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Recent Progress in the Chemically Catalyzed Enantioselective Synthesis of Cyanohydrins

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Keywords: Asymmetric catalysis / Cyanides / Aldehydes / Ketones / Cyanohydrins / Enantioselectivity

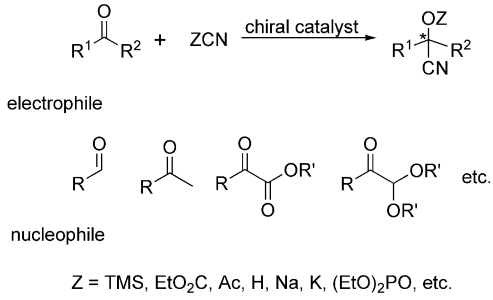
The catalytic enantioselective cyanation of aldehydes and ketones has received growing attention because the resulting enantiomerically pure cyanohydrins are versatile building blocks for many biologically active compounds. To date, both metal-based and organic catalysts have been successfully developed to promote these reactions enantioselectively. Great advances have been made in the catalytic enantioselective addition of various cyanide sources to carbonyl compounds. In this microreview, recent progress, including substrate scope and limitations, and probable reaction mechanisms are discussed. In addition, the application of this methodology to the synthesis of natural products is also presented briefly where appropriate.

1. Introduction

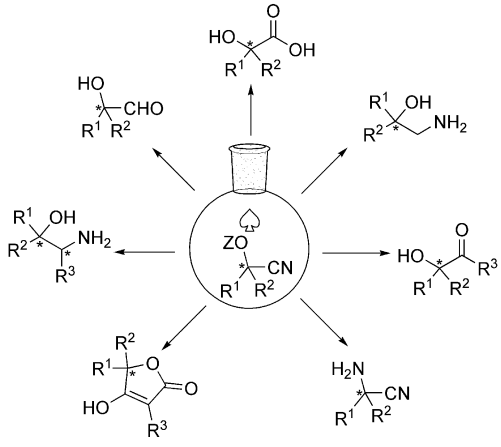
Enantiomerically pure cyanohydrins are important subunits frequently found in biologically active compounds and versatile building blocks for further transformations.[1] The nucleophilic addition of cyanide to aldehydes and ketones (Scheme 1) is one of the most powerful synthetic methods for the formation of these linchpins. The reaction allows the creation of a stereogenic center bearing hydroxy (which may be prepared in protected form) and cyano functional groups. The resulting cyanohydrins can be readily transformed into a variety of compounds such as α-hydroxy acids,[2] α-hydroxy aldehydes,[3] α-hydroxy ketones,[3] β-amino alcohols,[4] and α-amino acids among others (Scheme 2). For all these reasons it is not surprising that the chemistry of cyanohydrins has received continuous attention.

To date, many protocols have been successfully used for the enantioselective synthesis of cyanohydrins from various sources of cyanide and carbonyl compounds, including both chemically and enzymatically catalyzed approaches. Over the past century, the synthesis of enantiomerically pure cyanohydrins using enzymes has been developed into large-scale industrial processes and has been the focus of numerous reviews.[5] Thus, it will not discussed in this microreview.

This microreview focuses on recent advances, mainly of the past decade, and our own work on the chemically catalyzed enantioselective cyanation of aldehydes and ketones. It is inevitable that some early works have been omitted from the discussion sections. We apologize for this. Fortunately, many reviews and books have already described these works.[1] Most of the procedures reviewed herein involve the use of trimethylsilyl cyanide (TMSCN) or cyano-



Scheme 1. Nucleophilic addition of cyanide to carbonyl compounds.



Scheme 2. Various transformations of chiral cyanohydrins.

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formate esters (CNCOOR) as the cyanide sources. Thus, we have organized this microreview on the basis of cyanide sources. Each section is usually classified by the Lewis acidic element and organic molecule, and then by the nature of the chiral ligands if appropriate. In this manner, the continued development of ligand architectural design can be more easily observed.

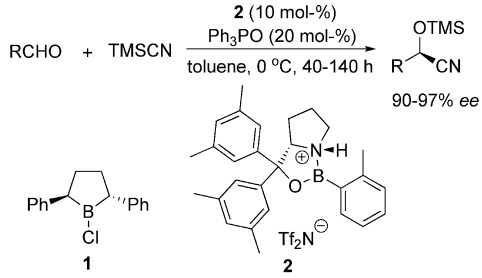
2. Use of TMSCN in the Catalytic Enantioselective Cyanation of Aldehydes and Ketones

Trimethylsilyl cyanide (TMSCN) has most commonly been employed as the cyanide source in the cyanation of carbonyl compounds, providing direct access to TMS-protected cyanohydrins. The protecting group prevents racemization by preventing the reverse reaction. On the other hand, the interest in Me_3SiCN addition has been stimulated by the properties of the silicon atom, which allows the generation of active nucleophilic species (CN^-) under different conditions. However, TMSCN is relatively expensive and will contribute considerably to the financial cost when used on a large scale.

2.1 Cyanosilylation of Aldehydes

2.1.1 Chiral Boron-Based Catalysts

The first enantioselective addition of TMSCN to an aldehyde catalyzed by chiral boron-based catalysts was reported by Reetz et al. in 1986. Although poor enantioselectivities (only 16% *ee*) were obtained at a very low temperature (–78 °C) in the presence of 20 mol-% **1**,[6a] these studies effectively demonstrated the potential of chiral Lewis acid catalysts in asymmetric cyanohydrin synthesis. The breakthrough was achieved in 2004 by Ryu and Corey (Scheme 3).[6b] They described the use of the new chiral boron-based catalyst **2** in the enantioselective addition of



Scheme 3. Asymmetric addition of TMSCN to aldehydes catalyzed by chiral boron-based catalysts.

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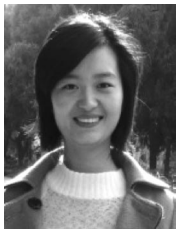
Xiaohua Liu was born in Hubei, China, in 1977. She received her B.S. degree from Hubei Normal University. Then she studied chemistry at Sichuan University and received her M.S. degree under the supervision of Professor Jiayuan Hu in 2003 and her Ph.D. under the supervision of Professor Xiaoming Feng in 2006. She was appointed as an associate professor in 2006 and joined Professor Feng's group. Her current research interests include the chemistry of chiral Lewis bases and their catalytic reactions.



Lili Lin was born in Shandong, China, in 1981. She received her B.S. degree from Sichuan University in 2003 and her Ph.D. under the direction of Professor Xiaoming Feng in 2008 at Sichuan University researching hetero-Diels-Alder reactions. She is currently an assistant professor at the College of Chemistry, Sichuan University. Her research interests lie in the development of new methodologies in asymmetric catalysis.

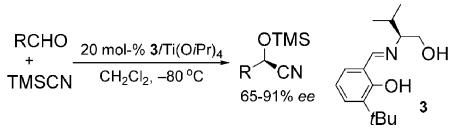
Xiaoming Feng was born in Sichuan, China, in 1964. Between 1981 and 1988 he studied chemistry at Lanzhou University. He received his B.S. degree in 1985 and his M.S. degree in 1988 from the same university. He then became an associate professor at Southwest Normal University in 1991 until 1993. In 1996 he received his Ph.D. from the Chinese Academy of Sciences under the supervision of Professors Zhitang Huang and Yaozhong Jiang. In 1997 he received his full professorship at the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences. After postdoctoral research at Colorado State University (1998–1999) with Professor Yian Shi, he went to the Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, as a professor (1999–2000). In 2000 he moved to Sichuan University as a professor, focusing on the development of new synthetic methods and the synthesis of bioactive compounds.

TMSCN to various aldehydes, which provided the corresponding products with 90–97% *ee*. Remarkably, the chiral precursor of the catalyst is readily recoverable.

2.1.2 Chiral Titanium Complexes

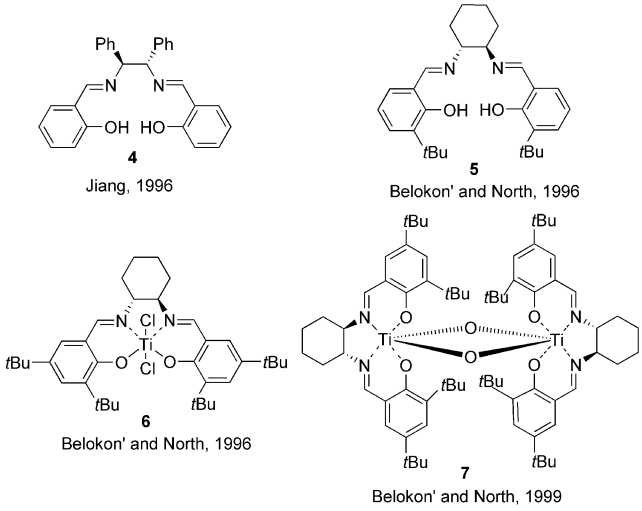
Following the work of Reetz et al., a large number of Lewis acid systems were successfully developed for the synthesis of optically active cyanohydrins. Undoubtedly the metal-catalyzed enantioselective cyanosilylation of aldehydes is dominated by the use of chiral titanium complexes.[7–10]

In 1991, Oguni and co-workers used for the first time a number of chiral tridentate Schiff bases derived from β-amino alcohols as ligands in the cyanosilylation of aldehydes.[7a–7c] The cyanation of a wide range of aldehydes was tested with the chiral titanium complex prepared in situ from Schiff base **3** and Ti(O*i*Pr)$_4$ to demonstrate its general applicability (up to 91% *ee*, Scheme 4). A significant rate enhancement was observed on addition of the Schiff base ligand to the titanium alkoxide. Mechanistic studies based on ^{13}C NMR spectroscopy, MS, and control experiments were also discussed. Very recently, Yoshinaga and Nagata reported a novel titanium catalyst prepared from partially hydrolyzed titanium alkoxide and tridentate Schiff base ligand **3** for the reaction.[7u] The corresponding cyanohydrin derivatives were obtained in excellent yields (86 to >99%) with high *ee* values (86–97%) using 0.2–1.0 mol-% catalyst at room temperature.



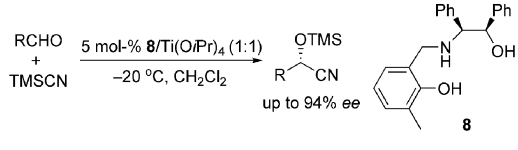
Scheme 4. Enantioselective trimethylsilylcyanation of aldehydes using the chiral Schiff base **3**/Ti(O*i*Pr)$_4$ system of Oguni and co-workers.[7a–7c]

Chiral salen ligands have also been used in the asymmetric cyanosilylation of aldehydes. In 1996, Jiang and co-workers reported the use of the C_2-symmetric Schiff base **4**/Ti(O*i*Pr)$_4$ complex in the trimethylsilylcyanation of aldehydes (Scheme 5).[7d] A number of aldehydes were tested and the corresponding cyanohydrin silyl ethers were formed with up to 87% *ee*. Belokon' and North and co-workers independently reported chiral salen **5** derived from enantiopure 1,2-diaminocyclohexane in the same year (Scheme 5).[7f] In the presence of 20 mol-% of the titanium complex prepared in situ from **5** and Ti(O*i*Pr)$_4$, a number of aldehydes were converted into cyanohydrins with moderate enantioselectivities (62–77% *ee*). Subsequently they described the use of complex **6** as a highly active (only 0.1 mol-% catalyst loading) catalyst for the asymmetric addition of TMSCN to benzaldehyde at room temperature.[7h] Moreover, various aldehydes were tolerated and the products were obtained with up to 86% *ee*. However, inconsistent results were occasionally observed when carrying out these experiments. After careful investigation of the reaction conditions, they found that water plays a key role in these reactions because under strictly anhydrous conditions much lower *ee* values were obtained. In fact, the real catalyst precursor is the dimeric complex **7**, which is more active than the dichloride precursor **6**. The corresponding cyanohydrin trimethylsilyl ethers (up to 92% *ee*) were obtained with a substrate-to-catalyst ratio (S/C) between 100 and 1000:1 in less than 1 h at room temperature.

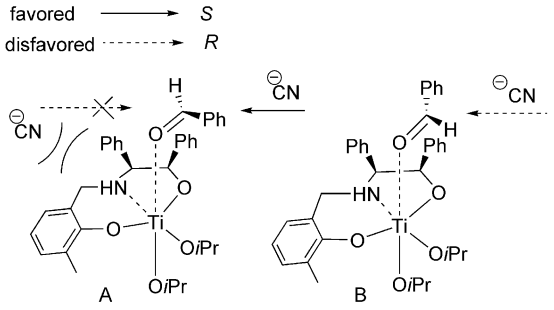


Scheme 5. Chiral salen ligands developed by Jiang,[7d] Belokon' and North[7f,7h] and their co-workers.

Subsequently we synthesized a series of chiral β-amino alcohol ligands derived from Schiff bases. In the presence of 5 mol-% of the **8**/Ti(O*i*Pr)$_4$ complex, aromatic, conjugated, heteroaromatic, and aliphatic aldehydes were converted into the corresponding cyanohydrin trimethylsilyl ethers in 90–99% yields with up to 94% *ee* (Scheme 6).[7l] Compared with Schiff bases, changing the C=N bond to the C–N single bond made molecule **8** more flexible. In view of the electronic and steric effects of substituents on the ligands as well as the observed absolute configuration of the adducts, a reaction mechanism was proposed (Scheme 7). In the transition state, the *Re* face of the carbonyl of benzaldehyde is much more accessible to the cyanide ion than the *Si* face because the latter is strongly shielded by the nearby phenyl group (Model A, Scheme 7). On the other hand, benzaldehyde could not bond to Ti^{IV} by the other aspect of C=O owing to the large steric hindrance between two phenyl subunits (Model B, Scheme 7). Thus, the cyanide ion attacks the highly polarized C=O of benzaldehyde from the less stereo-hindered direction (*Re*) to give the product with *S* configuration.

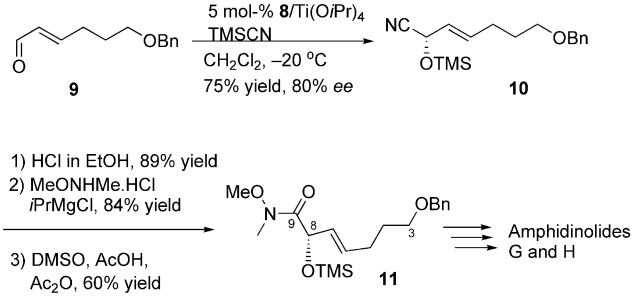


Scheme 6. Cyanosilylation of aldehydes using the **8**/Ti(O*i*Pr)$_4$ complex.



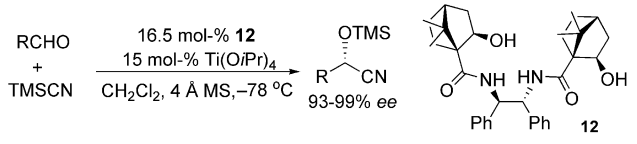
Scheme 7. Proposed reaction mechanism for the attack of CN^- on Ti-coordinated benzaldehyde.

The titanium complex of **8** developed by our group was used by Crews and co-workers to construct the subunit of the natural products Amphidinolides G and H (Scheme 8).[7v] The key was to synthesize the C3–C9 fragment **11** by asymmetric cyanosilylation of aldehyde **9**. By using 5 mol-% of the **8**/Ti(O*i*Pr)$_4$ complex, the desired cyanohydrin derivative **10** was obtained (75% yield, 80% *ee*) with the *S* configuration.



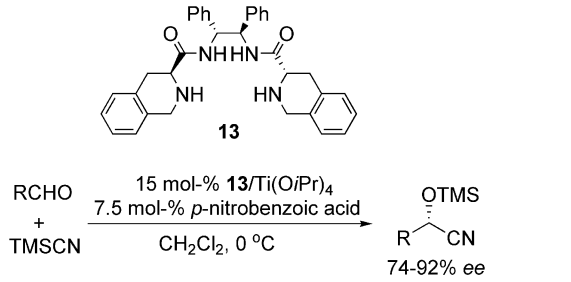
Scheme 8. Application of the **8**/Ti(O*i*Pr)$_4$ complex in the synthesis of Amphidinolides G and H.

In 2002, Uang and co-workers studied the C_2-symmetric amide **12**/Ti(O*i*Pr)$_4$ as a new chiral catalyst, which efficiently promoted the addition of TMSCN to both aromatic and aliphatic aldehydes with excellent enantioselectivities (93–99% *ee*; Scheme 9).[8b] Another highlight of this system was the recovery of chiral diamide **12** after completion of the reaction.



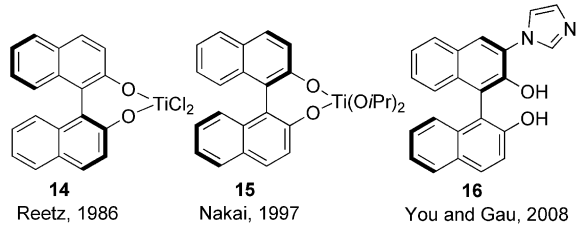
Scheme 9. Cyanosilylation of aldehydes using the **12**/Ti(O*i*Pr)$_4$ complex.

In 2006, we reported the enantioselective cyanosilylation of aldehydes using the novel and easily prepared C_2-symmetric chiral tetraaza **13**/Ti(O*i*Pr)$_4$ complex. Good yields (49–98%) and high enantioselectivities (74–92% *ee*) were obtained in the presence of 15 mol-% catalyst loading (Scheme 10).[8d]



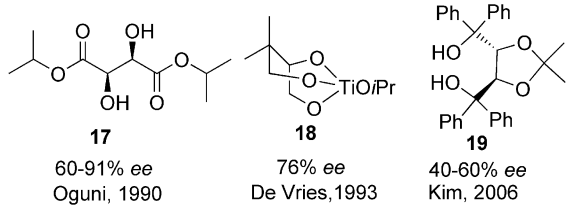
Scheme 10. Cyanosilylation of aldehydes using the **13**/Ti(O*i*Pr)$_4$ system.

The use of chiral 1,1′-bi-2-naphthol (BINOL)-derived titanium complexes has also been investigated for the cyanosilylation of aldehydes (Scheme 11).[9] The first report came from Reetz et al. In the presence of 20 mol-% **14**, isobutanal was converted into the corresponding silylated cyanohydrin in 85% yield with 82% *ee* at –78 °C in 10 h.[9a] A similar catalytic system was developed by Nakai and co-workers in 1997. Complex **15** gave moderate *ee* values (33–75%) for aliphatic aldehydes but poor results (<10% *ee*) for aromatic aldehydes.[9b] In 2008, inspired by the bifunctional concept, Gau and You and co-workers reported a BINOL-based ligand **16** with only one imidazolyl moiety attached at the 3-position.[9d] It was found that the titanium complex of ligand **16** was very effective, giving 97% yield with 98% *ee* for the addition of TMSCN to benzaldehyde at –40 °C. This catalyst system is notable because excellent enantioselectivities (90–98% *ee*) were obtained for both aliphatic and aromatic substrates using 2–10 mol-% **16**/Ti(O*i*Pr)$_4$.



Scheme 11. Chiral BINOL-based titanium complexes **14**–**16**.

Chiral alcohol-based titanium complexes developed for the catalytic asymmetric cyanosilylation of aldehydes are depicted in Scheme 12.[10]



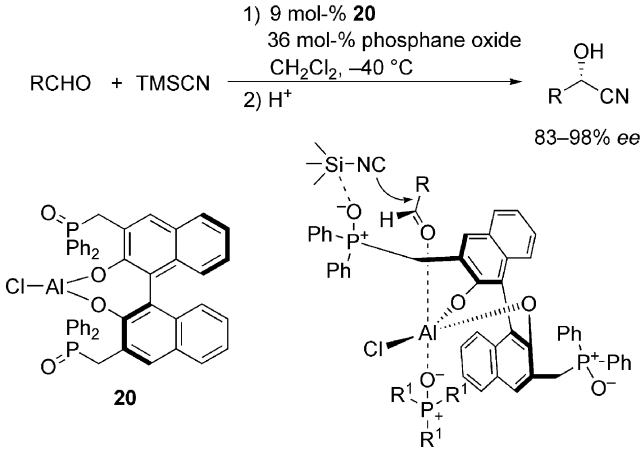
Scheme 12. Chiral alcohol-based titanium complexes.

2.1.3 Chiral Aluminium Complexes

As is well known, the use of base additives can activate nucleophiles and electrophiles can be well activated by an acidic site of the catalyst in asymmetric synthesis. This dual activation phenomenon has led many researchers to fabricate catalysts with both acid and base functionalities. These

catalysts are also known as bifunctional catalysts.[11] The work of Shibasaki and co-workers is an outstanding contribution to this area.

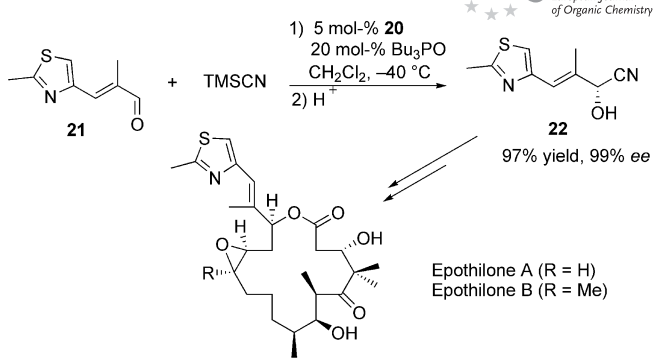
In 1999, Shibasaki and co-workers reported a highly enantioselective cyanosilylation of aldehydes with broad generality catalyzed by the new bifunctional catalyst **20** (Scheme 13).[12b,12c] They assumed that the aluminium would act as a Lewis acid to activate the carbonyl group and the oxygen atom of the phosphane oxide would act as a Lewis base to activate the silylated nucleophiles. This mechanism was supported by the experimental results of structural modifications. The aluminium complex formed by replacing the $CH_2P(O)Ph_2$ groups of **20** at the 3,3′-positions with CH_2CHPh_2 groups showed both lower reactivity and enantioselectivity (50% yield and 12% *ee* in the case of the asymmetric addition of TMSCN to benzaldehyde). Based on kinetic studies, a mechanism for the cyanosilylation of aldehydes catalyzed by **20** was proposed: the aldehyde was activated by the pentavalent aluminium and TMSCN interacting with the internal phosphane oxide could then transfer the cyanide to the aldehyde to give the observed *S* product.



Scheme 13. Asymmetric cyanosilylation of aldehydes catalyzed by the bifunctional aluminium complex **20**.

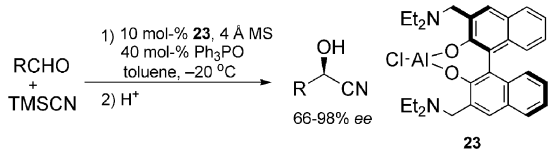
Catalyst **20** was then applied in the synthesis of natural anti-tumor agents Epothilone A and B by Shibasaki and co-workers in 2000 (Scheme 14).[12d,12e] The key step is the asymmetric addition of TMSCN to the α,β-unsaturated aldehyde **21**. After a careful investigation of different conditions, cyanohydrin **22** was obtained in 97% yield and 99% *ee* using 5 mol-% of the catalyst **20** in the presence of 20 mol-% of tributylphosphane oxide in CH_2Cl_2 at –40 °C. Note that slow addition of TMSCN over 50 h was essential to achieve this result.

Nájera and Saá and co-workers designed the recoverable bifunctional catalyst BINOLAM [(*S*)- or (*R*)-2,2′-bis(diethylaminomethyl)-substituted binaphthol] based on a monometallic aluminium complex for the highly enantioselective cyanosilylation of aldehydes (Scheme 15).[12i] Excellent results (up to 99% yield with 98% *ee*) were obtained for a range of aldehydes. The methodology was also



Scheme 14. Application of catalyst **20** in the total synthesis of natural products Epothilone A and B.

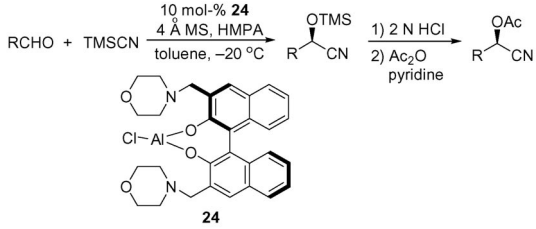
successfully used for the synthesis of a precursor of Epothilone A. Moreover, slow addition of TMSCN was not necessary.

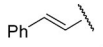
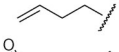
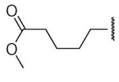


Scheme 15. Asymmetric cyanosilylation of aldehydes catalyzed by (*S*)-BINOLAM.

The asymmetric trimethylsilylcyanation of a variety of aliphatic aldehydes using an optically active dimorpholinyl-BINOL-derived bifunctional ligand was devised by Pu and co-workers (Table 1).[12k] Using 10 mol-% of the catalyst **24**

Table 1. Asymmetric cyanosilylation of aliphatic aldehydes promoted by the catalyst system of Pu and co-workers.[12k]



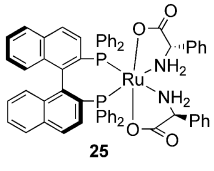
R	*t* (h)	Yield (%)	*ee* (%)
$CH_3(CH_2)_6$	24	91	97
$CH_3(CH_2)_7$	24	92	98
$CH_3(CH_2)_3$	24	87	96
1-cyclohexenyl	24	90	99
*i*Pr	24	65	97
	24	72	96
	24	86	95
	24	70	98
	24	74	94
	24	67	96
	24	90	92
Ph	24	99	94

generated in situ from the above ligand and dimethylaluminium chloride in the presence of 4 Å molecular sieves and 40 mol-% HMPA, a range of aliphatic aldehydes, including linear, branched, α,β-unsaturated, and functionalized substrates, were converted into the corresponding cyanohydrins with 92–99% *ee*. In addition, a remarkable positive nonlinear effect implied that the catalytic process may involve aggregated Al complexes.

2.1.4 Chiral Ruthenium Complexes

Very recently, Ohkuma and co-workers disclosed a strategy for the cyanosilylation of aldehydes that involved the use of the highly active, robust, and enantioselective catalyst **25** composed of [Ru(phgly)$_2$(binap)] {phgly = phenylglycinate, binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl} and Li_2CO_3 (Table 2).[13] The reaction was conducted with a substrate-to-catalyst ratio (S/C) of 10000:1 at –78 to –70 °C and with an S/C of 100000:1 at –40 °C. A series of aromatic, heteroaromatic, aliphatic, and α,β-unsaturated aldehydes were converted into the silylated cyanohydrins with up to 98% *ee*. On the basis of ESI-MS and NMR analyses, it was assumed that the formation of an active chiral Ru–Li bimetallic complex was crucial for the reaction system.

Table 2. Asymmetric cyanosilylation of aldehydes catalyzed by Ohkuma and co-workers's robust catalyst system.[13]



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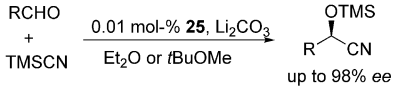


R	*T* [°C]	S/C	*t* [h]	Yield [%]	*ee* [%]
Ph	–78	10000:1	12	98	97
Ph	–40	100000:1	24	94	90
2-MeC_6H_4	–78	10000:1	18	99	96
2-FC_6H_4	–78	10000:1	12	97	96
2-ClC_6H_4	–78	10000:1	12	97	94
3-ClC_6H_4	–78	10000:1	12	98	98
4-ClC_6H_4	–70	10000:1	12	96	97
4-MeC_6H_4	–70	10000:1	24	95	97
4-MeOC_6H_4	–70	10000:1	24	99	96
4-$CF_3C_6H_4$	–78	10000:1	12	98	94
1-Naphthyl	–70	10000:1	18	97	95
2-Furyl	–70	10000:1	18	97	93
3-Pyridyl	–78	10000:1	18	91	93
*t*Bu	–78	10000:1	18	92	95
1-Cyclohexenyl	–70	10000:1	18	92	93
(*E*)-C_6H_5CH=CH	–78	10000:1	18	93	91

2.1.5 Other Metal Complexes

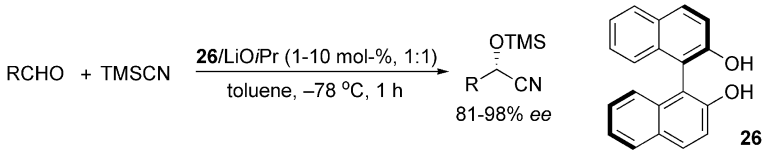
Other efficient chiral metal complexes have also been successfully applied to the catalytic enantioselective cyanosilylation of aldehydes. They included magnesium,[14] vanadium,[15] manganese,[16] cobalt,[17] yttrium,[18] tin,[19] lanthanide,[20] rhenium,[21] and bismuth complexes.[22]

2.1.6 Chiral Base Catalysts

The catalytic asymmetric addition of TMSCN to aldehydes mainly involves chiral Lewis acids. In 2000, Holmes and Kagan reported the first catalytic enantioselective cyanosilylation of aldehydes using chiral bases as catalysts.[23a] They screened a range of chiral phenols including BINOL and Schiff bases. The results indicated that the monolithium salt of (*S*)-BINOL was the best catalyst for the cyanosilylation of aromatic aldehydes. A maximum of 59% *ee* was observed for *p*-tolualdehyde in 15 min at –78 °C in Et_2O. However, poor enantioselectivities for aliphatic and many other aromatic aldehydes were obtained with this system.

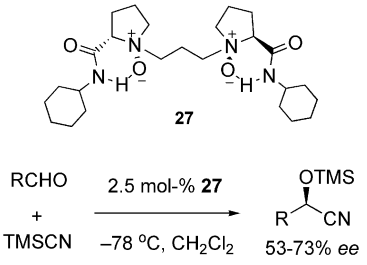
Recently, Ishihara and co-workers achieved a significant improvement over Holme and Kagan's results by using simple and inexpensive chiral lithium binaphtholate aqua or alcohol complexes (Scheme 16).[23c] The results showed that, in general, the reactions took place efficiently (85 to >99% yields) with high levels of enantioselectivity (81–98% *ee*) for aromatic aldehydes in 1 h with 1–10 mol-% catalyst loading. Notably, the protocol was suitable for a practical gram-scale cyanohydrin synthesis in minimum solvent. On the basis of nonlinear effect studies, the authors assumed that the presence of hydroxy compounds, just like water, would cause dissociation of oligomeric complexes of low activity to give highly active monomers.

On the other hand, some achiral *N*-oxides have been used as bases in the synthesis of racemic cyanohydrins.[24] Therefore we wondered whether chiral *N*-oxides could catalyze the asymmetric cyanosilylation of aldehydes (Scheme 17). After a careful test of reaction conditions, L-proline-based *N*,*N*′-dioxide **27** was identified as the most effective chiral base for the asymmetric cyanosilylation of aldehydes with 2.5 mol-% catalyst loading at –78 °C.[25a] Aromatic aldehydes gave better results with good yields and up to 73% *ee*. In general, alkyl, alkoxy, and halogen groups at the *meta* position of the aromatic ring were tolerated well (66–71% *ee*), whereas substituents at the *para* position gave slightly



Scheme 16. Asymmetric cyanosilylation of aldehydes catalyzed by the monolithium salt of (*R*)-BINOL (**26**).

lower *ee* values. Heterocyclic and aliphatic aldehydes gave moderate enantioselectivities (53–62% *ee*). Even so, this is one of the few examples of catalytic asymmetric cyanosilylation of aldehydes using organocatalysts.[25,31c]



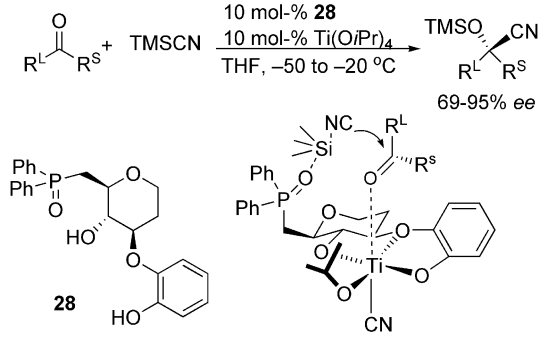
Scheme 17. Asymmetric cyanosilylation of aldehydes catalyzed by the chiral organocatalyst *N*,*N*′-dioxide **27**.

2.2 Cyanosilylation of Ketones

In sharp contrast, the development of the cyanosilylation of ketones has been quite slow due to the decreased steric discrimination and the lower reactivity of ketones relative to aldehydes. However, the corresponding cyanohydrins are currently quite important building blocks as precursors of chiral quaternary α-hydroxy carbonyl derivatives in organic synthesis. Recently, breakthroughs to resolve the long-standing problems associated with ketones have been achieved.

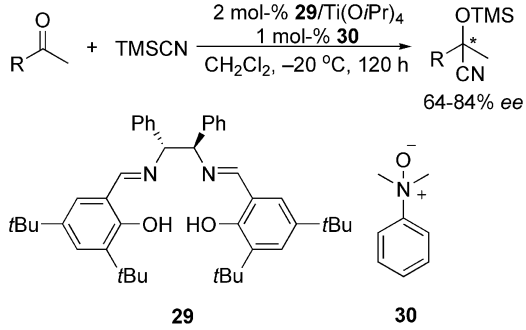
2.2.1 Chiral Titanium Complexes

In 2000, the first general and highly enantioselective cyanosilylation of ketones was reported by Shibasaki and coworkers (Scheme 18) using a novel bifunctional catalyst containing titanium and phosphane oxide.[26c] This catalyst system is tolerated by a range of ketones, including even sterically hindered and cyclic ketones, many of which had been thought of as extremely difficult to address, giving tertiary (*R*)-cyanohydrin *O*-TMS ethers in 72–92% yields with 69–95% *ee*. Based on these excellent results, the mechanism of the reaction was investigated and a proposed scheme is depicted in Scheme 18.



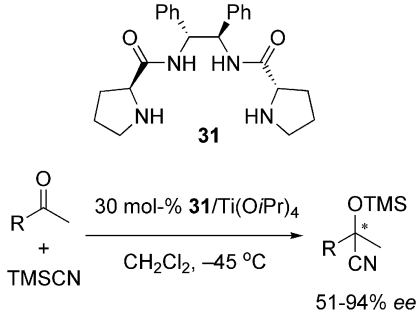
Scheme 18. Asymmetric cyanosilylation of ketones catalyzed by the **28**/Ti(O*i*Pr)$_4$ complex.

In 2003, we developed a highly efficient catalyst system for the enantioselective cyanosilylation of ketones through a catalytic double-activation method (CDAM) in which a chiral Lewis acid [**29**/Ti(O*i*Pr)$_4$, 2 mol-%] activates the electrophile and an achiral Lewis base (*N*-oxide **30**, 1 mol-%) activates the nucleophile (Scheme 19).[26g] Remarkably, a one-step synthesis of the catalyst from commercially available materials, low catalyst loading, and mild reaction conditions all make this protocol practical. However, the reaction time is quite long.



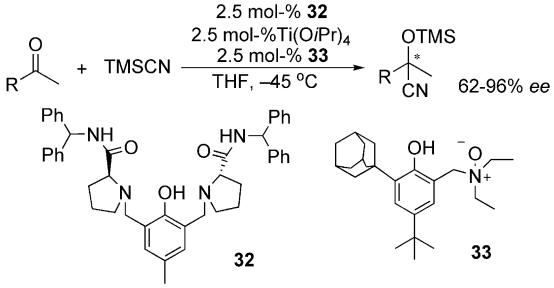
Scheme 19. Chiral Schiff base **29** and achiral *N*-oxide **30** used in the dual activation method.

We also investigated other scaffolds applicable as bifunctional catalyst ligands. We used the diamine derivative **31** to form a complex with Ti(O*i*Pr)$_4$, which gave up to 94% *ee* for the trimethylsilylcyanation of ketones (Scheme 20).[26l]



Scheme 20. Cyanosilylation of ketones using the **31**/Ti(O*i*Pr)$_4$ complex.

Later we investigated a new bifunctional catalyst system consisting of (*S*)-prolinamide, Ti(O*i*Pr)$_4$, and phenolic *N*-oxide for a highly enantioselective cyanosilylation of ketones (Scheme 21).[26m] In the presence of 2.5 mol-% catalyst, a variety of aromatic and aliphatic ketones were converted into the corresponding tertiary cyanohydrin *O*-TMS ethers in excellent yields (up to 96%) and high enantioselectivities (up to 96% *ee*). In a plausible catalytic cycle, titanium(IV) could act as a Lewis acid to activate the carbonyl group and the *N*-oxide moiety could act as a Lewis base to activate TMSCN simultaneously.



Scheme 21. Enantioselective trimethylsilylcyanation of ketones using the **32**/**33**/Ti(O*i*Pr)$_4$ catalytic system.

2.2.2 Lanthanide-Based Catalysts

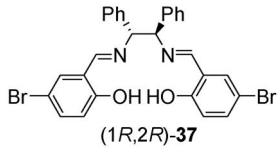
In 2001, Shibasaki and co-workers demonstrated a highly enantioselective cyanosilylation of ketones catalyzed by a chiral gadolinium system. The catalyst prepared from ligand **28** and Gd(O*i*Pr)$_3$ gave excellent results for aryl and alkyl ketones, giving cyanohydrin trimethylsilyl ethers in 85–97% yields and with 62–97% *ee*.[27a] Notably, this system gave products with opposite absolute configurations in comparison with the titanium complex of **28**. Ligand **28** complexed to Sm(O*i*Pr)$_3$ was applied to the preparation of a key intermediate in the synthesis of Camptothecin (Scheme 22). The samarium catalyst could generate **35** from precursor **34** in 98% yield and with 84% *ee*. Subsequently, synthetic intermediates **36** could be purified by recrystallization to give a final enantiomeric excess of 99%.

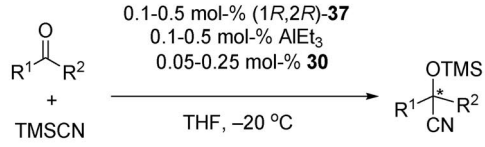
2.2.3 Chiral Aluminium Catalysts

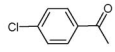
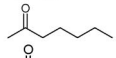
The catalytic double-activation method was not limited to the titanium system. We have shown that catalyst systems composed of the chiral salen (1*R*,2*R*)-**37**/AlEt$_3$ complex and *N*-oxide **30** have even higher catalytic turnovers (200 for aromatic ketones, 1000 for aliphatic ones) with high enantioselectivity (up to 94% *ee* for aromatic ketones, up to 90% *ee* for aliphatic ones) under mild conditions (Table 3).[28a]

Control experiments were performed to provide an insight into the mechanism. Neither the (1*R*,2*R*)-**37**/AlEt$_3$ complex nor the *N*-oxide **30** on its own was effective enough to accelerate the addition of TMSCN to acetophenone.

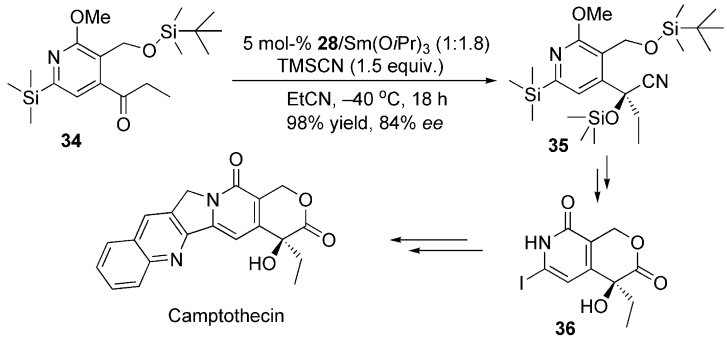
Table 3. Enantioselective cyanosilylation of ketones catalyzed by the (1*R*,2*R*)-**37**/AlEt$_3$ complex and *N*-oxide **30**.[a]



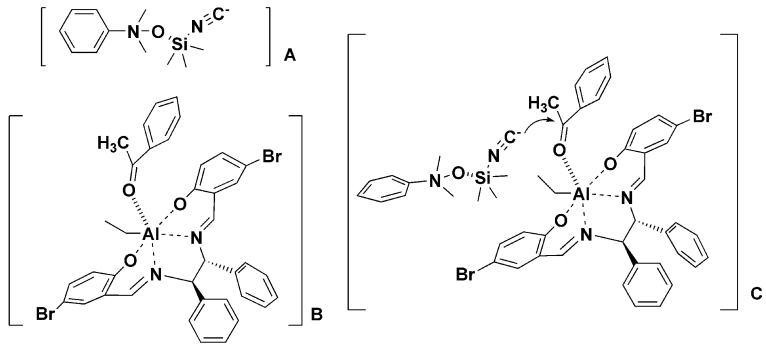


Ketones	Method	*t* (h/d)	Yield (%)	*ee* (%)
	A	46 h	94	93
	B	16 d	99	94
	A	48 h	99	92
	B	9.5 d	99	90
	A	28 h	98	92
	A	66 h	99	90
	A	24 h	99	92
	A	32 h	99	88
	B	9 d	99	92
	A	40 h	99	86
	B	7 d	99	90
	A	36 h	95	90
	B	9 d	95	90
	A	40 h	92	84
	B	13 d	99	87
	A	3 d	96	79
	B	16 d	99	81
	B	36 h	99	79
	B	36 h	95	80
	B	36 h	80	90

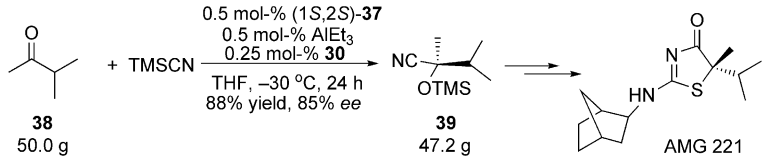
[a] Method A: (1*R*,2*R*)-**37**/AlEt$_3$ complex (1:1, 0.5 mol-%), **30** (0.25 mol-%), TMSCN (2.0 equiv.), –20 °C, [ketone] = 1.5 M in THF. Method B: (1*R*,2*R*)-**37**/AlEt$_3$ complex (1:1, 0.1 mol-%), **30** (0.05 mol-%), TMSCN (2.0 equiv.), –20 °C, [ketone] = 2.4 M in THF.



Scheme 22. Asymmetric addition of TMSCN to **34**.



Scheme 23. Proposed intermediate and transition state involved in the double-activation catalysis.



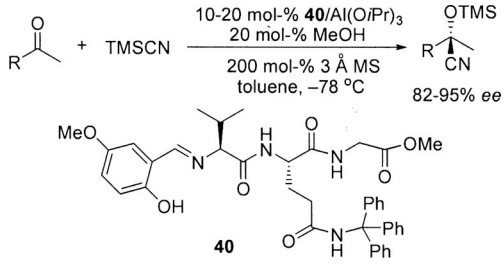
Scheme 24. Application of the catalytic double-activation method to the synthesis of AMG 221.

Only when the two were used synergistically in a double-activation way would this transformation perform perfectly. In addition, when the *N*-oxide was mixed with the Lewis acid at the start of the reaction, rather than following the usual procedure, the product was obtained with comparable enantioselectivity but in low yield. Direct evidence for the coordination of the *N*-oxide to TMSCN was obtained by ^{1}H NMR analysis.

Therefore the salen/Al complex and *N*-oxide should work cooperatively in asymmetric double-activation catalysis. The aluminium complex acted as a Lewis acid to activate the ketone and the *N*-oxide as a Lewis base to activate TMSCN. The corresponding intermediates A and B are shown in Scheme 23, with an isocyanide species formed in the former. The activated nucleophile and substrate attracted and approached each other and so the transition state C was formed. Formation of a more stable O–Si bond then promoted the intramolecular transfer of the cyanide to the carbonyl group to give the cyanohydrin *O*-TMS ether as product.

The elegant asymmetric synthesis of AMG 221 by Caille et al. in 2009 involved the enantioselective cyanosilylation of ketones as the key step (Scheme 24).[28f] By using our catalyst system, the key intermediate **39** was isolated in 88% yield (47.2 g) with 85% *ee* in the presence of 0.5 mol-% (1*S*,2*S*)-**37**/AlEt$_3$ (1:1) and 0.25 mol-% **30**. Six additional steps allowed the synthesis of AMG 221, which is an inhibitor of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).

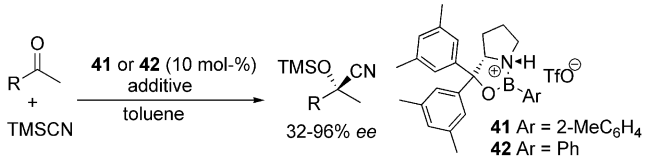
Snapper and Hoveyda and co-workers investigated a chiral peptide/aluminium complex for the cyanosilylation of ketones (Scheme 25).[28c] This catalyst system exhibited excellent results (67–97% yields and 82–95% *ee*) for aromatic and aliphatic ketones (saturated and unsaturated). Notably, the chiral ligand **40** was readily modified and easily synthesized in six steps with 75% overall yield.



Scheme 25. Enantioselective trimethylsilylcyanation of ketones promoted by the **40**/Al(O*i*Pr)$_3$ catalyst system.

2.2.4 Chiral Boron-Based Catalyst

After successfully applying the boron-based catalyst in the asymmetric cyanosilylation of aldehydes,[6b] Ryu and Corey studied the use of **41** and **42** in the enantioselective addition of TMSCN to ketones (Scheme 26).[29] Under optimized conditions, the catalysts were applied in the reactions of various methyl ketones in the presence of triphenylphosphane oxide or methyl diphenylphosphane oxide (11–20 mol-%) as additive, which gave the desired products with good-to-excellent results. The reaction times (2–14 days) were, however, slightly extended.

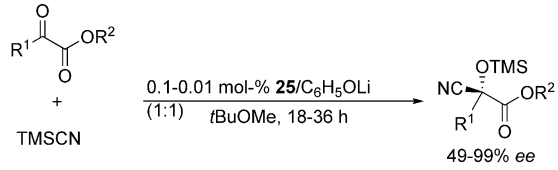


Scheme 26. Chiral boron-based catalysts **41** and **42** used in the addition of TMSCN to ketones.

2.2.5 Chiral Ruthenium Complexes

Very recently, Ohkuma and co-workers described the first example of the enantioselective cyanosilylation of α-

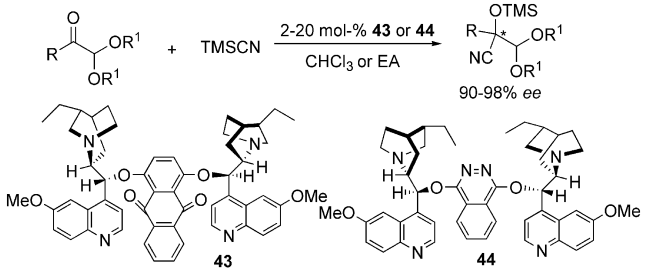
keto esters using a catalyst system consisting of the [Ru(phgly)$_2$(binap)] complex (**25**) and C_6H_5OLi (Scheme 27). A variety of aromatic, heteroaromatic, aliphatic, and α,β-unsaturated α-keto esters were tested and the corresponding silylated cyanohydrins were obtained with excellent results (49–99% *ee* and 92–98% yields) with 0.1–0.01 mol-% catalyst loading.[30]



Scheme 27. The first catalytic asymmetric cyanosilylation of α-keto esters.

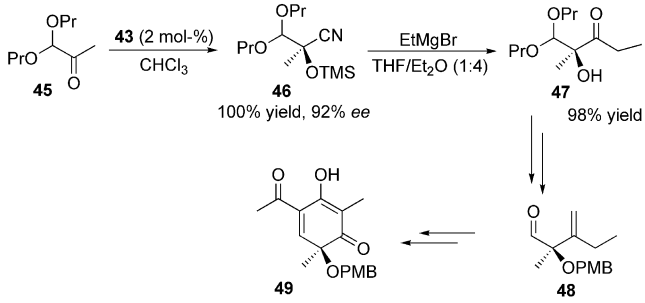
2.2.6 Chiral Organocatalysts

The cyanosilylation of α,α′-dialkoxy ketone (acetal ketone) has attracted great interest owing to the importance of the acetal group as a precursor to many functionalities. In 2003, Deng and co-workers reported the first highly enantioselective cyanosilylation of ketones catalyzed by recyclable chiral Lewis base **43** or **44** (Scheme 28).[31a] Under optimized conditions, enantiomeric excesses of 90–98% were obtained for acetal ketones bearing a broad range of aryl, alkenyl, alkynyl, and alkyl substituents. They also demonstrated the application of the catalyst to the synthesis of several optically active multifunctional chiral building blocks bearing a quaternary stereocenter.



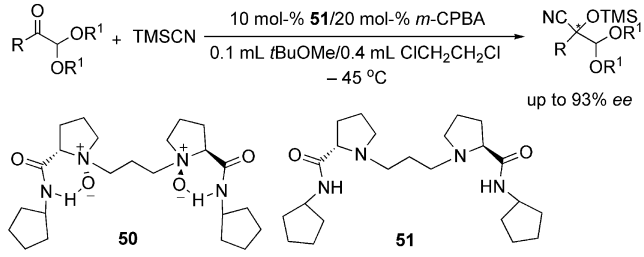
Scheme 28. The first highly enantioselective cyanosilylation of ketones catalyzed by chiral bases.

In 2005, Deng and co-workers successfully applied their catalyst system to the enantioselective total synthesis of bisorbicillinolide, bisorbicillinol, and bisorbibutenolide.[31b] The key intermediate quinol **49** was derived from aldehyde **48** by Knoevenagel condensation and subsequent Claisen–Vorländer condensation. Aldehyde **48** was obtained from cyanohydrin **46**, which was prepared in 92% *ee* and 100% yield on a multigram scale by enantioselective cyanosilylation of acetal **45** with **43** as catalyst (Scheme 29).



Scheme 29. Application of Lewis base **43** to the cycanosilylation of acetal **45**.

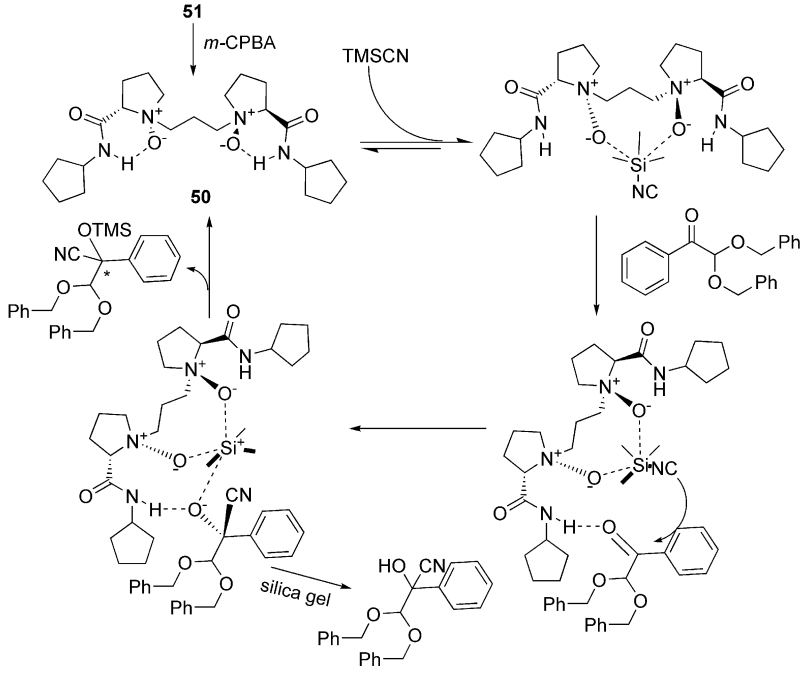
Building on the successful application of *N*,*N*′-dioxide **27** to the asymmetric cyanosilylation of aldehydes,[25a] we studied the asymmetric addition of TMSCN to acetophenone in the presence of *N*,*N*′-dioxide **27**. Unfortunately, the reaction proceeded sluggishly. However, α,α′-diethoxy-1-phenylethanone showed better reactivity and enantioselectivity.[31e] Further studies showed that the *N*,*N*′-dioxide **50** generated in situ from the amide **51** and *m*-CPBA retained the same reactivity and enantioselectivity. With aromatic acetal ketones, the bulkier dibenzyl acetal was superior to the dimethyl and diethyl ones. With a diisopropyl acetal group in the aliphatic ketone, an increased reaction rate and comparable enantioselectivity were detected. Excellent yields (73–99%) and high enantioselectivities (85–93% *ee*) of the cyanohydrin trimethylsilyl ethers were obtained with acetal ketones bearing a broad range of aryl, alkenyl, and alkyl substituents under optimized conditions (Scheme 30).



Scheme 30. Highly enantioselective cyanosilylation of α,α′-dialkoxy ketones catalyzed by *N*,*N*′-dioxide organocatalyst **50**.

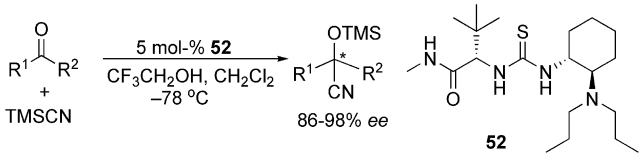
A strong linear correlation effect between the product and the catalyst **50** revealed that the Si atom of TMSCN might be activated by one molecule of the *N*-oxide catalyst. ^{1}H NMR spectroscopy also confirmed that one of the amidic NH protons served as a Brønsted acid to activate the carbonyl group of the substrate. These experiments have again demonstrated that the *N*,*N*′-dioxide is an efficient bifunctional organocatalyst in asymmetric cyanosilylation reactions. The assumed catalytic cycle of this enantioselective reaction is shown in Scheme 31.

Based on their research on chiral urea and thiourea catalysts, Jacobsen and co-workers described in 2005 a highly enantioselective cyanosilylation of ketones with new bifunctional thiourea-amine derivative **52** (Scheme 32).[31c,31d] The catalyst system could be applied to a variety of ketones to



Scheme 31. Proposed catalytic cycle.

give the corresponding adducts in excellent yields (81–98%) and *ee* values (86–98%) by using 5 mol-% catalyst loading for 12–48 h. Notably, **52** was also found to be an efficient catalyst for the cyanosilylation of aldehydes. Benzaldehyde and *trans*-cinnamaldehyde reacted with TMSCN in the presence of **52** (0.05 mol-%) and CF_3CH_2OH (20 mol-%) within 2 h to give products with 96 and 93% *ee*, respectively.



Scheme 32. Asymmetric cyanosilylation of ketones catalyzed by thiourea **52**.

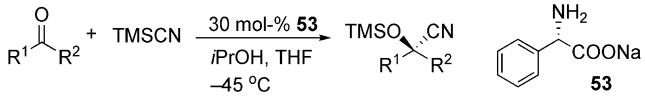
2.2.7 Chiral Organic Acid Salts

As well as with *N*-oxides, R_3SiX compounds can be activated by nucleophiles such as RCO_2^-, RO^-, HMPA, and DMF via the formation of hypervalent silicon intermediates.[32] Inspired by the interesting finding that K_2CO_3 can be used as an efficient heterogeneous catalyst for the synthesis of racemic cyanohydrins,[24] we extended this approach to the asymmetric cyanation of ketones with readily accessible amino acid salts.[33a]

The initial catalyst screening revealed that L-phenylglycine sodium salt **53** was the most effective catalyst. Both the primary amine and metal carboxylate moieties of the catalyst are essential for catalytic activity and asymmetric induction. Moreover, some key features should be noted: 1) The system experienced large solvent effects and in THF a higher *ee* value was obtained. 2) The experimental procedure had a large influence on the enantioselectivity: When the catalyst was stirred with TMSCN in THF for 1 h at 30 °C before acetophenone was added, the enantioselectivity was greatly improved from 54 to 80% *ee* at –20 °C and up to 94% *ee* at –45 °C. 3) It was found that a small amount of water in the catalyst was crucial for high enantioselectivity and only a racemic product was formed without the protonic additive. 4) Introduction of *i*PrOH significantly increased the reaction rate, with complete conversion of acetophenone within 24 h at –45 °C without loss of enantioselectivity.

The scope of the L-phenylglycine sodium salt catalyzed enantioselective cyanosilylation was explored with a variety of ketones. Table 4 summarizes the most significant results

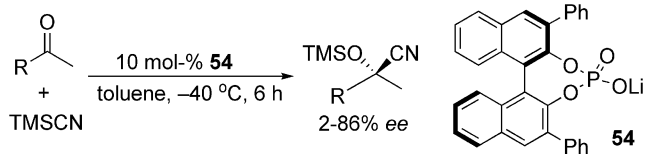
Table 4. Cyanosilylation of ketones catalyzed by the chiral amino acid salt **53**.



Ketones	*t* [h]	Yield [%]	*ee* [%]
PhCOMe	24	96	94
4-$MeOC_6H_4COMe$	54	81	92
4-MeC_6H_4COMe	54	75	97
4-FC_6H_4COMe	27	90	92
4-ClC_6H_4COMe	40	83	90
3-ClC_6H_4COMe	54	80	96
2-FC_6H_4COMe	36	77	90
2-Acetylthiophene	54	84	86
trans-PhCH=CHCOMe	27	96	97
β-Acetonaphthone	27	90	96
Benzylacetone	20	97	81
3-Methylbutanone	20	92	55

obtained under optimized conditions. Up to 97% *ee* was obtained for a variety of aromatic and heteroaromatic ketones and a moderate enantioselectivity was obtained for the aliphatic ketone 3-methylbutanone. L-Phenylglycine could be easily and efficiently recovered for reuse after the reaction by simple filtration and acidic treatment.

In 2008, Ishihara and co-workers developed a catalytic asymmetric cyanosilylation of aromatic ketones promoted by the chiral lithium salt **54**.[33b] The corresponding tertiary cyanohydrin *O*-TMS ethers were obtained in high yields with moderate-to-high enantioselectivities (up to 86% *ee*; Scheme 33).



Scheme 33. Cyanosilylation of ketones catalyzed by the chiral lithium salt **54**.

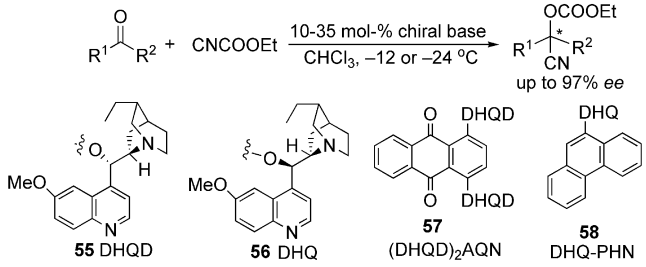
These reactions were mechanistically interesting as the chiral organic salt approach differs from the known enzyme- and transition-metal-based methods and provides an alternative method for the creation of asymmetric quaternary atoms. Another intriguing catalytic process is the cyanosilylation of aldehydes using BINOLates and "salenates" discovered by Holmes and Kagan[23] and later improved by Ishihara and co-workers as described above. Further studies on chiral anion salts as well as chiral cation salts in asymmetric catalysis will undoubtedly continue to be the focus of much research.

3. Use of CNCOOR in the Catalytic Enantioselective Cyanation of Aldehydes and Ketones

The high cost and toxicity of TMSCN is a major barrier to its use on an industrial scale. In this regard, cyanoformate esters (CNCOOR) are a cheaper and less toxic source of cyanide. Moreover, alkyl-carbonylated cyanohydrins are stable and not easily hydrolyzed by moisture in air. They are useful synthetic intermediates and can be applied in the synthesis of α-amino alcohols and β-substituted unsaturated nitriles from *O*-carbonylated allylic cyanohydrins.

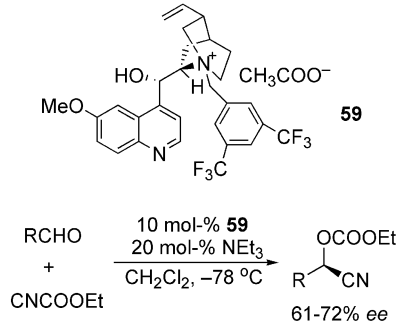
3.1 Chiral Organocatalysts

The first report on the use of ethyl cyanoformate (CNCOOEt) in the asymmetric synthesis of cyanohydrin carbonates was by Tian and Deng in 2001 (Scheme 34).[34a] In this case, dimeric chincona alkaloid derivatives **57** and **58** were used as catalysts for the addition of ethyl cyanoformate to alkyl, cyclic, and hindered ketones, which gave cyanohydrin ethyl carbonates with 59–97% *ee*.



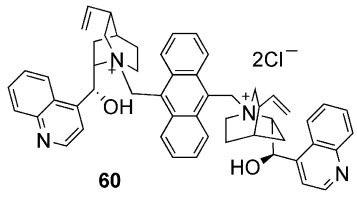
Scheme 34. The first organocatalytic enantioselective cyanoformylation of ketones.

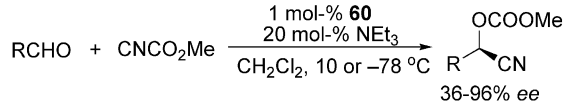
Based on the fact that the quaternary ammonium salt **59** might activate the carbonyl group through the positively charged nitrogen atom and the free hydroxy group, and triethylamine might function as a Lewis base to activate ethyl cyanoformate, we developed an efficient enantioselective cyanation of aldehydes with CNCOOEt (Scheme 35).[34c] The reactions gave excellent yields (up to 97%) with moderate enantioselectivities (up to 72% *ee*) and represent the first organocatalytic enantioselective cyanation of aldehydes with $CNCO_2Et$.



Scheme 35. The first organocatalytic enantioselective cyanoformylation of aldehydes.

In more recent work, Chinchilla et al. reported an enantioselective cyanoformylation of aldehydes using the recyclable dimeric cinchonidine ammonium salt **60** as an organocatalyst.[34e] High yields (43–99%) and enantioselectivities (36–96% *ee*) of the corresponding (*R*)-*O*-methoxycarbonylcyanohydrins were obtained using only 1 mol-% catalyst loading (Scheme 36).



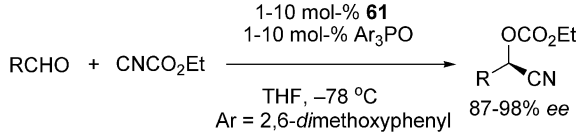


Scheme 36. Asymmetric addition of methyl cyanoformate to aldehydes.

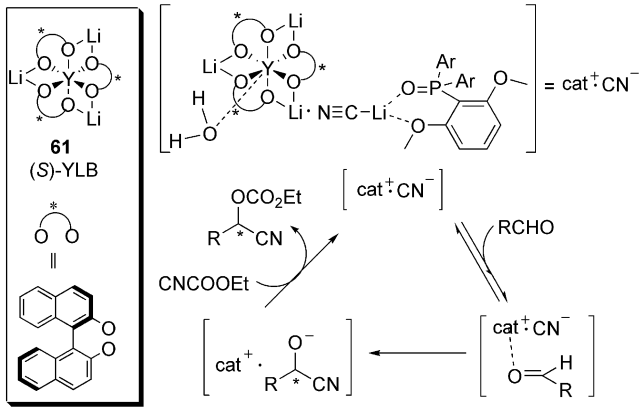
3.2 Chiral Yttrium Complexes

In 2002, Shibasaki and co-workers achieved the first asymmetric cyanoformylation of aldehydes with ethyl cyanoformate using BINOL-based heterobimetallic complex (*S*)-YLB **61** as catalyst (Table 5).[35a,35b] The short reaction time (<3 h) for all aldehydes and broad substrate generality are notable. Based on their elaborate mechanistic studies, a postulated catalytic cycle for the reaction is depicted in Scheme 37.

Table 5. Asymmetric cyanoformylation of aldehydes using (*S*)-YLB.



R	*t* [h]	Yield [%]	*ee* [%]
Ph	2	96	94
1-Naphthyl	2	97	90
(*E*)-$CH_3(CH_2)_2CH$=CH	3	100	92
(*E*)-PhCH=CH	3	100	91
$CH_3(CH_2)_4$	3	93	94
CH_3CH_2	2	79	92
$(CH_3)_2CH$	2	88	98
cC_6H_{11}	2	97	96
$(CH_3)_3C$	3	93	87

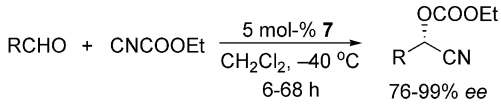


Scheme 37. Proposed catalytic cycle for the asymmetric cyanoformylation of aldehydes with ethyl cyanoformate using (*S*)-YLB **61** as catalyst.

They then used this catalyst system in the total synthesis of (+)-patulolide C (Scheme 38).[35c] The key step is the enantioselective cyanoformylation of the α,β-unsaturated aldehyde **62** followed by thermal 1,3-sigmatropic rearrangement to yield the intermediate **64**.

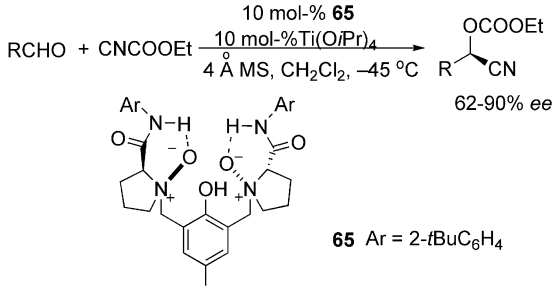
3.3 Chiral Titanium Complexes

In 2003, Belokon' and North and co-workers applied their dimeric Ti/salen complex **7** in the asymmetric addition of ethyl cyanoformate to aldehydes (Scheme 39),[36a] which provided cyanohydrin carbonates with excellent enantiomeric excesses (76–99%).

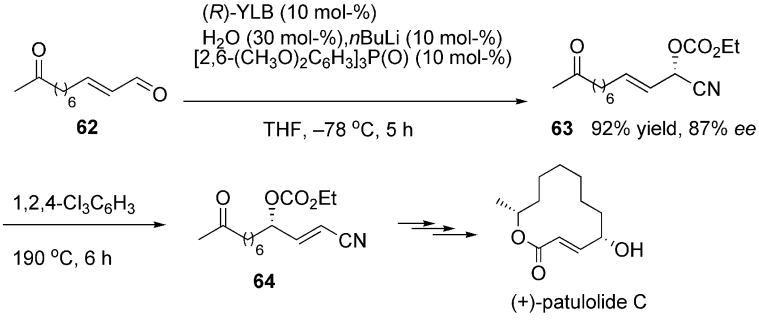


Scheme 39. Asymmetric addition of ethyl cyanoformate to aldehydes.

In our continued efforts to develop *N*,*N*′-dioxide catalysts, we synthesized a series of new chiral prolinamide-derived *N*,*N*′-dioxide ligands.[36e] The enantioselective addition of ethyl cyanoformate to a range of aldehydes was efficiently catalyzed by the easily prepared C_2-symmetric chiral *N*,*N*′-dioxide **65**/Ti(O*i*Pr)$_4$ complex, which gave the product cyanohydrins in high yields with up to 90% *ee* (Scheme 40). Finally, a clear linear effect was observed in this reaction. The result simply indicates that homochiral polymeric **65**/Ti(O*i*Pr)$_4$ (1:1) complexes are more stable than heterochiral polymers in the stereo-discriminating step of the reaction.

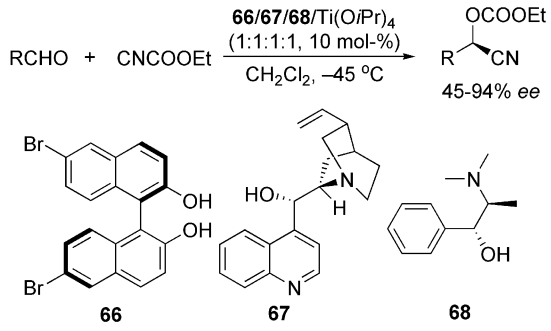


Scheme 40. Asymmetric cyanoformylation of aldehydes catalyzed by the **65**/Ti(O*i*Pr)$_4$ complex.



Scheme 38. Application of (*R*)-YLB catalyst system in the total synthesis of (+)-patulolide C.

Stimulated by the bifunctional catalysis methods, we wished to explore whether the combination of BINOL derivatives with chiral amines would improve enantioselectivity and reactivity: In such a system a metallic reagent (titanium) would act as a Lewis acid to activate the substrate (carbonyl group) and the nitrogen atom of the amine would act as a Lewis base to activate the nucleophile (CNCOOEt). Thus, a multicomponent bifunctional catalyst system based on titanium was designed for the efficient enantioselective cyanoethoxycarbonylation of aldehydes (Scheme 41).[36f] The catalyst was readily prepared from $Ti(OiPr)_4$, (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol **(66)**, cinchonine **(67)**, and (1*R*,2*S*)-(–)-*N*-methylephedrine **(68)**. The reaction proceeded smoothly in the presence of 10 mol-% of the multicomponent titanium catalyst to afford the desired cyanohydrin ethyl carbonates in moderate-to-excellent yields (up to 95%) with high enantioselectivities (up to 94% *ee*).



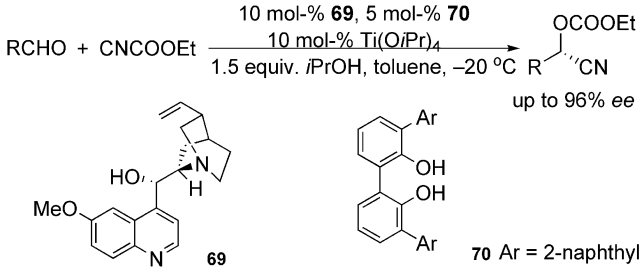
Scheme 41. Asymmetric cyanoformylation of aldehydes catalyzed by a multicomponent titanium complex.

Next we focused on whether the chiral BINOL derivatives could be replaced by achiral 2,2′-biphenol (bipol) derivatives, wherein asymmetric synthesis or resolution is not required. After systematic optimization, the substrate scope was investigated under the optimized conditions and the results are reported in Table 6.[36j] Not only aromatic and heteroaromatic aldehydes but also aliphatic aldehydes worked well in this reaction with excellent yields (91–99%) and enantioselectivities (84–96% *ee*) obtained. In particular, 3-phenoxybenzaldehyde, which is useful for the synthesis of the insecticide fenvalerate A_α, gave the product in high yield with the best *ee* (96%),.

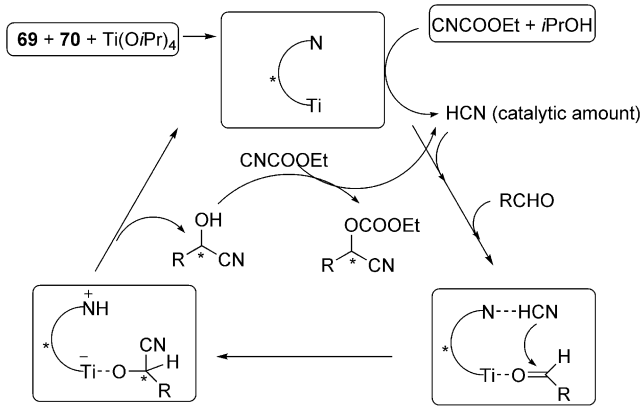
On the basis of control experiments, spectroscopic data, and discussions, the catalyst structure and the real cyanide reagent were identified. It is reasonable to assume that the reaction proceeds through a dual activation mechanism. As illustrated in Scheme 42, Ti^{IV} acts as Lewis acid to activate the electrophile (C=O) whereas the tertiary amine in **69** works as a Lewis base to activate nucleophile HCN (catalytic amount) generated in situ from *i*PrOH and CNCOOEt.

Owing to the limitations of the three-component catalyst system mentioned above, such as the requirement of high catalyst loading and long reaction time, we developed a relatively simple self-assembled catalyst system from $Ti(OiPr)_4$, Schiff base **71**, and cinchonine **(67)** for the asymmetric cyanoformylation of aldehydes (Scheme 43).[36i] Excellent reactivities and enantioselectivities could be generated (up to 99% yield and 94% *ee*) in the presence of 5 mol-% catalyst loading in 2.5 h.

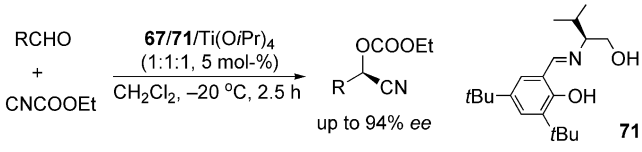
Table 6. Asymmetric cyanoformylation of aldehydes catalyzed by the **69/70**/$Ti(OiPr)_4$ complex.



R	*t* [h]	Yield [%]	*ee* [%]
Ph	5	98	94
4-FC_6H_4	5	95	90
4-ClC_6H_4	7	90	92
4-BrC_6H_4	7	91	91
4-PhC_6H_4	5	94	93
4-MeC_6H_4	5	97	93
4-$MeOC_6H_4$	7	99	90
3-$PhOC_6H_4$	15	95	96
3-$MeOC_6H_4$	7	99	93
3-MeC_6H_4	7	99	92
2-MeC_6H_4	7	98	90
2-Naphthyl	15	99	90
2-Furyl	15	96	93
2-Thienyl	15	98	90
Cinnamyl	15	99	84
*t*Bu	15	92	95



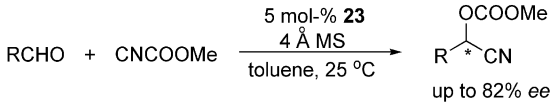
Scheme 42. Proposed catalytic cycle for the asymmetric cyanoformylation of aldehydes catalyzed by the **69/70**/$Ti(OiPr)_4$ complex.



Scheme 43. Asymmetric cyanoformylation of aldehydes catalyzed by the self-assembled titanium complex **67/71**/$Ti(OiPr)_4$.

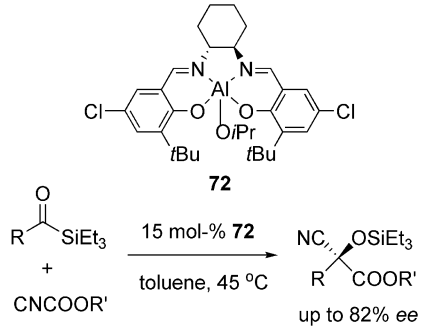
3.4 Chiral Aluminium Complexes

Nájera and Saá and co-workers applied their bifunctional catalyst BINOLAM [(*R*)- or (*S*)-**23**] in the asymmetric addition of methyl cyanoformate to aldehydes at room temperature, which gave the corresponding products with up to 82% *ee* (Scheme 44).[37a]

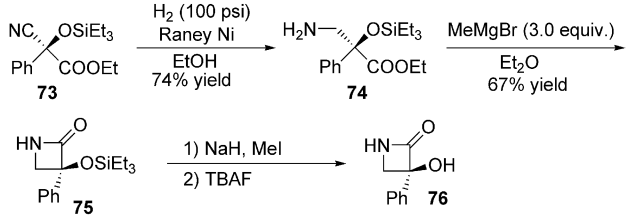


Scheme 44. Asymmetric addition of methyl cyanoformate to aldehydes.

Johnson and co-workers found that aluminium/salen complex **72** is an effective catalyst for the asymmetric cyanation of silyl ketones with ethyl and benzyl cyanoformate (Scheme 45).[37b,37c] The reaction took place through a cyanation/1,2-Brook rearrangement/*C*-acylation process to deliver various cyanohydrin triethylsilyl ethers of α-keto esters with moderate-to-good enantioselectivities (61–82% *ee*). Chemoselective reduction of the product **73** provided new enantioenriched α-hydroxy α-aryl β-amino acid derivative **74** and β-lactams **75** and **76** (Scheme 46). This reaction is a simple method for the construction of a new series of chiral building blocks.



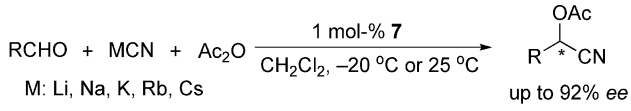
Scheme 45. Asymmetric cyanation/Brook rearrangement/*C*-acylation of acylsilanes.



Scheme 46. Derivatization of the product **73**.

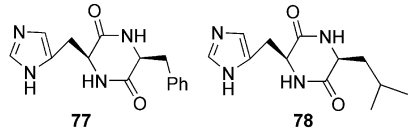
4. Use of Other Cyanide Sources in the Catalytic Enantioselective Cyanation of Aldehydes and Ketones

Sodium and potassium cyanides are the basic raw materials of all other cyanide sources and the cheapest source of cyanide. However, they are highly toxic on direct contact 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. However, they are still used as sources of cyanide in the asymmetric cyanation of aldehydes. Belokon' and North and co-workers reported a highly enantioselective addition of alkali cyanide and acetic anhydride to various aliphatic and aromatic aldehydes catalyzed by only 1 mol-% of the dimeric Ti/salen complex **7**, which gave enantiomerically enriched cyanohydrin esters in high yields (up to 99%) and enantioselectivities (up to 92%) (Scheme 47).[38a]



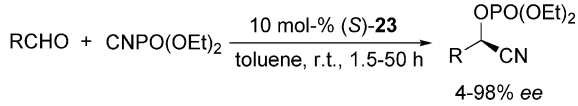
Scheme 47. Asymmetric addition of alkali cyanides to aldehydes catalyzed by the dimeric Ti/salen complex **7**.

As early as 1979, a highly enantioselective synthesis of cyanohydrins was achieved by Inoue and co-workers using a cyclic dipeptide as catalyst (Scheme 48). However, they used hydrogen cyanide (HCN) as the cyanide source, which is a highly toxic gas and requires careful containment and handling. Catalysts **77** and **78** were demonstrated to be general catalysts for the asymmetric addition of hydrogen cyanide to aromatic or aliphatic aldehydes (up to 97% *ee*). They also investigated the use of peptide/titanium complexes in the asymmetric addition of HCN to aldehydes.[39a–39c]



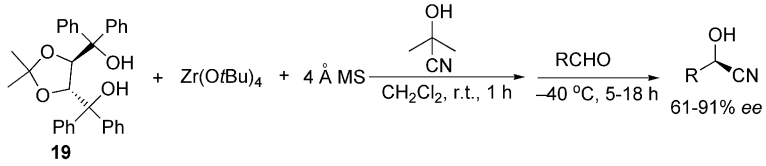
Scheme 48. Asymmetric addition of HCN to aldehydes catalyzed by cyclic dipeptide.

Nájera and Saá and co-workers reported the cyanophosphorylation of aldehydes with commercially available diethyl cyanophosphonate as a source of cyanide with various Lewis acids under different reaction conditions.[40a] Under the optimized conditions, as shown in Scheme 49, the product cyanophosphates were obtained in high yields (up to 90%) with *ee* values of up to 98% using 10 mol-% of the catalyst (*S*)-**23** in 1.5–50 h. Recently, these authors published a detailed report on the cyanophosphorylation of various aldehydes with mechanistic studies using the same catalyst under similar reaction conditions.[40b,40c]



Scheme 49. Asymmetric addition of diethyl cyanophosphonate to aldehydes catalyzed by (*S*)-**23**.

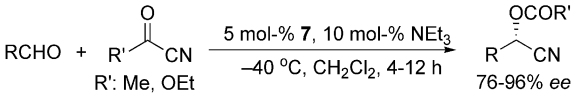
Acetone cyanohydrin is another important cyanating agent readily available on the commercially and is more manageable than HCN and alkali cyanides. Maruoka and



Scheme 50. Asymmetric addition of acetone cyanohydrin to aldehydes catalyzed by the TADDOL **19**/Zr(O*t*Bu)$_4$ complex.

co-workers first used it for the asymmetric cyanation of various aldehydes, which gave the corresponding cyanohydrins with high *ee* values (61–92%; Scheme 50).[41a,41b]

In 2005, Moberg and co-workers applied the catalyst **7** (5 mol-%) to the cyanation of various aldehydes using keto nitrile (acetyl cyanide) in the presence of 10 mol-% NEt_3, which produced the corresponding *O*-acetylated cyanohydrins in 64–90% yields and 76–96% *ee* (Scheme 51).[42a]



Scheme 51. Enantioselective cyanation of aldehydes through the dual Lewis acid–Lewis base activation method.

5. Conclusions

Despite the impressive number of contributions and results obtained for the catalytic enantioselective cyanation of aldehydes and ketones, many challenges remain. First, a better understanding of the various reaction mechanisms, as well as the further application of current catalyst systems, is necessary. The accumulation of such knowledge would contribute to the future development of catalytic asymmetric reactions in general. Secondly, there is still large room for improvement in both substrate scope and mildness of the reaction conditions for many of the methods described above. The catalytic enantioselective cyanation of unsymmetric diaryl ketones is still to be achieved. Reaction temperature, time, catalyst loading, modification of scale, and environmentally friendly protocols are all areas that undoubtedly will see considerable research effort. The recent work of Ohkuma and co-workers seems to offer possible ways to achieving these goals,[13,30] although the low reaction temperatures required are a disadvantage from a practical viewpoint. Finally, one can reasonably anticipate that future studies will provide new applications of chiral cyanohydrins, as well as fine-tuning of the reactions, with the opportunity of pursuing new protocols providing the driving force for future innovation in the field of enantioselective synthesis of cyanohydrins and chemistry as a whole.

Acknowledgments

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