexes					
12	 **15** With 20 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = −80 °C; time = 12–36 h	58–81	65–91	[69]
13	 **16** 40 mol% with 20 mol% Ti(O*i*Pr)$_4$	Solvent = CH_2Cl_2; temperature = −80 °C; time = 60 h	31–76	49–92	[70]
14	 R_1/ R_2 = H/Me/*t*-Bu/OMe/Cl/Br/*i*-Pr/CH_2Ph **17** 1-20 mol%	Solvent = CH_2Cl_2; temperature = −20 °C; time = 20–44 h	33–99	80–94	[71]

Table 1 (*Continued*)

Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
15	 R_1 = NH_2, OH, R_2=*t*Bu, Cl **18** With 20 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 36 h	82–98	34–66	[65]
16	 R_1 = H, *t*-Bu, OCH_3, Br, R_2 = H, *t*-Bu, CH_3, Br **19** With 20 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 36 h	15–73	0–85	[72,73]
17	 R_1 = *t*-Bu, R_2 = *t*-Bu, $CH(CH_3)_2$ R_3-R_4 = $CH_2C_6H_4$ **20** With 20 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 36 h	16–85	12–85	[74]
18	 R=Ph, *n*-Pr, R'=H, Me,CH_2Ph, CPh_3, $SiiPr_3$, R''=H,*t*Bu, **21** With 20 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −40 °C; time = 96 h	77–100	28–77	[75]
19	 **22** 10 mol% with 10 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −65 °C; time = 48 h	90–100	90–96	[76]

working model (Scheme 5) for the transition states during the catalytic cycle. They proposed that the difference in chiral induction effects comes from the formation of the N–Ti bond and there remains only one isopropoxy on titanium instead of two. In this transition state, the *Re* face of the carbonyl of benzaldehyde is much more accessible to a nucleophile than the *Si* face since the latter is strongly shielded by the nearby phenyl subunits (model 17a, Scheme 5). In the other aspect of C=O the interaction between the aldehyde and Ti(IV) is hindered by large steric hindrance between the two phenyl subunits (model 17b, Scheme 5). The nucleophile CN^- will preferably attack the highly polarized C=O of benzaldehyde from a less stereohindered direction (*Re*) to give the product in the (*S*)-configuration.

Choi et al. [76] reported a sulfonamide ligand **22** derived from chiral 1,2-aminoalcohol. Structurally this ligand is closely related with C_1-symmetric Schiff bases hence included here. 10 mol% of ligand **22** with 10 mol% of $Ti(O^iPr)_4$ was good catalyst for cyanosilylation of both aliphatic and aromatic aldehydes at −65 °C to obtain the corresponding cyanohydrins with up to 96% ee.



Scheme 3. Plausible mechanism and postulated transition states for the cyanosilylation of aldehyde catalyzed by titanium Schiff base complex.

3.1.3. Amide-based ligands with titanium

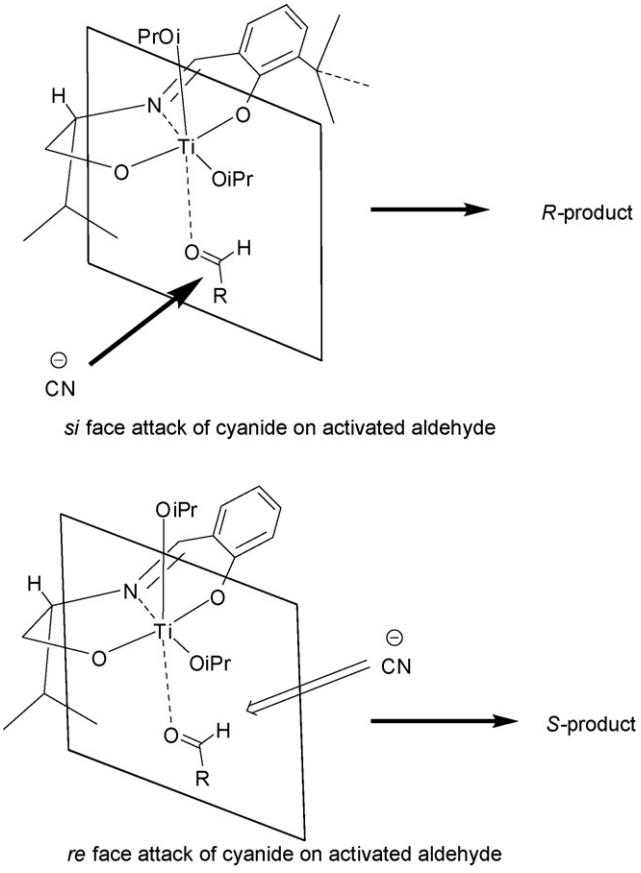
Other highly used ligands are the C_2 symmetric amides derived from an enantiopure 1,2-diamine and an acid including pyridyl or pinene motif (Table 2). These systems invariably required a very low temperature for extended time periods in order to give high enantioselectivity for the product in reasonably high yields. However, both aromatic and aliphatic aldehydes were effectively cyanosilylated with very high ee values using this class of catalysts with TMSCN as a cyanide source.

An additional class of proline-based C_2-symmetric diamide ligand was explored for the cyanosilylation of various aldehydes (Table 2, entry 6). Though there was no metal involved, this report is included here to provide useful information on activation of TMSCN and substrate by the acidic and basic sites present on the ligand [82].

A chiral sulfoximine ligand with titanium **29** was reported by Bolm and Müller [83] for the cyanation of various aromatic and aliphatic aldehydes using TMSCN as cyanide source (Scheme 6). The product cyanohydrin was obtained after the hydrolysis of its *O*-TMS ether in high ee (up to 91%) and yield (92%) at −50 °C in 20 h. Although this reaction was stoichiometric, we found that it would be worthwhile to include this example here for the sake of completeness of the review.

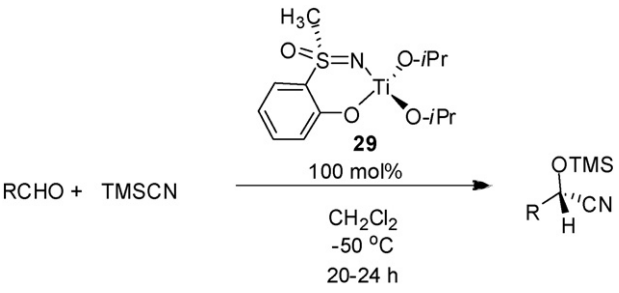
3.1.4. Binol-derived titanium complexes

Chiral binol-derived complexes have been investigated to catalyze the enantioselective cyanosilylation of various aldehydes

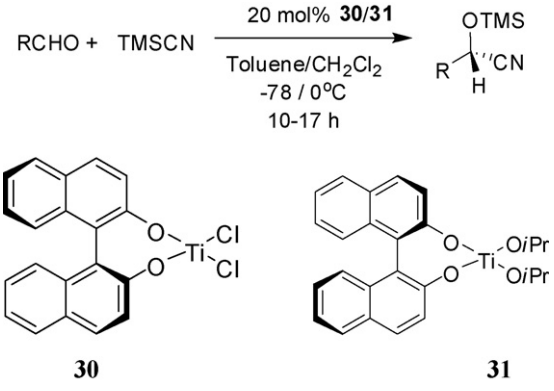


Scheme 4. The proposed mechanism of cyanosilylation of an aldehyde using C_1 symmetric titanium complex for the *R* and *S* product formation.

with TMSCN [84]. Complex **30** gives 85% yield with 82% ee for the cyanosilylation of isobutanal at −78 °C in 10 h [85] while the complex **31** effected <10% ee (yield > 90%) for aromatic aldehydes at 0 °C in 17 h [86]. However, complex **31** gave moderate ee (33–75%) with >90% yield for cyanosilylated products of aliphatic aldehydes. This is a rare example in the literature where much higher ee values were obtained with aliphatic aldehydes as compared to aromatic aldehydes (Scheme 7).



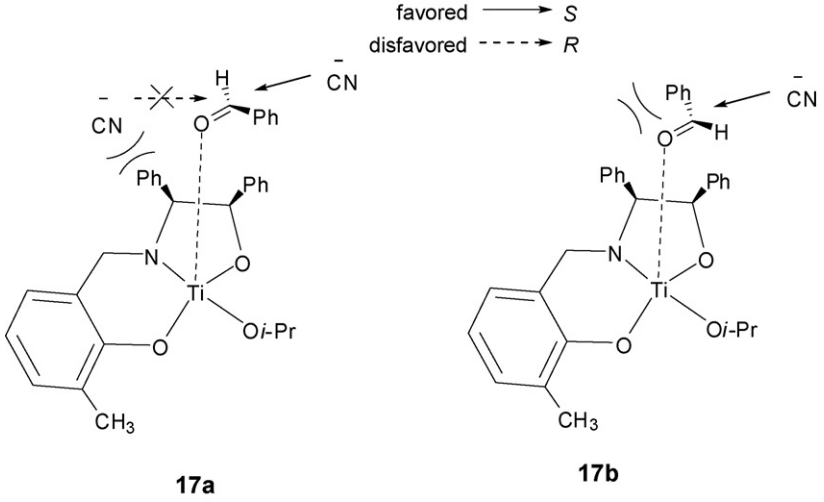
Scheme 6. Asymmetric cyanosilylation of aldehydes with titanium(IV) chiral sulfoximine complex.



Scheme 7. Trimethylsilylation of aldehydes catalyzed by titanium binol system.

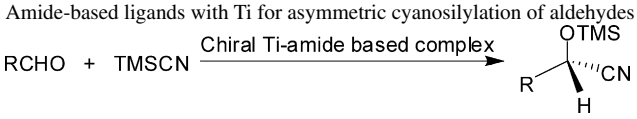
3.1.5. Titanium–chiral alcohol complexes

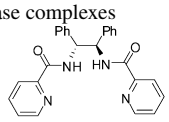
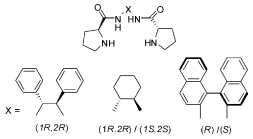
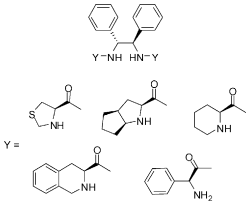
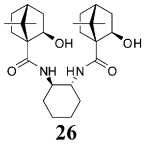
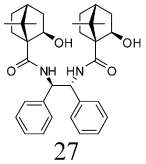
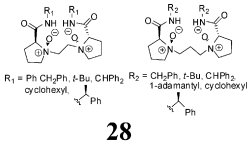
The use of poly-hydroxy ligand with titanium to catalyze asymmetric formation of cyanohydrin using TMSCN as cyanide source is among the earliest reports on this topic. Among such systems, the Taddol ligand **32** (Table 3, entry 1) was used to give a maximum ee of 96% with 79% yield at −78 °C in 12 h for the cyanosilylation of benzaldehyde using stoichiomet-



Scheme 5. Proposed working model for asymmetric cyanosilylation of benzaldehyde.

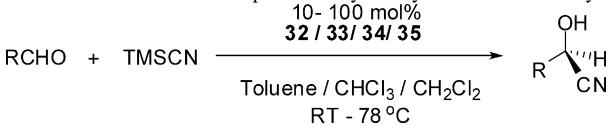
Table 2
Amide-based ligands with Ti for asymmetric cyanosilylation of aldehydes

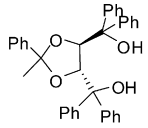
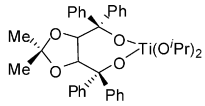
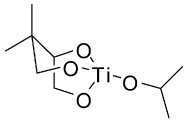
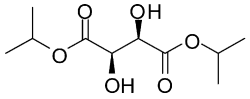


Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
Ti–amide base complexes					
1	 23 1-10 mol% with $Ti(O^iPr)_4$	Solvent = CH_2Cl_2; temperature = RT; time = 4 h	95–95	57–60	[78]
2	 24 With10 mol% $Ti(O^iPr)_4$	Solvent = CH_2Cl_2; temperature = 0 °C; time = 14 h	49–86	18–55	[79]
3	 25 10-20 mol% with $Ti(O^iPr)_4$	Solvent = CH_2Cl_2; temperature = 0 °C; time = 14–17 h	63–98	16–84	[79]
4	 **26** 16.5 mol% with 15 mol% $Ti(O^iPr)_4$	Solvent = CH_2Cl_2 4A MS; temperature = −78 °C; time = 36–120 h	51–96	89–97	[80]
5	 27 16.5 mol% with 15 mol% $Ti(O^iPr)_4$	Solvent = CH_2Cl_2 4A MS; temperature = −78 °C; time = 6 h	72–92	93–99	[81]
6	 **28** 5 mol %	Solvent = CH_2Cl_2; temperature = −20 °C; time = 10 h	57–92	53–73	[82]

ric quantities of the reagents [87]. An attempt to reduce the quantity of the reagent decreased the yield concomitantly. A variant of titanium complex of Taddol **33**, however, while catalytic, imparted only moderate enantioselectivity at 10 mol% catalysts loading. This system also required 10 mol% $Ph_3P{=}O$ as an additive, in absence of which the reaction does not proceed [88]. Callant et al., [89] used a stoichiometric quantity of titanium-chiral trialcohol complex **34** to convert benzaldehyde to (*S*)-mandelonitrile in 92% yield with 76% ee after 2 h at −20 °C in the presence of molecular sieves (MS) 4A using TMSCN as a source of cyanide (Table 3, entry 3). Interestingly, Callant et al., originally used **34** as a catalyst with HCN as an inexpensive source of cyanide for the asymmetric cyanation of aldehydes but failed to obtain any conversion. Hayashi et al., [90] reported the use of Sharpless epoxidation catalyst (L-(+)-diisopropyl tartrate **35** with $Ti(O^iPr)_4$) in a sub-stoichiometric quantity for the

Table 3
Titanium–chiral alcohol complexes for cyanosilylation of benzaldehyde

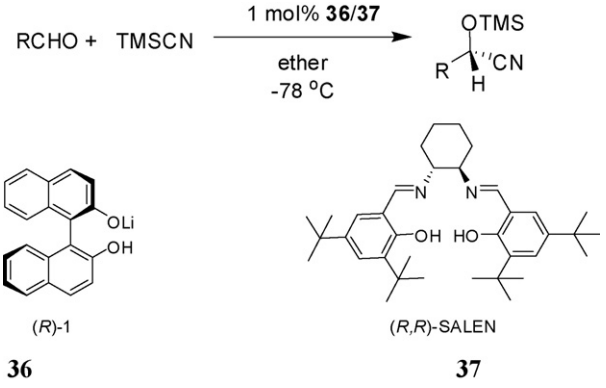


Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
1	 **32** 110 mol% with 100 mol% $TiCl_2(O^iPr)_2$	Solvent = toluene 4A MS; temperature = −78 to 22 °C; time = 12–120 h	66–89	68–93	[87]
2	 **33** 10 mol%, $Ph_3P{=}O$ 10 mol% (optimized)	Solvent = $CHCl_3$ (optimized); temperature = −10 °C (optimized); time = 20 h	95 (optimum)	50 (maximum)	[88]
3	 **34** 100 mol%	Solvent = CH_2Cl_2 4A MS; temperature = −20 °C; time = 2 h	92	76	[89]
4	 **35** 22 mol% with 20 mol% Ti ($OiPr)_4$ and 40 mol% *i*PrOH	Solvent = CH_2Cl_2; temperature = 0 °C; time = 18 h	79–92	60–91	[90]

preparation of enantioenriched cyanohydrins at 0 °C. The use of 40 mol% of propane-2-ol as an additive was essential in order to obtain high enantioselectivity (ee up to 91%). The role of the additive (propan-2-ol) as supported by mechanistic studies was to hydrolyze TMSCN to generate HCN which eventually initiates the reaction.

3.1.6. Chiral base catalyst

Addition of TMSCN to aldehydes and ketones is predominantly catalyzed by a chiral Lewis acid. Kagan and co-workers for the first time showed the application of chiral bases as catalysts for the addition of TMSCN to aldehydes [91,92]. They used a range of chiral phenols including binol **36** and Schiff bases **37** (Scheme 8). Out of several binaphthols, the monolithium salt of chirally pure binol **36** was a better catalyst for the cyanosilylation of aromatic aldehydes giving a maximum of 59% ee for the cyanohydrin of *p*-tolualdehyde in 15 min at −78 °C in ether. However, this system inducted poor enantioselectivity for aliphatic and many other aromatic aldehydes. Further, this protocol required a great deal of care as the reaction is highly exothermic making this methodology of limited application. On the other hand, the monolithium salt of chiral salen **37** was a better catalyst than the monolithium salt of binol **36** under similar reaction conditions. For example *m*-tolualdehyde gave 97% ee with 88% yield in 20 min for its *O*-TMS cyanohydrin with **37** while catalyst **36** inducted 55% ee (yield, 93%) in 40 min for the same reaction.



Scheme 8. Cyanosilylation of aldehydes using monolithium salt of chirally pure binol and salen ligand.

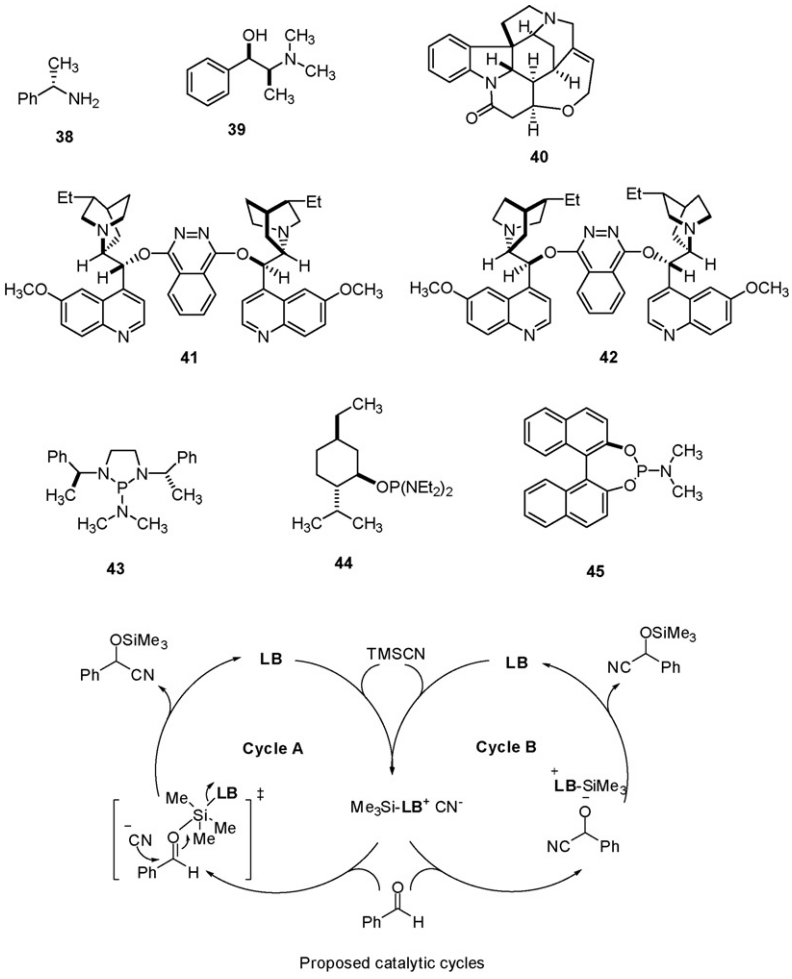


Fig. 4. Structure of Lewis bases (LB) used as catalyst for the addition of trimethylsilyl cyanide to aldehydes and the proposed mechanism.

Recently, Ishihara and co-workers reported [93] an improvement over the Kagan-protocol by using the catalyst **36** with a catalytic amount of water or alcohol as a co-activator. Using this protocol a maximum of 98% ee with >99% yield was achieved for the cyanosilylation of benzaldehyde in 1 h at −78 °C in toluene.

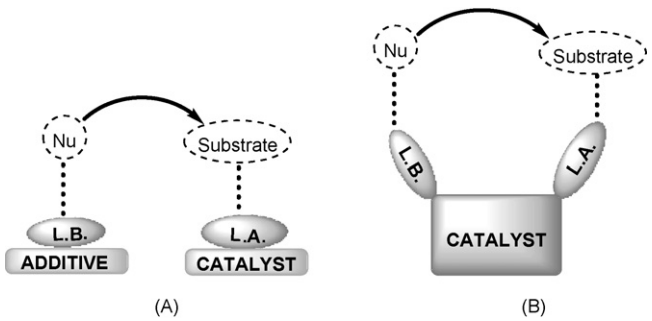
Later, Denmark and Chung reported [94] an extensive mechanistic study on Lewis base catalyzed addition of trimethylsilyl cyanide to aldehydes. During their study they surveyed several chiral amines (**38**–**42**) and phosphines (**43**–**45**) (Fig. 4) for the addition of TMSCN to several aldehydes in different solvents over a temperature range of −30 °C to RT. According to their study the reaction was first order with respect to aldehyde, first order in Lewis base (LB), and zeroth order in TMSCN, suggesting the formation of [Me_3Si–LB^+ CN^-] complex in the catalytic cycle. They also suggested that there can be at least two possible pathways (cycles A and B) for the product formation, however, in absence of low selectivity observed, it was not clear which pathway is operative.

3.1.7. Bifunctional catalysts

The use of a base additive is well known in asymmetric catalysis to activate nucleophile while the substrate is activated by an acidic site of the catalyst (Scheme 9, A). This dual activation phenomenon has led many researchers to fabricate catalysts having built in acid and base functionalities (Scheme 9, B). This class of catalysts is also known as a bifunctional catalyst. Some such catalysts used for the asymmetric cyanation of aldehydes using TMSCN as the source of cyanide, are tabulated in Table 4

.

Shibasaki and co-workers [103] in their efforts to develop multifunctional asymmetric catalysts conceptualized the ligand design where activation of substrates and nucleophiles occurs



Scheme 9. Dual activation of reactants by (A) two separate catalysts; (B) bifunctional catalysts.

Table 4
Bifunctional catalysts for cyanosilylation of aldehydes

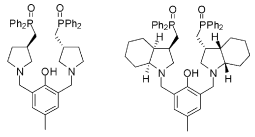
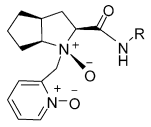
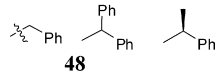
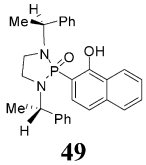
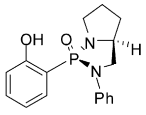
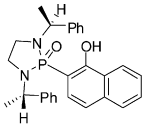
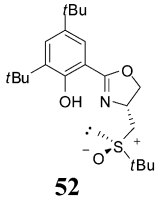
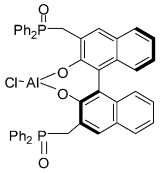
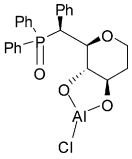
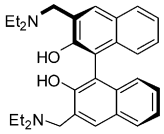
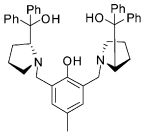
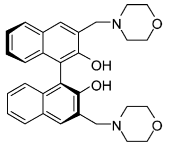
Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
1	 **46** **47** 10 mol% with 10 mol% $Ti(OiPr)_4$ 20 mol% $Ph_3P{=}O$ as Additive	Solvent = CH_2Cl_2/toluene; temperature = −10 to −20 °C; time = 24–36 h	54–80	34–87	[95]
2	 R = Ar, 1-adamentyl, cyclohexyl  **48** 10 mol% with 5 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −78 °C; time = 20–28 h	80–99	45–79	[96]
3	 **49** 40 mol% with 10 mol% $Ti(OiPr)_4$ and propan-2-ol 20 mol%	Solvent = CH_2Cl_2; temperature = 20 °C; time = 24 h	50–96	26–98	[97–99]
4	 **50** 40 mol% with 10 mol% $Ti(OiPr)_4$ and propan-2-ol 20 mol%	Solvent = CH_2Cl_2; temperature = 20 °C; time = 12 h	70–95	3–98	[100]
5	 **51** 40 mol% with 10 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = 0–20 °C; time = 24 h	80–98	8–90	[101]
6	 **52** 10 mol% with 9 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −84 °C; time = 60 h	48–85	10–57	[102]

Table 4 (*Continued*)

Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
7	 **53** 9 mol% with 36 mol% phosphine oxide	Solvent = CH_2Cl_2; temperature = −40 °C; time = 37–96 h	87–100	90–98	[103]
8	 **54** 5-9 mol%	Solvent = CH_2Cl_2; temperature = −60 °C; time = 38–76 h	82–98	70–80	[104]
9	 **55** 10 mlo% with 10 mol% Me_2AlCl and 40 mol% Ph_3PO	Solvent = toluene MS 4A; temperature = −20 °C; time = 3.5–48 h	70–99	70–>98	[105,106]
11	 **56** 11 mol% with 10 mol% $AlMe_3$ (optimized)	Solvent = PhCl (optimized); temperature = −4 °C; time = 24 h	50–80	57–86	[107]
12	 **57** 10 mol% with 10 Me_2AlCl and HMPA as additive	Solvent = hexanes (optimized) MS 4A; temperature = −20 °C; time = 3–48 h	92	92–99	[108]

simultaneously at the Lewis acid and the Brönsted base moiety in the catalyst **53**, thus affording high enantioselectivity (Fig. 5A). Based on kinetic studies they proposed a working model of the transition state (Fig. 5B) for the cyanosilylation of aldehydes using TMSCN as a source of cyanide. In this model, aldehyde positioned itself at the apical site of the pentavalent aluminum which is in close proximity to the internal phosphine oxide. TMSCN, interacting with the internal phosphine oxide, could then transfer cyanide to the aldehyde thus giving the product in desired enantioselectivity.

3.1.8. Pyridine-2,6-bisoxazoline (pybox)-based complexes

Pyridine-2,6-bisoxazoline (pybox) is another versatile ligand that can be used in a variety of enantioselective reactions. Although titanium is more frequently used with variety of ligand systems for enantioselective cyanation reaction, it is conspicuously absent with pybox ligand. Iovel and co-workers in 1997 for the first time used pybox ligand with $AlCl_3$ in enantioselective cyanosilylation of aldehydes [109] (Table 5, entry 1). This catalyst afforded high yields of a variety of cyanohydrins, but the enantiomeric excess obtained for the reaction with benzalde-

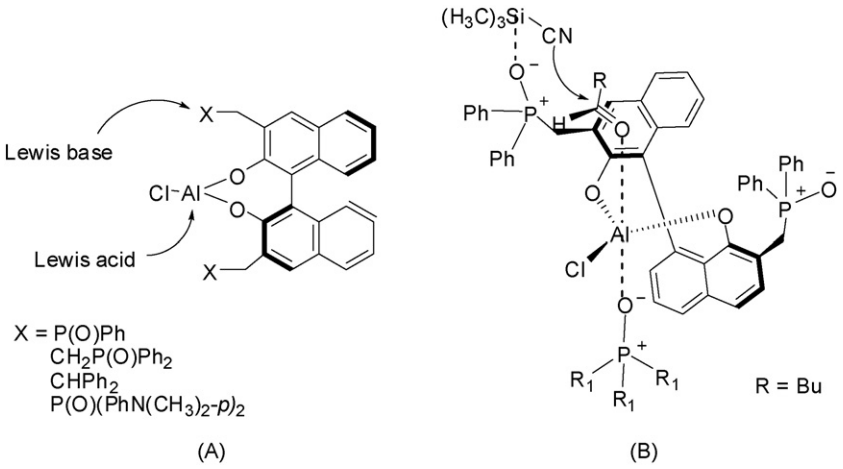
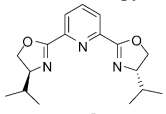
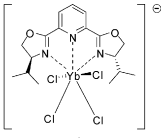
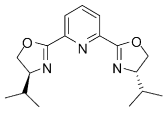
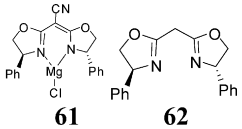


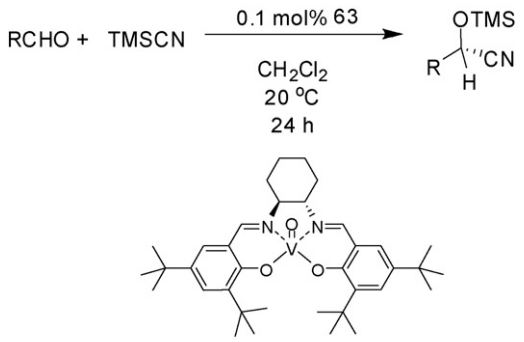
Fig. 5. Structure for chiral Al–binol complex as multifunctional asymmetric catalyst.

hyde was maximum (90% ee). Later on, Greeves et al. [110,111] used pybox ligand system with lanthanum metals (Specifically ytterbium) as catalyst for cyanosilylation of aldehydes. This system was quite active at moderate temperatures for a variety of aliphatic and aromatic aldehydes. Due to the congenial reaction conditions and short reaction time it has been suggested that this ligand system deserves more studies in terms of metal, additive and ligand design, etc.

Due to the close structural resemblance with pybox, bidentate ligands derived from bisoxazoline (Table 5, entry 4) have been included here. Mg metal complex of these ligands found application as catalysts in the cyanosilylation of various aldehydes.

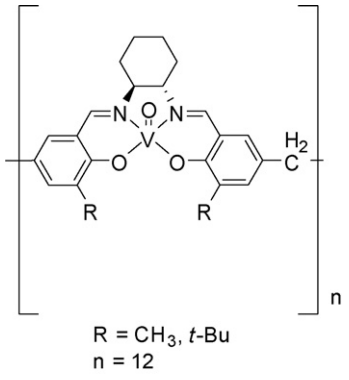
Table 5
Pyridine-2,6-bisoxazoline (pybox)-based complexes for cyanosilylation of aldehydes

Entry	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
Pyridine-2,6-bisoxazoline (pybox)-based complexes					
1	 **58** 20 mol% with 20 mol% $AlCl_3$	Solvent = CH_2Cl_2; temperature = RT (4 h) 0–10 °C (16 h)	87–92	44–90	[109]
2	 **59** 5 mol%	Solvent = CH_3CN (optimized); temperature = 0 °C-RT; time = 1 h	88	67	[110,111]
3	 **60** 20 mol% with 10 mol% $YbCl_3$	Solvent = CH_3CN (optimized); temperature = 0 °C; time = 1.5 h	88	67	[112]
4	 **61** **62** 20 mol% of **61** and 12 mol% of **62**	Solvent = CH_2Cl_2/C_2H_5CN; temperature = −78 °C; time = 5–45 h	24–94	52–95	[113]



63

Scheme 10. Cyanosilylation of aldehydes using oxo-vanadium(IV) complex.

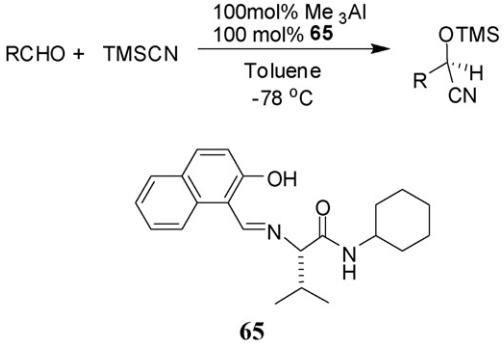


64

Fig. 6. Structure of V(V) polymeric salen complex.

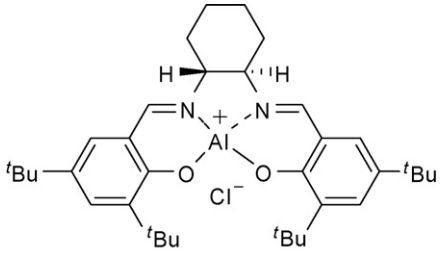
Interestingly, the Mg complex **61** with **62** was more enantioselective for cyanosilylation of aliphatic aldehydes (ee up to 94%) as compared to benzaldehyde (ee, 52%) [113].

So far in this review we have organized the literature based on ligand types used with mostly titanium metal as catalyst for cyanosilylation of aldehydes. However, some of the ligand systems described in previous sections and a few others have also been used as catalysts in combination with various other metal ions. Hence it would be convenient to organize these systems based on the metal types.



65

Scheme 11. Cyanosilylation of aldehydes using Schiff base-capped peptides.



66

Fig. 7. Structure of Al–salen complex for cyanosilylation of aldehydes.

3.1.9. Vanadium-based catalysts

Belokon et al. [114,115] while working on Ti–salen system for asymmetric cyanation reactions also prepared its oxo-vanadium(IV) complex **63** and showed that this complex is far more active than its Ti-counterpart (Scheme 10) (for comparison with Ti system please refer to Table 1, entry **6**).

Accordingly, this complex **63** with a catalyst loading of 0.1 mol% is sufficient to catalyze aromatic and aliphatic aldehydes into corresponding *O*-trimethylsilyethers of cyanohydrins with 94% ee and >95% yield in 24 h at ambient temperature. Later, Khan et al. reported a polymeric version of Belokon's vanadium catalyst.

The V(V)–polymeric salen complex **64** (Fig. 6) although soluble in the reaction medium (CH_2Cl_2), could, however, be easily precipitated out with the use of a non-polar solvent in a post catalysis work-up, hence it was recycled without any loss in their performance for the reported four cycles. The polymeric complex **64** was more active (reaction time 18 h) than its monomeric version as reported with the use of Belokon's vanadium complex **63** for similar product yields and ee of aliphatic and aromatic *O*-trimethylsilyl cyanohydrins at 5 mol% catalyst loading [116].

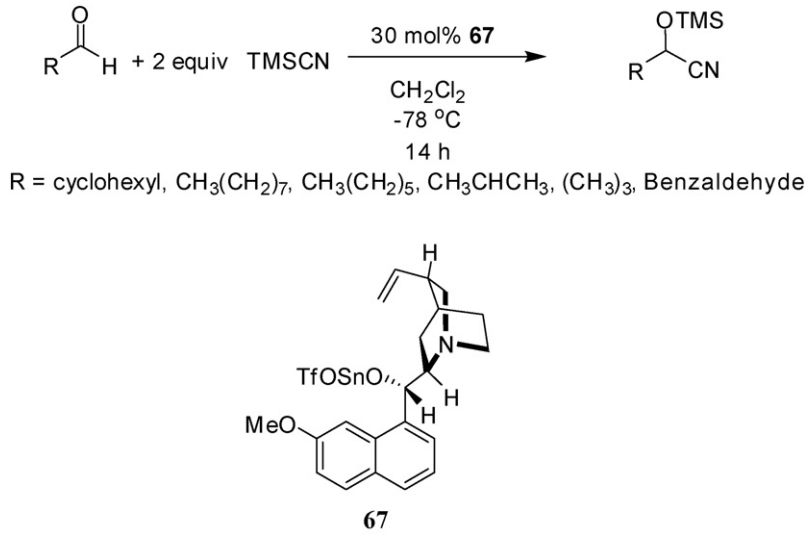
3.1.10. Aluminum complexes

We have already included some of the Al-based complexes along with bifunctional and pybox catalysts. However, it is pertinent to include one of the earliest reports on Al-catalyzed systems used in asymmetric cyanation reactions, such as Schiff base-capped peptides **65** (Scheme 11). Though, this system is not catalytic in true sense, it has been shown that Al can also be effectively used to catalyze cyanation reaction. The ligand **65** with Me_3AlCl produces cyanohydrins of various aliphatic and aromatic aldehydes in excellent yield (66–92%) with good ee (37–71%) in 0.5–24 h at −78 °C [117].

Recently, Kim and co-workers reported [118] the Al–salen complex **66** (Fig. 7) at a catalyst loading of 1 mol% for the cyanosilylation of different aldehydes in the presence of $Ph_3P{=}O$ as an additive at −40 to −50 °C in CH_2Cl_2. Excellent yields (91–96%) with 72–86% ee were achieved in 18–26 h for *O*-TMS ether of respective cyanohydrins.

3.1.11. Tin complexes

The sole example of a tin-complex **67** catalyzed asymmetric cyanation of aldehydes was reported by Kobayashi as early as 1991 [119]. This complex at 30 mol% loading catalyzes the



Scheme 12. Cyanosilylation of aldehydes using tin-complex.

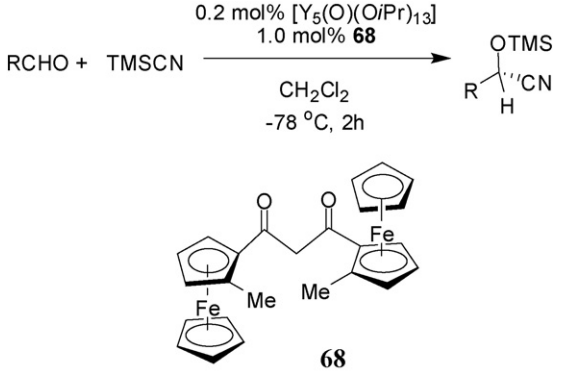
asymmetric addition of TMSCN to aldehydes at −78 °C in 14 h, however, only aliphatic aldehydes were successful candidates to give up to 96% ee with 79% yield of *O*-TMS ether of cyanohydrins but this system failed to catalyze the formation of cyanohydrin from benzaldehyde (Scheme 12).

3.1.12. Yttrium complexes

Abiko and Wang [120,121] reported a yttrium complex of the chiral acetoacetate analogue of 1,3-bis-(2-methylferrocenyl)propane-1,3-dione **68** as an efficient catalyst for asymmetric addition of TMSCN to aldehydes (Scheme 13). The reaction recipe required 1 mol% of **68** with 0.2 mol% of $[Y_5(O)(O^iPr)_{13}]$ to give *O*-TMS ether of cyanohydrins in excellent yield (up to 98%) with ee up to 91% at −78 °C in 2 h.

3.1.13. Bismuth catalysts

Wada et al. [122] reported some of the interesting results on asymmetric cyanosilylation of aldehydes and ketones along with its non-chiral version using a bismuth complex generated *in situ* by the interaction of *n*-BuLi and dialkyl ester of tartaric acid with $BiCl_3$. Their protocol gave quantitative yields of respective *O*-TMS cyanohydrins however, a maximum of 73% ee was achieved by the use of diethyl tartrate **69** with benzaldehyde as a substrate in CH_2Cl_2 at −23 °C (Scheme 14).



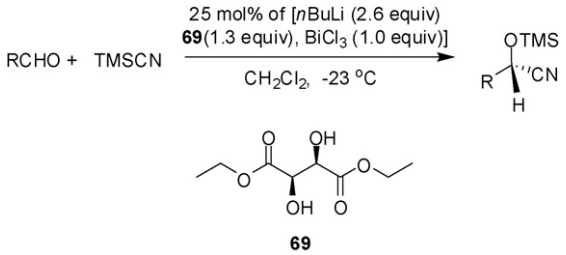
Scheme 13. Cyanosilylation of aldehydes using chiral acetoacetate analogue of 1,3-bis-(2-methylferrocenyl)propane-1,3-dione with yttrium.

3.1.14. Lanthanide complexes

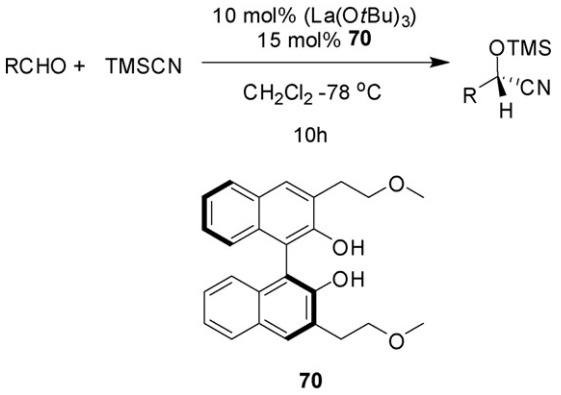
Besides pybox ligands, the use of lanthanide metal ions was restricted to a substituted binol (*S*)-3,3′-bis(methoxyethyl)binol) **70** [123] and a bis-phosphoramidate **71** ligands [124] with La and Sm metal ion for the cyanosilylation of various aldehydes. In binol-based system the active catalyst was generated *in situ* using 15 mol% of **70** with 10 mol% of $La(O^tBu)_3$ and the cyanosilylation reaction was conducted at −78 °C for 10 h to give *O*-TMS of cyanohydrins in up to 82% yield with maximum 73% ee for the *p*-methylbenzaldehyde as substrate (Scheme 15).

On the other hand bis-phosphoramidate **71** derived Sm complex [124] was more active and enantioselective (ee up to 90%; yield >95%) at relatively moderate reaction condition (−15 °C) at a very low catalyst loading (Scheme 16).

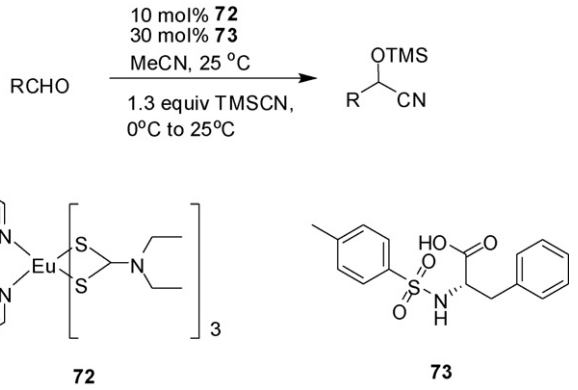
Recently, Vale et al. [125] reported a new chiral lanthanide complex derived from europium dithiocarbamate complex **72** and *N*-tosylated-L-phenylalanine **73** as catalyst for asymmetric addition of TMSCN to aromatic aldehydes. Interestingly, a high yield (up to 93%) with high chiral induction (ee,



Scheme 14. Cyanosilylation of aldehydes using chiral dialkyl ester of tartaric acid with bismuth trichloride.



Scheme 15. Cyanosilylation of aldehydes using chiral binol with lanthanum.



Scheme 17. Asymmetric addition of acetone cyanohydrin to aldehydes with europium dithiocarbamate complex and *N*-tosylated-L-phenylalanine.

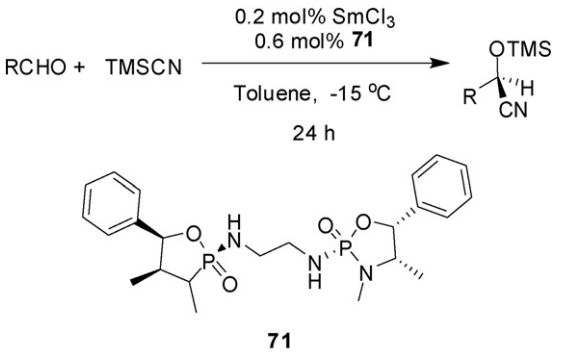
99%) was achieved in the case of electronically depleted aldehydes, e.g., 2- and 4-nitrobenzaldehydes in 1 h at 0–25 °C (Scheme 17).

3.1.15. Alternative source of cyanides

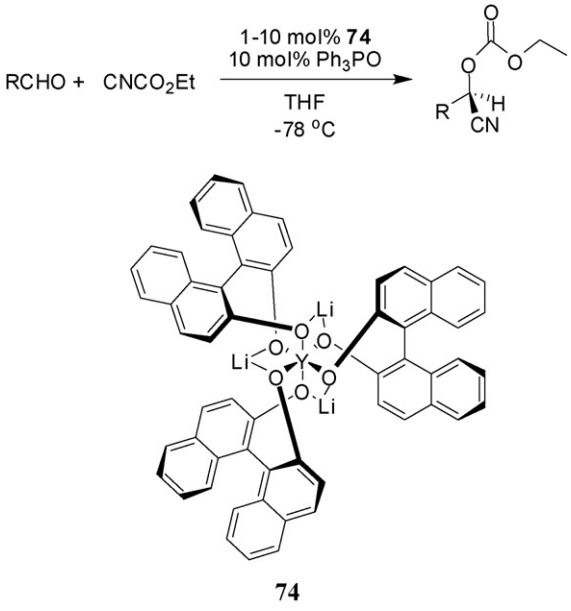
Though, the metal catalyzed asymmetric cyanation of aldehydes is dominated by the use of TMSCN as a source of cyanide, the high cost and toxicity of TMSCN is a major barrier for its utilization on an industrial scale. Further TMSCN is highly volatile and moisture sensitive, hence, requires extreme care in handling; further the chiral *O*-TMS ethers of cyanohydrins are prone to racemization. In this backdrop, alkyl cyanoformates are relatively cheaper and a less toxic source of cyanide. Moreover, alkyl carbonylated/phosphate cyanohydrins are stable and not easily hydrolyzed by moisture in air. They are useful synthetic intermediates and can be applied in the synthesis of β-amino alcohols and γ-substituted unsaturated nitriles from *O*-carbonylated allylic cyanohydrins. After the first report on the use of ethyl cyanoformates in the cyanation of ketones by Tian and Deng in 2001 [126], it was Shibasaki and co-workers [127] who used a binol-based heterobimetallic complex **74** in combination with phosphine oxides for the addition of ethyl cyanoformate to aldehydes (Scheme 18).

Using 10 mol% of catalyst **74** at −78 °C in THF, cyanohydrins were formed with up to 98% ee with high yield. Later on the same group successfully employed this catalyst for the catalytic asymmetric cyanation-ethoxycarbonylation reactions of α,β-unsaturated aldehydes for the two-step synthesis of optically active γ-oxy-α-β-unsaturated nitriles [128]. Shibasaki et al. also reported a detailed mechanistic study for the cyanation reaction of aldehydes using complex **75** with ethyl cyanoformates as cyanide source along with three achiral additives viz., H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide and BuLi. [129]. Using the catalyst **74** (10 mol%) Shibasaki and co-workers [130] also reported a highly enantioselective cyanophosphorylation of aldehydes in the presence of H_2O (30 mol%), tris(2,6-dimethoxyphenyl)phosphine oxide (10 mol%) and BuLi (10 mol%) using diethyl cyanophosphonate as a source of cyanide to afford respective cyanohydrin *O*-phosphates in up to 98% yield and 97% ee (Scheme 19).

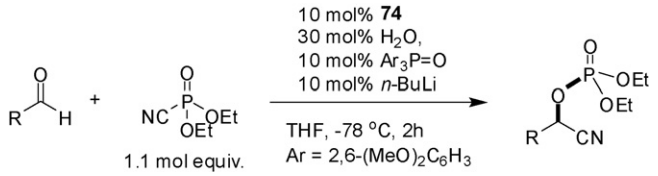
Nájera et al. [131] used a monometallic bifunctional catalyst derived from substituted binol **75** with Me_2AlCl (Scheme 20) which was highly active at room temperature for the enantioselective cyano-methoxycarbonylation of aldehydes using methyl cyanoformates as a source of cyanide. The catalyst was recov-



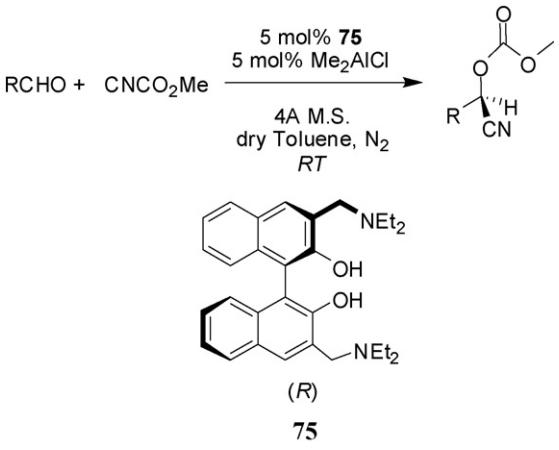
Scheme 16. Cyanosilylation of aldehydes using bis-phosphoramidate derived samarium complex.



Scheme 18. Asymmetric addition of ethyl cyanoformate to aldehydes using yttrium binol-based heterobimetallic complex.



Scheme 19. Cyano-phosphorylation of aldehydes using yttrium binol-based heterobimetallic complex.



Scheme 20. Cyano-methoxycarbonylation of aldehydes using chiral substituted binol with Me_2AlCl.

erable (no data provided) while giving methoxy carbonylated cyanohydrins in >98% yield and ee up to 82% in 12–28 h.

Same authors [132,133] have also reported cyanophosphorylation of aldehydes with commercially available diethyl cyanophosphonate as a source of cyanide with various Lewis acids under different reaction conditions [131]. However, under optimized conditions as mentioned in Scheme 21, the product cyanophosphate was achieved in high yields (up to 90%) with ee up to 98% using 10 mol% of (*S*)-**76** as catalyst in 2–50 h. Recently these authors published a detailed report on cyanophosphorylation of various aldehydes with mechanistic studies using same catalyst under similar reaction condition.Nájera et al. [134] used the bifunctional ligand **77** (10 mol%) with titanium isopropoxide (10 mol%) to catalyze enantioselective cyanobenzoylation of different aldehydes using benzoylcyanide as a source of cyanide in THF at RT under nitrogen. Respective bezoylcyanohydrins were achieved in 91% yield with 38–68% ee (Scheme 22).

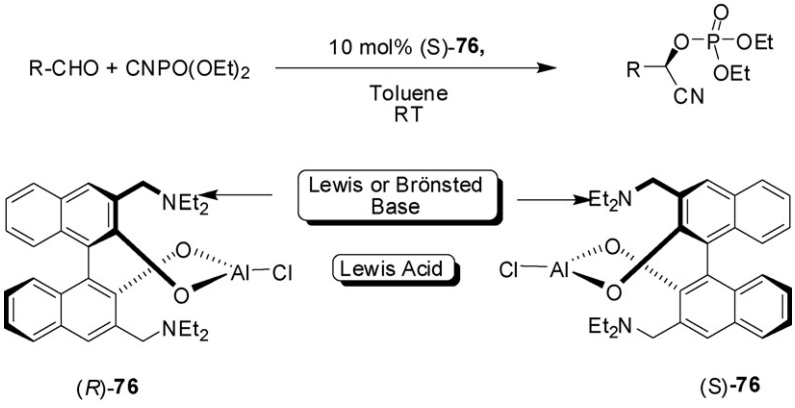
Belokon et al. [135] investigated the bimetallic Ti–salen complex **10** (entry 7, Table 1) as a catalyst for the synthesis of cyanohydrincarbonates from various aliphatic and aromatic aldehydes using ethylcyanoformate as a source of cyanide over a temperature range of −40 to −85 °C. Under the optimized reaction conditions they were able to achieve aliphatic cyanohydrincarbonates with 23–69% isolated yield and 76–84% ee whereas, aromatic cyanohydrincarbonates were obtained with up to 95% yield and 76–99% ee at −40 °C (Scheme 23).

The same group [136] also utilized the catalyst **10** (5 mol%) (please refer to Table 1 entry 7) for the cyanation of various aldehydes using ethylcyanoformate to give respective cyanohydrin ethylcarbonate with up to 96% yield and 99% ee at −20 °C in CH_2Cl_2 for 17–68 h. They also explored the use of KCN as a source of cyanide with the catalyst **10** (1 mol%) in the presence of various acid anhydrides, water and ^{t}BuOH to give acetylated cyanohydrins in quantitative yields with up to 95% ee at −40 °C in CH_2Cl_2 (Scheme 24).

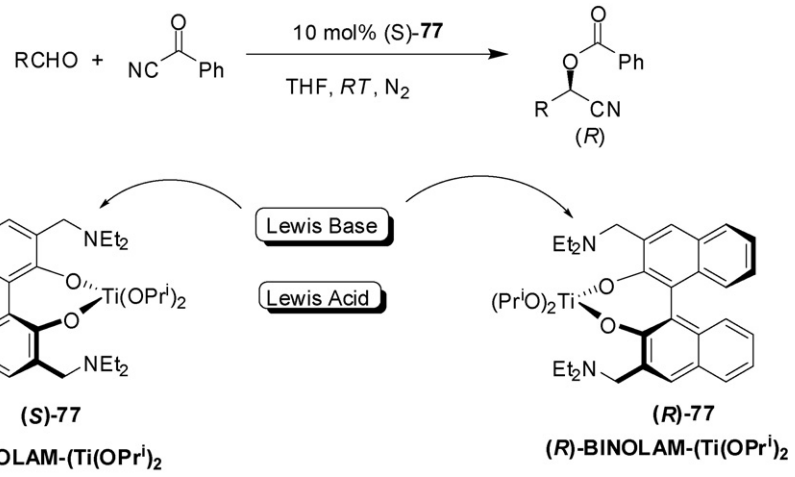
Moberg et al. [137,138] used catalyst **10** (5 mol%) (please refer to Table 1 entry 7) for the cyanation of various aldehydes using two different cyanide sources, viz., ethyl cyanoformate and α-ketonitrile (acetyl cyanide) in the presence of 10 mo% of various bases (Et_3N was best among others used in this study). Among the two cyanide sources used, ethyl cyanoformates were more active than acetyl cyanide for identical substrates under similar reaction conditions. Also, better product yields (81–97%) for respective *O*-alkoxy carbonylated cyanohydrins were obtained in 4–6 h with ee 73–94% with ethyl cyanoformates (Scheme 25). On the other hand, *O*-acetylated cyanohydrins were obtained in 64–90% yield with 76–96% ee in 6–12 h under similar reaction conditions using acetyl cyanide as a source of cyanide.

Feng et al. [139] reported prolinamide derived C_2-symmetric chiral *N,N′*-dioxide–Ti(IV) complexes **78** as catalyst for the addition of ethyl cyanoformate to various aldehydes (Scheme 26).

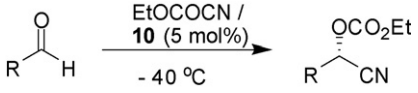
A range of aldehydes gave respective cyanohydrin carbonates in excellent isolated yields (81–92%) and 62–90% ee using *in*



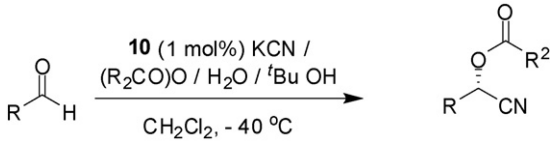
Scheme 21. Cyanophosphorylation of aldehydes using chiral substituted BINOL with Al.



Scheme 22. Cyanobenzoylation of aldehydes using chiral substituted binol with Ti.



Scheme 23. Cyanohydrincarbonate synthesis with bimetallic Ti–salen complex.



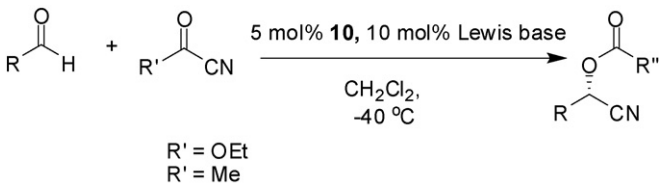
Scheme 24. Acetylated cyanohydrin synthesis using bimetallic Ti–salen complex.

situ generated **78**-Ti complex as catalyst with ethylcyanoformate as cyanide source in CH_2Cl_2 at −45 °C in 48 h.

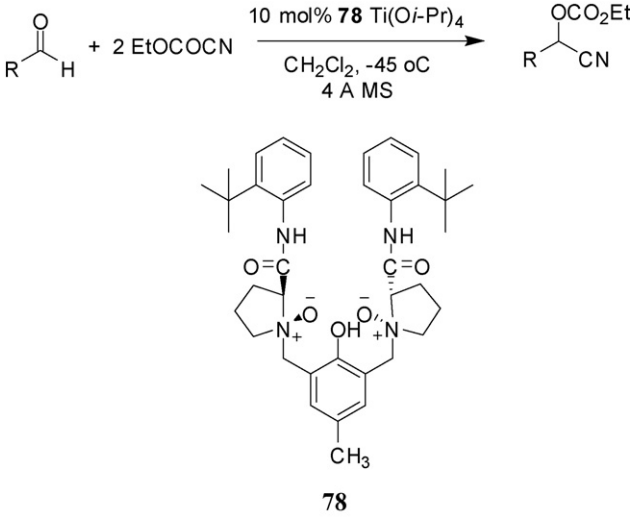
Acetone cyanohydrin is another important cyanating agent readily available on commercial scale and is more manageable than HCN and alkali cyanides. Maruoka and co-workers [140,141] used this source of cyanide for the first time for the asymmetric cyanation of various aldehydes to produce the respective cyanohydrins with moderate ee (up to 72%). Out of various chiral ligands used with $Zr(O^tBu)_4$ to form active catalyst, Taddol **79** was most promising candidate for achieving a high ee in the product cyanohydrins. They could achieve a maximum of 91% ee at −78 °C for the cyanation of 3-phenylpropanal using the above recipe (Scheme 27).

Katsuki et al. [142] have also reported the use of acetone cyanohydrin for the cyanation of various aliphatic aldehydes with oxo-vanadium-(V)-(salen) complex **80** to obtain good to high enantioselectivities (67–84%) at 10 °C in 48 h. This cyanation showed a positive nonlinear effect [143] (Scheme 28).

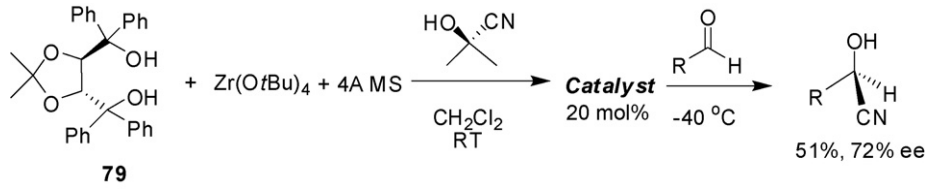
Sodium and potassium cyanides are the basic raw materials for all other cyanide sources discussed in preceding sections and are the cheapest source of cyanide. These are primarily used as bulk chemical in metallurgy and electrochemical-based industries. These are highly toxic when contacted directly and also release highly toxic hydrogen cyanide gas when in contact with moisture. Therefore, great care is required in handling these two sources of cyanide. Nevertheless, they are used as source of cyanide for the asymmetric cyanation of aldehydes. Belokon and co-workers reported the use of dimeric Ti–salen complex **10** and V–salen complex **63** as catalysts (1 mol%) for the first time to induce the asymmetric addition of alkali cyanide and acetic anhydride to various aliphatic and aromatic aldehydes, giving enantiomerically enriched cyanohydrin esters in high yield (up to 99%) and ee up to 92% in CH_2Cl_2 at −42 °C [144,145]. The best results were obtained with KCN as compared to other



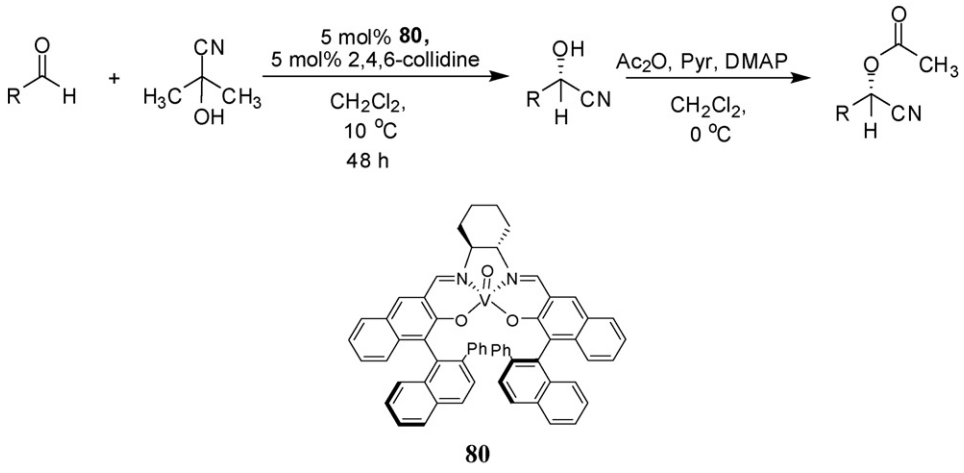
Scheme 25. Acetylated cyanohydrin synthesis using bimetallic Ti–salen complex.



Scheme 26. Asymmetric addition of ethyl cyanoformate to aldehydes using chiral *N*,*N*′-dioxide–Ti(IV) complex.



Scheme 27. Asymmetric addition of acetone cyanohydrin to aldehydes using taddol ligand with $Zr(O^tBu)_4$.



Scheme 28. Asymmetric addition of acetone cyanohydrin to aldehydes using oxo-vanadium(V)(salen) complex.

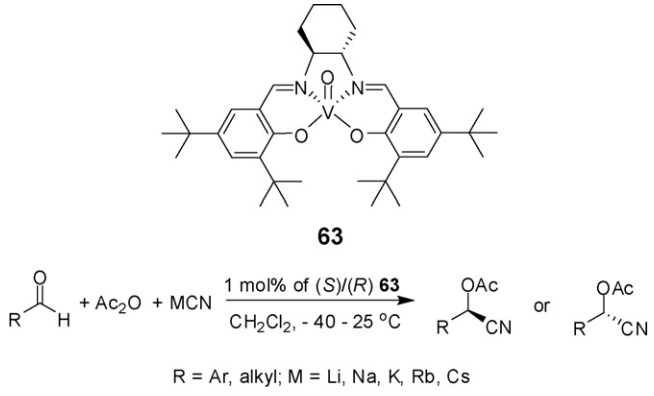
alkali cyanides, e.g., NaCN, LiCN, CeCN and RbCN used by them (Scheme 29).

Khan and co-workers [146,147] reported recyclable polymeric **64** and dimeric salen **81** (Fig. 8) Ti(IV) and V(V) complexes as catalysts for the cyanation of aliphatic and aromatic aldehydes in the presence of acetic anhydride using sodium and potassium cyanide as cyanide source at −20 °C to obtain respective acetylated cyanohydrins in >99% yield and ee up to 96%. Remarkably, these complexes were recycled for five successive catalytic runs with retention of enantioselectivity.

3.1.16. Supported catalysts

Chiral catalysts being expensive are desired to be recycled for their commercial viability. In recent years many efforts have been dedicated to recyclable metal catalysis, such as organic or inorganic supported catalyst and ionic liquids. In order to develop green technology with improved catalyst performance, Corma et al. [148] reported the use of V(V)–salen **63** (1 mol%) for the cyanation of various aldehydes in different ionic liquids with TMSCN as a cyanide source at RT in 24 h. A conversion in the range 76–97% for the product *O*-TMS cyanohydrin was achieved with ee 83–98% (Scheme 30). This was the first attempt to support a cyanation catalyst in ionic liquid to achieve recyclablity of the catalyst which they have demonstrated by five consecutive catalytic runs with retention of activity and selectivity.

Corma et al., [149] further extended this work by synthesizing the V(V)–salen complex **63** with built-in imidazolium cation **63IL** (Fig. 9). Though, these complexes were very active reusable cyanation catalysts for the preparation of non-chiral *O*-TMS cyanohydrins, its chiral version was only moderately enantioselective (ee up to 57%) for cyanosilylation of benzaldehyde.



Scheme 29. Asymmetric addition of alkali cyanides using oxo-vanadium(V)-(salen) complex.

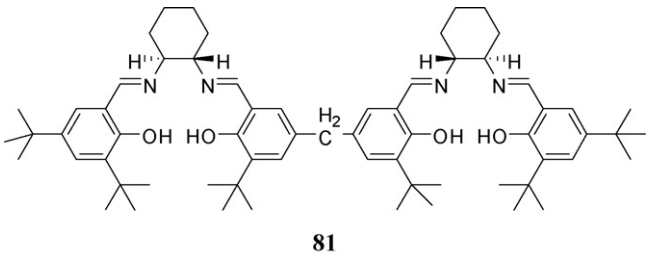
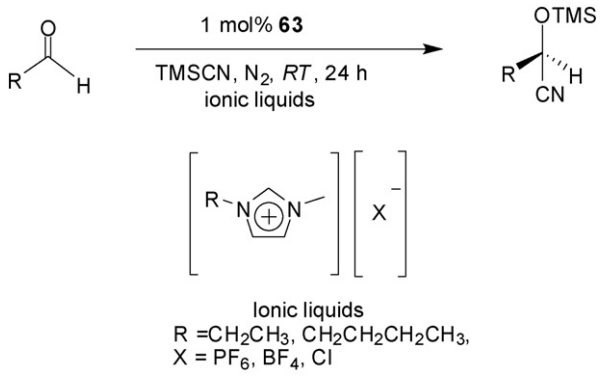
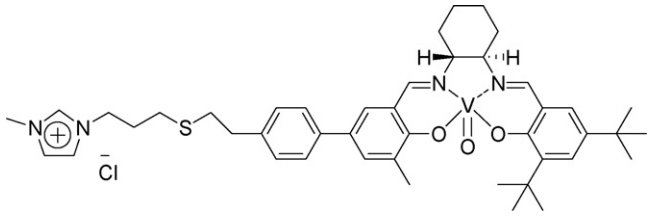


Fig. 8. Structure of chiral dimeric salen ligand with Ti(IV) and V(V) for addition of sodium and potassium cyanide to aldehydes.



Scheme 30. V(V)–salen complex **63** with ionic liquid as catalyst for cyanosilylation of aldehydes.



63-IL

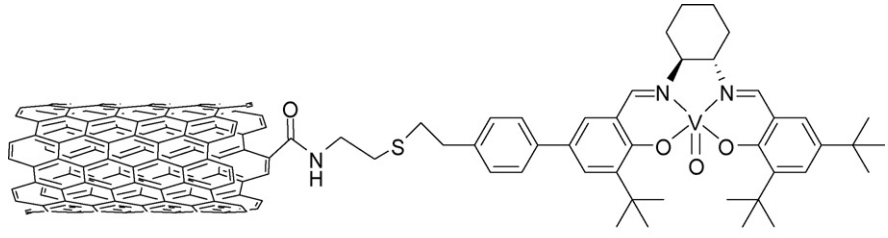
Fig. 9. V(V)–salen with built-in imidazolium cation as catalyst for cyanosilylation of aldehydes.

In their continued efforts to develop recyclable supported catalyst Corma et al. further synthesized oxo-vanadium–salen complexes anchored on single wall carbon nanotube (**63**-SWNT) and three large surface area silicas, namely amorphous silica (**63**-SiO_2), ITQ-2 (a novel delaminated zeolite) (**63**-ITQ-2), and MCM-41 (**63**-MCM-41) through mercaptopropylsilyl groups [150,151]. The catalytic addition of TMSCN to benzaldehyde in CH_2Cl_2 and nitrobenzene in the presence of vanadyl salen complexes (Fig. 10) (100 mg, 0.24 mol%) resulted in the *O*-TMS of phenylcyanohydrin in 40–70% yield with 48–66% ee at RT. These catalysts were recycled for 5 repeated catalytic runs with gradual loss in activity though enantioselectivity was somewhat retained.

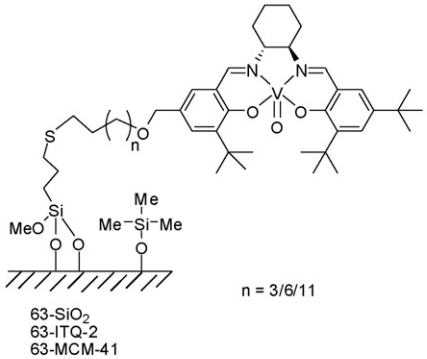
Kim and Kim also reported [152] the Ti–salen complex anchored on MCM-41 **82** with shorter linker length than reported by Corma et al. They also tried direct anchoring method to support Ti–salen complex **83**. In both the cases (Fig. 11) only moderate conversions (23–40%) and ee (43–93%) were achieved for the trimethylcyanosilylation of benzaldehyde at RT in 24 h.

Zheng et al. [153,154] prepared crosslinked polymeric salen ligands **84** and linear polymeric salen ligands **85** and used their Ti(IV) and V(V) complexes as catalysts (Fig. 12) for enantioselective *O*-acetyl cyanation of aldehydes with KCN in presence of acetic anhydride. The crosslinked polymeric salen–Ti(IV) showed good conversion (99%) with ee up to 91% at −20 °C with 1 mol% of catalyst, which was easily recovered and recycled for six consecutive catalytic runs with no obvious decrease in either activity or enantioselectivity. Linear polymeric salen–V(V) catalyst showed good catalytic efficiency too where up to 94% ee with 99% conversion was obtained at −42 °C with 5 mol% of the catalyst.

Moberg et al. [155] immobilized pybox ligand on two tentagel resins. The resulting immobilized ligands were then complexed with ytterbium(III) chloride and were used as heterogeneous catalysts for the addition of trimethylsilylcyanide to benzaldehyde to obtain the product in 66–89% yield and ee up to 81%

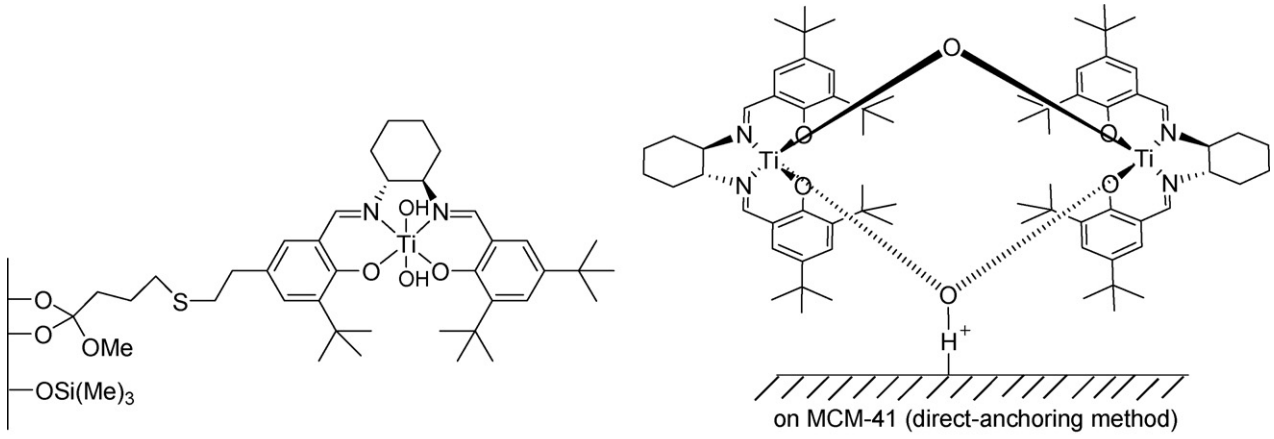


63-SWNT



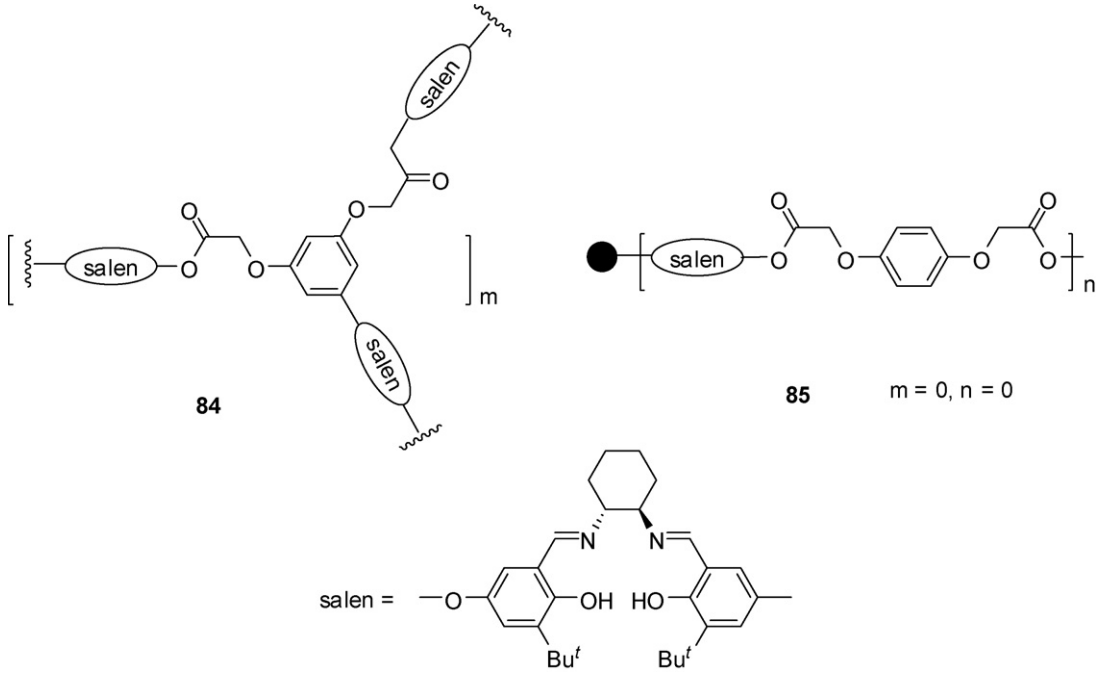
78

Fig. 10. Vanadium–salen complexes anchored on SWCNT, amorphous silica, ITQ-2 and MCM-41 for cyanosilylation reaction.



82 83

Fig. 11. Ti–salen complexes anchored on MCM-41 as supported catalysts for cyanosilylation of aldehydes.



84 85

Fig. 12. Structures of polymeric salen ligands: crosslinked (**84**) and linear (**85**).

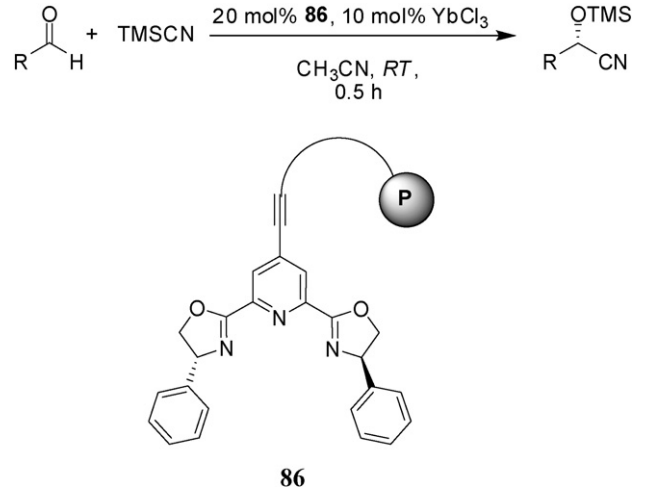
(Scheme 31). The catalyst was recycled four times however; the ligand was recycled for more than 30 times.

4. Asymmetric cyanation of ketones

Unlike aldehydes, the reactivity of the carbonyl group in ketones is affected by greater steric hindrance and lower electrophilicity. Nevertheless, the asymmetric addition of cyanide to ketones did not go unchallenged. Choi et al. [156] published the first report on trimethylsilylcyanation of acetophenone catalyzed by a reusable catalyst **34** (1 mol%) derived from (*S*)-3,3-dimethyl-1,2,4-butanetriol and titanium isopropoxide under high pressure at 18 °C producing the corresponding cyanohydrin with ee up to 60% in 93% yield (Scheme 32). However, reactions of 4′-substituted acetophenones to the corresponding cyanohydrins gave lower ee and yields.

Belokon et al. [157] however, were the first to report the asymmetric cyanation of aromatic–aliphatic ketones at room temperature and atmospheric pressure using 0.5 mol% of the Ti–bimetallic catalyst **10** (Table 1, entry 7) to yield corresponding cyanohydrin silyl ethers in 27–100% yield with 30–72% ee.

Later, Feng et al. [158] used the monomeric Ti–salen catalyst **87** in the presence of a base catalyst **88a–g** in order to further improve the catalyst performance (Scheme 33). However, there was only marginal improvement in the ee of the product (up to 84% at −20 °C) over the Belokon's protocol (ee up to 72% at RT). They also reported [159–161] monomeric and dimeric ver-

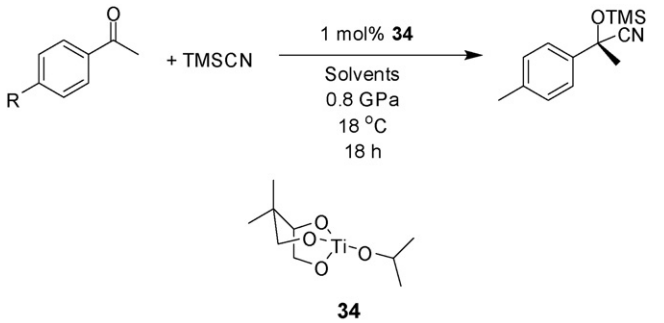


Scheme 31. Structure of immobilized pybox ligand on two tentagel resins with ytterbium for cyanosilylation of aldehydes.

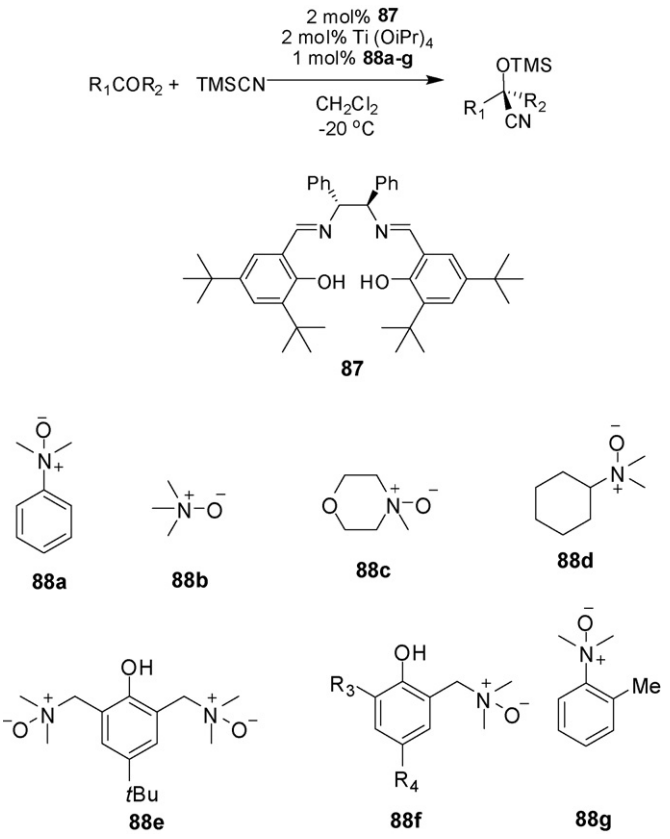
sions of the salen ligand with titanium isopropoxide as catalysts with a number of bases though the ee remained up to 86% at −20 °C in 96–120 h.

Feng et al. [161] studied in detail the effect of several reaction parameters viz., catalyst loading, temperature, solvents, and amount of additive (*N*-oxides) for the cyanosilylation of acetophenone. They also studied the effect of the various substituents in the salen ligand with variation in metal ions and substituents on *N*-oxides on the above reaction. Based on the analysis of the data collected they proposed a mechanism for the trimethylsilylcyanation of acetophenone (Scheme 34). The role of *N*-oxide was proposed to activate TMSCN, while the substrate was activated by the acidic center of the catalyst that is optimized for titanium. The catalytic cycle also predicts the sense of asymmetric induction; acetophenone is coordinated to the catalyst so as to minimize the interaction between the acetophenone and the phenyl groups of the ligand, which results in an orientation in which the *Si* face of the acetophenone is exposed to intermolecular attack by the cyanide of the activated TMSCN to produce the *R* enantiomer of the *O*-TMS cyanohydrin.

Feng et al. [162] in an another study screened various substituted salen ligands in combination with various metal sources, e.g., $Ti(O^iPr)_4$, $AlEt_3$, $Al(O^iPr)_3$, Et_2AlCN, Et_2AlCl, Et_2Zn,



Scheme 32. Cyanosilylation of ketones using (*S*)-3,3-dimethyl-1,2,4-butanetriol and titanium isopropixide.



Scheme 33. Cyanosilylation of ketones using chiral salen ligand **87** in the presence of titanium tetraisopropoxide and various N-oxides **88a**–**g**.

$Ni(acac)_2$, $Cu(OTf)_2$ and various *N*-oxides. Out of the various combinations of salen ligand and metal source, 4,4′-dibromosalen **89** (Fig. 13) with $AlEt_3$ was observed to be the best for the cyanosilylation of acetophenone in terms of ee (94%) with 99% yield for its *O*-TMS ether cyanohydrin.

Recently, Kim et al. [164] reported the use of Al–salen complex **66** [163] and Mn–salen complex **90** (Fig. 14) as catalyst for the asymmetric cyanosilylation of various ketones at RT in DCM using triphenylphosphine oxide as base for double activation. While Mn(III) catalyst inducted a maximum of 85% ee with 89% yield (in 5–70 h) for the product *O*-TMS cyanohydrin, Al(III) was better catalyst both in terms of ee (up to 92%) and reaction time (3–40 h).

Subsequent to the bifunctional catalysts where both acid and basic sites were separate chemical entities we organized the literature on built in bifunctional catalyst for the cyanosilylation of ketones in Table 6.

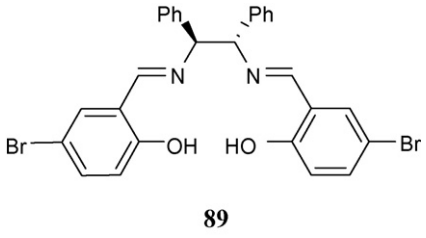
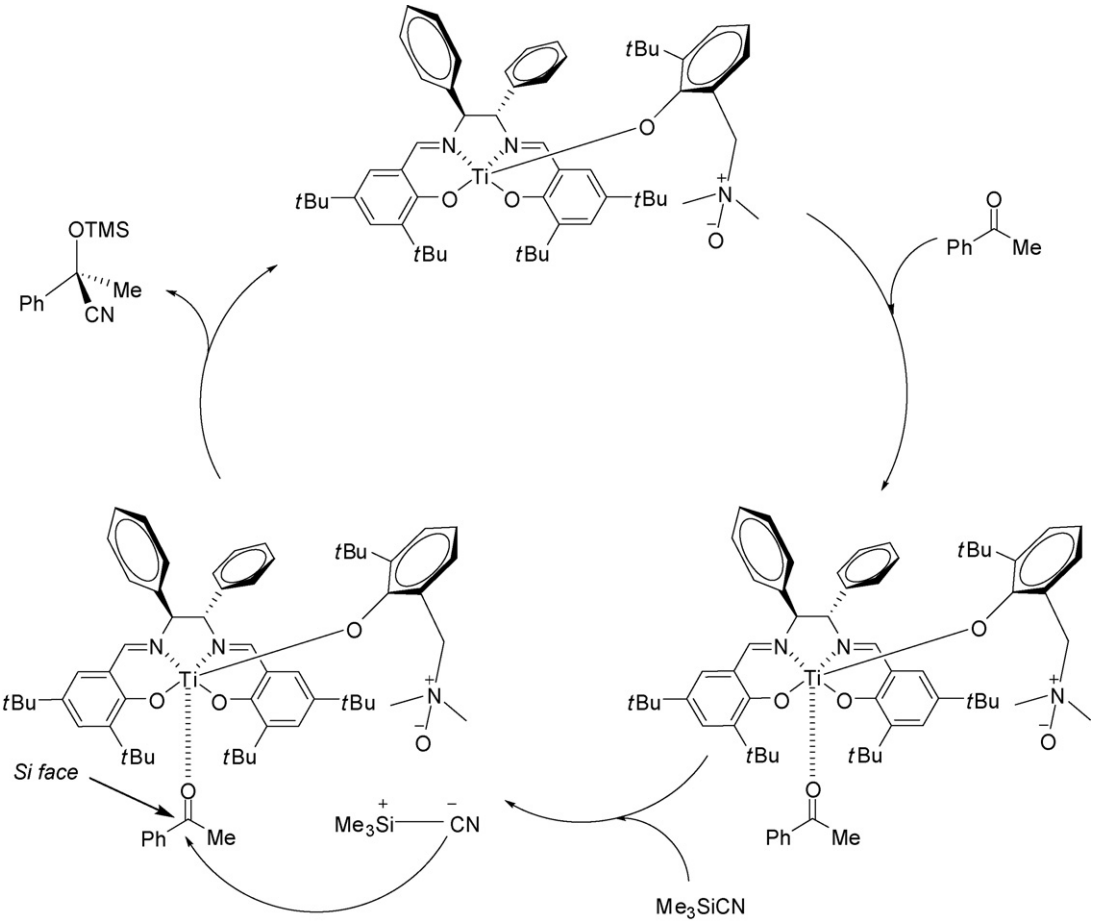
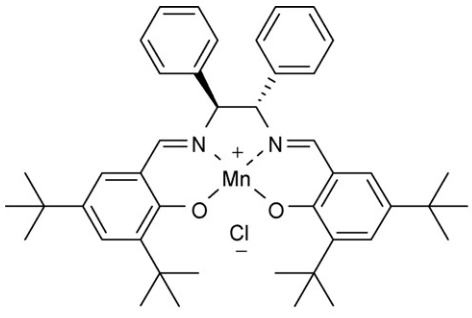


Fig. 13. Structure of 4,4′-dibromosalen ligand.



Scheme 34. Catalytic cycle for the cyanosilylation of actophenone using Ti–salen as catalyst.

Shibasaki et al., developed a novel chiral ligand **91** (as a precursor to build a bifunctional catalyst) from readily available D-glucose as a feed stock. The titanium complex of this ligand showed remarkable activity and enantioselectivity for the enantioselective cyanosilylation of ketones, giving (*R*)-cyanohydrins from a broad range of ketones (Table 6, entry 1). However, in the quest for the synthesis of (*S*)-cyanohydrins Shibasaki reported an interesting phenomenon of switching of the enantioselectivity when a lanthanide metal ion was used with ligand **91** [167]. Thus 5 mol% of Sm-**91** gave (*S*)-cyanohydrin of acetophenone in 85% yield with 82% ee at −40 °C for 2 h. The activity (yield 92% in 2 h) and enantioselectivity (ee 92%) for cyanosilylation of ketones was further improved when Gd-**91** was used as catalyst (Table 6, entry 2). A detailed mechanism for this interesting system is also discussed by the authors.

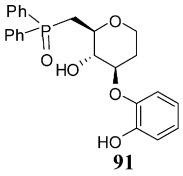
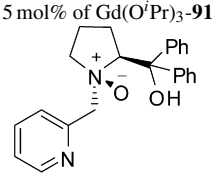
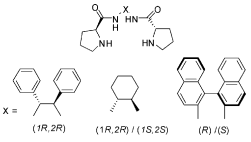
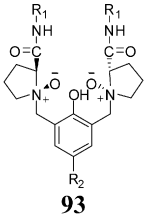
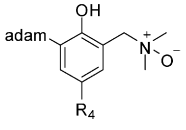


90

Fig. 14. (a) Structure of Mn–salen complex. (b) Cinchona alkaloid derived catalysts.

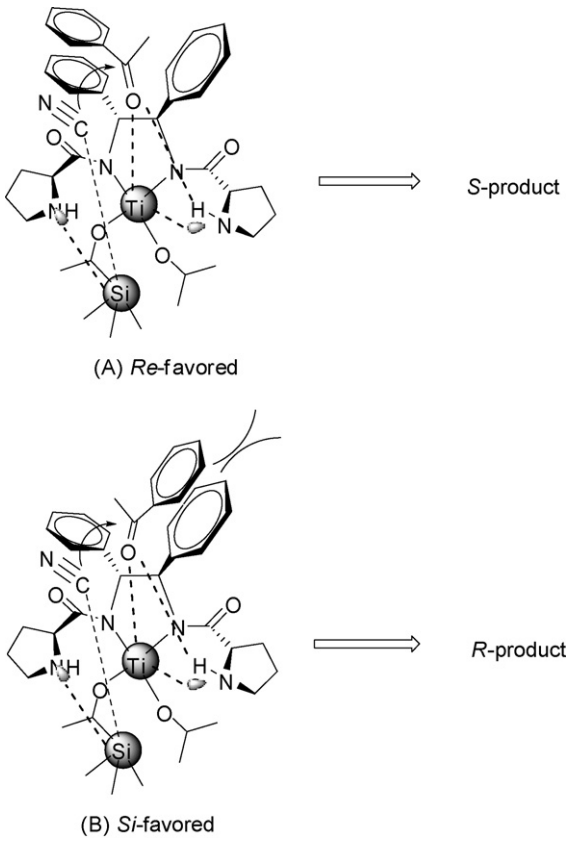
Feng et al. proposed a possible dual activation mechanism (Scheme 35), in which the acidic titanium activated the ketone as a Lewis acid and the basic nitrogen atom of one of the pyrrolidinyl groups activated TMSCN as a Lewis base, respectively. On the basis of the observed absolute configuration of the product the transition state involved, during the catalytic cycle was proposed. Accordingly, in transition state A, the *Re* face of the carbonyl of acetophenone is more accessible to a nucleophilic group CN than *Si* face since the interaction of the *Si* face and the attacking group CN will strongly increase the repulsion between phenyl subunits as in transition state B. According to them, *S*-proline also plays a vital role in inducing enantioselectivity, which causes a fit concave to define the position of the coordinated ketone at the *Re* face *syn* to the Lewis basic amine group of pyrrolidine. The activated nucleophile will attack the highly polarized C=O of acetophenone at the carbon atom from a less stereohindered direction (*Re*) to give the *S*-configuration.

Table 6
Built in bifunctional catalysts for cyanosilylation of ketones

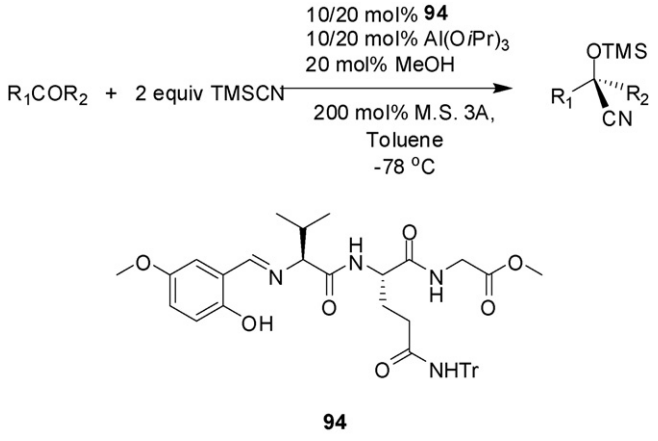
Serial no.	Catalyst system	Reaction condition	Yield (%)	ee (%)	Reference
1	 **91** 10 mol% with 10 mol% $Ti(OiPr)_4$ 5% of $Sm(OiPr)_3$-**91** (1:1.8) TMSCN (1.5 equiv.) or 5 mol% of $Gd(OiPr)_3$-**91** (1:2)	Solvent = THF; temperature = −20 to −50 °C; time = 34–96 h	72–92	76–95	[165,166]
2	5% of $Sm(O^iPr)_3$-**91** (1:1.8); TMSCN (1.5 equiv.) or 5 mol% of $Gd(O^iPr)_3$-**91** (1:2)	Solvent = THF; temperature = −30 to −60 °C; time = 1–55 h	85–97	62–97	[167]
3	 **92** 10 mol% with 12 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = 0 °C; time = 96–120 h	61–87	25–69	[168]
4	 **24** 30 mol% with 30 mol% $Ti(OiPr)_4$	Solvent = CH_2Cl_2; temperature = −45 °C; time = 100 h	48–90	51–94	[169]
5	 **93** R1 = cyclohexyl, 2-t-Butylphenyl, 1-adamentylphenyl diphenylmethyl  R2 = CH_3, Cl, t-Bu 5 mol% **93** with 5 mol% $Ti(OiPr)_4$ and 5 mol% of 	Solvent = THF; temperature = −45 °C; time = 36–72 h	62–90	78–92	[170]

Snapper, Hoveyda and co-workers in situ generated an aluminum complex of peptide **94** as catalyst for the cyanosilylation of ketones (Scheme 36). This system worked well for both aromatic and aliphatic ketones giving ee up to 95% with 98% yield in the presence of molecular sieves (MS) 3A and methanol at −78 °C for 48–72 h [171].

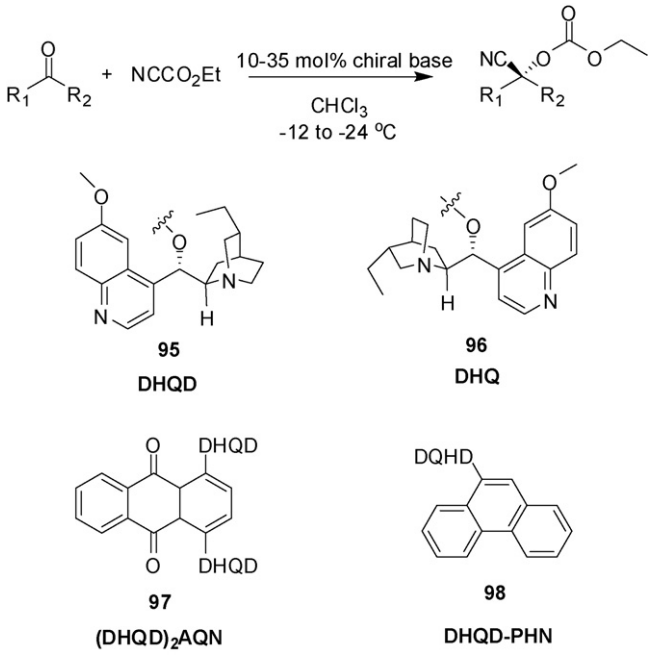
Ryu and Corey [172] recently reported a chiral oxazaborolidinium ion **3** (10 mol%) (the complex they used earlier to



Scheme 35. The proposed dual activation model for the cyanation of acetophenone.



Scheme 36. Cyanosilylation of ketones catalyzed by the aluminum catalyst generated from a peptide ligand **94**.



Scheme 37. Asymmetric addition of ethyl cyanoformate to ketones catalyzed by chiral organic bases derived from cinchona alkaloids.

catalyze the asymmetric cyanosilylation of aldehydes) in the presence of diphenylmethyl phosphine oxide (11–20 mol%) as an excellent catalyst system for the cyanation of aliphatic and aromatic ketones in toluene at 25–45 °C using TMSCN as a cyanide source. Corresponding *O*-TMS cyanohydrins were obtained in up to 97% yield with ee up to 96%. However, the reaction was slow and took 48–240 h to complete.

4.1. Non-metal synthetic/semi-synthetic organic compounds

To present a total picture of catalytic asymmetric cyanation of ketones, it would be proper to include here non-enzymatic but at the same time non-metal-based catalysts-essentially organic bases. In this regard Deng and Tian reported several chiral tertiary amines derived from modified Cinchona alkaloids as catalysts for the cyanation of unconjugated ketones using ethyl cyanoformates as source of cyanide in chloroform over a temperature range of −12 to −24 °C in 12–168 h [125]. The respective cyanohydrins were obtained in up to 100% yield with 97% ee (Scheme 37).

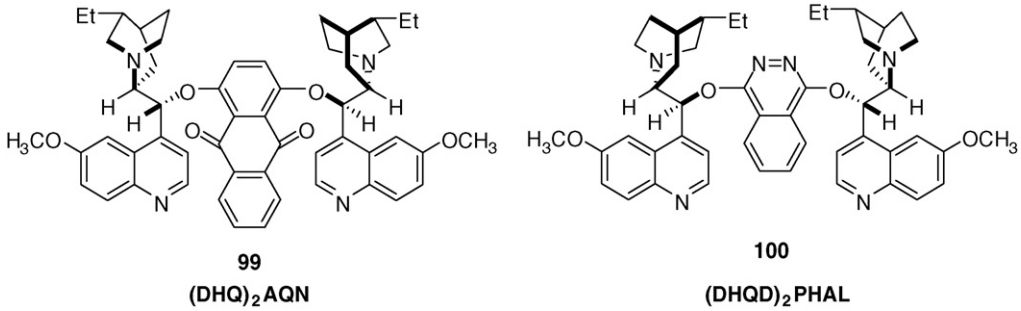
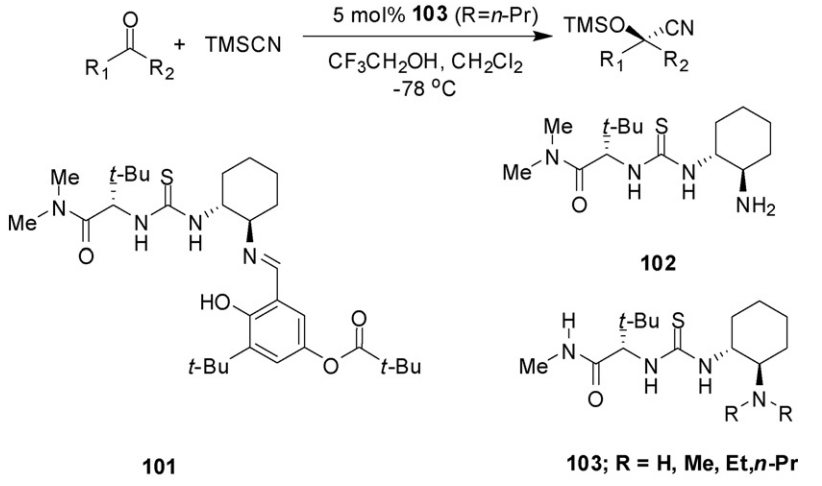
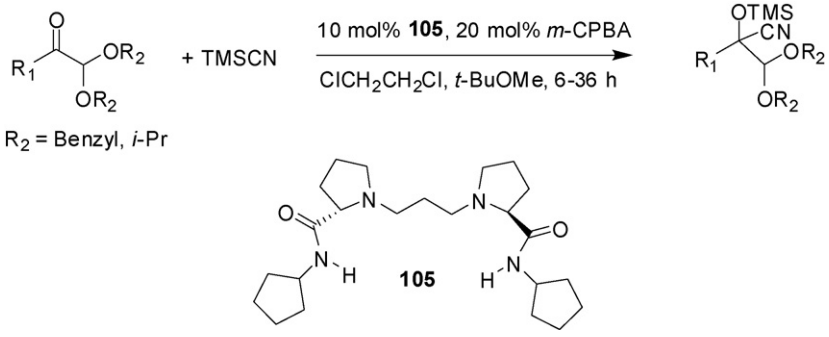


Fig. 15. Alkali metal salts of amino acids.



Scheme 38. Cyanosilylation of ketones using bifunctional thio-amine derivates.



Scheme 39. Cyanosilylation of ketones using bi-functional *N*,*N*′-dioxide catalyst.

Deng et al. [173] in an another study used $(DHQ)_2AQN$ **97** and $(DHQD)_2PHAL$ **100** as catalysts (2–20 mol%) for the cyanosilylation of various aliphatic and aromatic-aliphatic ketones at −24 to −50 °C in $CHCl_3$ (Fig. 14). The respective *O*-TMS ether of cyanohydrins were obtained in up to 99% yield with ee 98% in 18–94 h by using $(DHQD)_2PHAL$ **100** as catalyst. While $(DHQ)_2AQN$ **99** (recoverable) was more reactive than $DHQD)_2PHAL$ **100** as 100% conversion in 7–19 h was achieved with former, it was less enantioselective (ee 31–90%).

Giving an analogy with enzyme where hydrogen bonds play an important role in asymmetric syntheses, Fuerst and Jacobsen [174] proposed the synthesis of new bifunctional thiourea-amine derivatives (**101**–**103**) to catalyze the enantioselective cyanosilylation of ketones and aldehydes (Scheme 38).

Among the various thioureas reported by them **103** (R = *n*-Pr) (5 mol%) was most active and enantioselective catalyst for the 1,2-addition of TMSCN to a variety of ketones giving corresponding *O*-TMS ether of cyanohydrins in high yield (up to 98%) and ee (up to 98%) at −78 °C in 12–48 h. The system also required 1 equivalent of CF_3CH_2OH in order to facilitate *in situ* release of HCN.

Feng et al. [175] recently, explored the use of readily accessible aminoacid salts (30 mol%) for the cyanosilylation of ketones over a temperature range of −20 to −40 °C in THF using 2-propanol as an additive (Fig. 15). Under the optimized conditions they were able to achieve respective *O*-TMSCN cyanohydrin in up to 97% yield and ee using sodium salt of L-phenylglycine as catalyst.

Very recently Feng et al. [176] reported proline-based bifunctional *N*,*N*′-dioxide catalysts for the enantioselective cyanosilylation of ketones at −45 °C in 6–36 h. Best results (yield up to 99%, ee up to 93%) were achieved when *N*,*N*′-dioxide of **105** was generated *in situ* by the use of *m*-CPBA. This protocol can accommodate a range of ketones ranging from aliphatic to conjugated and aromatic-aliphatic ketones (Scheme 39).

5. Outlook

For reasons unknown, the asymmetric cyanation reaction of aldehydes and ketones was a late-starter considering the synthetic usefulness of the resultant chiral cyanohydrins in industry and academia. Nevertheless, for the last two decades this area of research has been vigorously pursued. As per the scope of this review, we have looked into mainly metal catalyzed asymmetric cyanation reaction, nevertheless, we have included some non-enzymatic–non-metal systems to draw an overall perspective of progress in the area of asymmetric cyanation of aldehydes and ketones. The area has progressed from initial stoichiometric amount of catalyst requirement to 0.1 mol% catalyst. Similarly, the requirements of very low temperature and very long reaction time (few days) have also been eased. Now, these reactions can

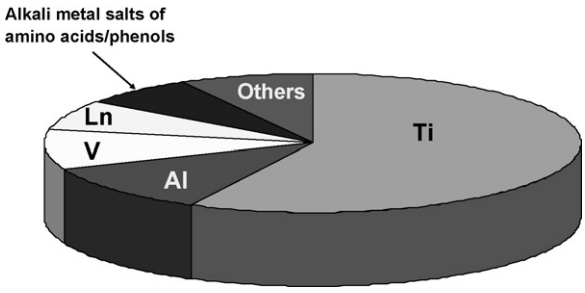


Fig. 16. Distribution of metal ions used as catalysts for the asymmetric cyanation of aldehydes and ketones.

be completed even at room temperature in a span of few hours (in some cases even within a few minutes) to give the desired cyanohydrins in high yield and chiral purity. The asymmetric cyanation reaction of carbonyl compounds is dominated by the use of titanium metal-based catalysts, however, aluminum, vanadium, lanthanides have also been applied effectively (Fig. 16). Other metal ions, viz., B, Mg, alkali metals, Mn, Y, Zr, Sn, Bi have also been used but these cases are few and require more attention in order to prove their synthetic utility. As for the chiral ligand types (Fig. 17) is concerned both C_2 and C_1 symmetric Schiff bases in combination with Ti, V, and Al metal ions have been extensively studied with some excellent results especially from Belokon's and North's group and Khan et al. Other successful systems were from Shibasaki and co-workers who have used chiral binol-based catalyst and Nájera, Saá and co-workers' bifunctional catalyst. One of the most important factors for taking the catalytic cyanation reaction to industry is the choice of source of cyanide. More than 90% of the literature has utilized TMSCN as a source of cyanide which is not only toxic, volatile, expensive and incongruous for large scale synthesis. The discovery by Belokon et al. and later by reports from Khan et al. who have used cheap and easily manageable alkali metal cyanides such as NaCN/KCN as source of cyanide holds potential as far as the industrial applications are concerned. Other cyanide sources such as alkyl cyanoformates, acetone cyanohydrin, acetyl cyanide, alkyl cyanophosphorylates are so far of academic interest though some very good results have been reported with their use. Further, the literature has overwhelming number of reports on the synthesis of chirally pure cyanohydrins from aldehydes. In the more challenging area of asymmetric cyanation of ketones, though actively practiced, there seems to be no definite clarity about the type of ligand system and choice of metal ion for taking this task near to practical

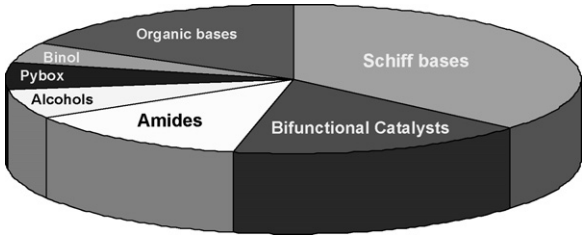


Fig. 17. Distribution of chiral ligands used for the catalytic asymmetric cyanation of aldehydes and ketones.

application. Nevertheless, studies reported from Shibasaki and Feng groups hold great promise. There are a couple of reports on supported catalysts primarily to address the issue of catalyst recycling and easy post-catalytic work up procedure. The works of Corma, Zheng and Khan's groups are noteworthy but is still far from the desired level of practical requirements. There is still a lot more work needed to address the issues of cost and recyclability of chiral catalysts, high turn over numbers, viable alternative to TMSCN and other expensive sources of cyanide, moderated reaction temperature (without sacrificing enantioselectivity) and reasonable reaction time preferably within eight hours of a working shift of an industry.

Acknowledgements

N.H. Khan is thankful to DST and CSIR Network project on Catalysis for financial assistance and also thankful to Dr. P.K. Ghosh, the Director, of the Institute for providing library facility.

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