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KEYWORDS. Asymmetric Catalysis. Organometallic chemistry. Organocatalysis. Physical Organic Chemistry.

ABSTRACT: Bis-imine derivatives of salicylaldehyde with chiral diamines (salens) are privileged ligands in asymmetric organometallic catalysis, which can be used in cooperation with organocatalysts, as additives. The latter can be a modifier of the metal reactivity by liganding, or a true co-catalyst working in tandem, or in a dual system. All scenarios encountered in the literature are reviewed and classified according to the organocatalyst. In each case, mechanistic and physical-organic chemistry considerations are discussed to better understand the gears of these complex catalytic settings.

Contents

1. Introduction

The chemistry of salen-type complexes can be traced back to 1889 when Alphonse Combes[1] prepared the first bis-imine of ethylenediamine with acetylacetone and made the corresponding copper complex (Figure 1).

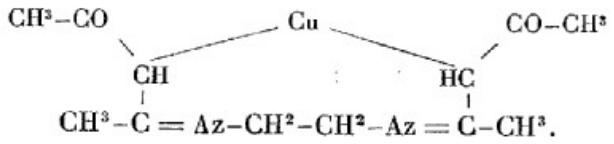


Figure 1. Bis-imine complex synthesized by Combes in 1889, as drawn in the original article (open source).

The field acquired its full maturity when the groups of Jacobsen and Katsuki developed asymmetric catalytic procedures with chiral versions of the salen ligand.[2,3] Since then numerous transformations have benefited from the use of elaborate complexes and this field was reviewed in 2019 for the most advanced examples by Shaw and White.[4] Beyond detailed information on the synthesis of these ligands and the corresponding complexes, this review describes their geometry and their coordination mode, leading to efficient C-C and carbon-heteroatom bonds formation, as well as transformations creating multiple bonds concomitantly, in a stereoselective manner. The present review focuses on a very elegant subfield of organometallic catalysis with salen complexes, when used with organocatalysts as co-promoters or additional ligands. The concept of co-catalysis, to achieve 'perfect asymmetric catalysis' was discussed by Shibasaki as early as 1999,[5] exposing the potential synergistic effect brought by the use of two promoters to reach enantioselectivities above 95%. The manifold advantages of multicatalysis in enantioselective tandem reactions was reviewed by Pelissier[6] in 2020 from a general per-

spective and challenges associated with the merging of organo- and transition metal catalysis were reviewed by Shao and Zhang.[7, 8]

Here we want to concentrate on dual or triple systems relying on a metallic complex with an enantiopure salen ligand, together with an additional organocatalyst (or two).

The array of asymmetric transformations based on salen-metal catalysts is vast enough to find within the field an appreciable number of reactions that were improved or rendered possible by the use of an organic additive to justify this focus. Moreover, the mechanistic considerations that were usually a major interest for the authors developing these intricate systems offer rich material to discuss the kinetic and thermodynamic parameters at play in each transformation.

Before discussing all the reactions in detail, we will present the different scenarios of combination of a salen-metal with an additive, as this classification will serve as an organizing scheme for this review. Then we will summarize some general information gained by physical-organic chemistry measurements on salen complexes and Lewis acids, then on organic Lewis bases, as the most represented co-catalysts.

The salen complex itself can be either a Lewis acid, or a redox center. In the first case, it coordinates with a substrate, which conversely undergoes an electrophilic activation. The affinities between (salen)Zn^{II} and various Lewis basic species were measured by Maccarrone *et al.*[9] giving the equilibrium constants for a small array of compounds (Figure 4). Larger tables of affinities were built using $SbCl_5$ or BF_3 as reference Lewis acids, allowing for the quantitative ranking of classical functions in organic chemistry (Figures 2 and 3).[10]

Figure 2. $SbCl_5$ affinities, (in $kJ.mol^{-1}$), of Lewis bases in 1,2-dichloroethane at 298 K.

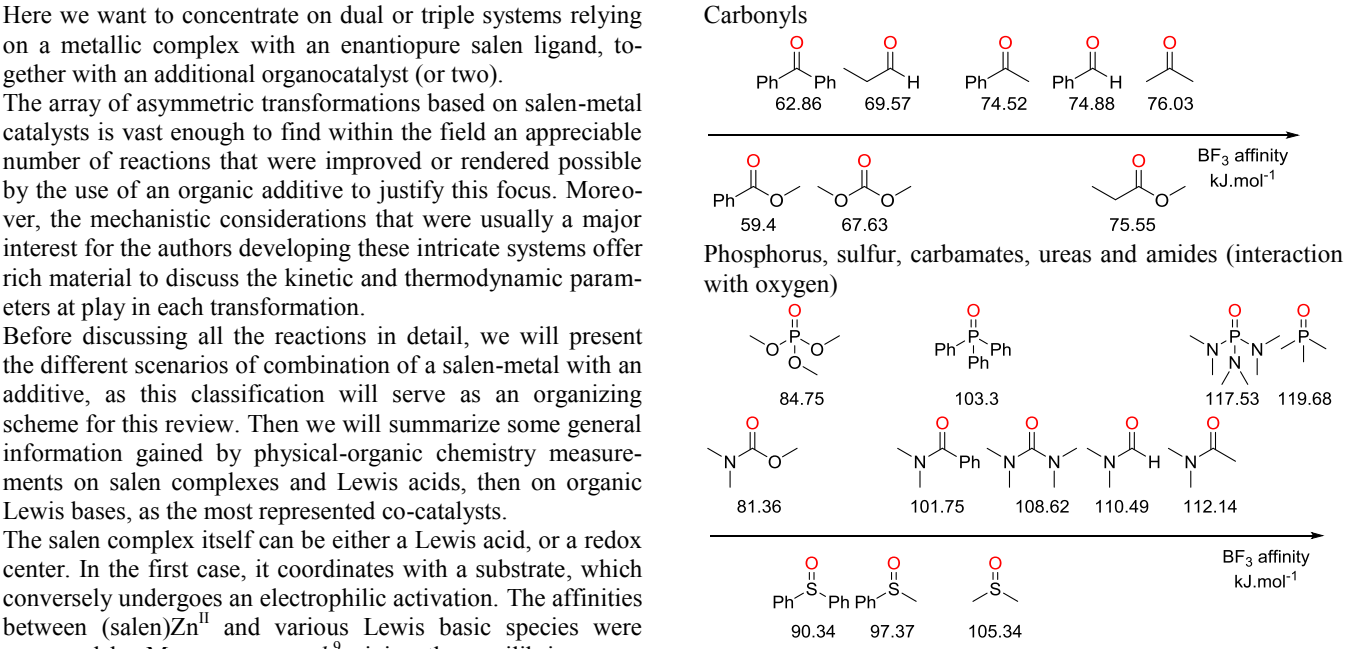


Figure 3. BF_3 affinities ($kJ.mol^{-1}$) of Lewis bases in dichloromethane at 298 K.

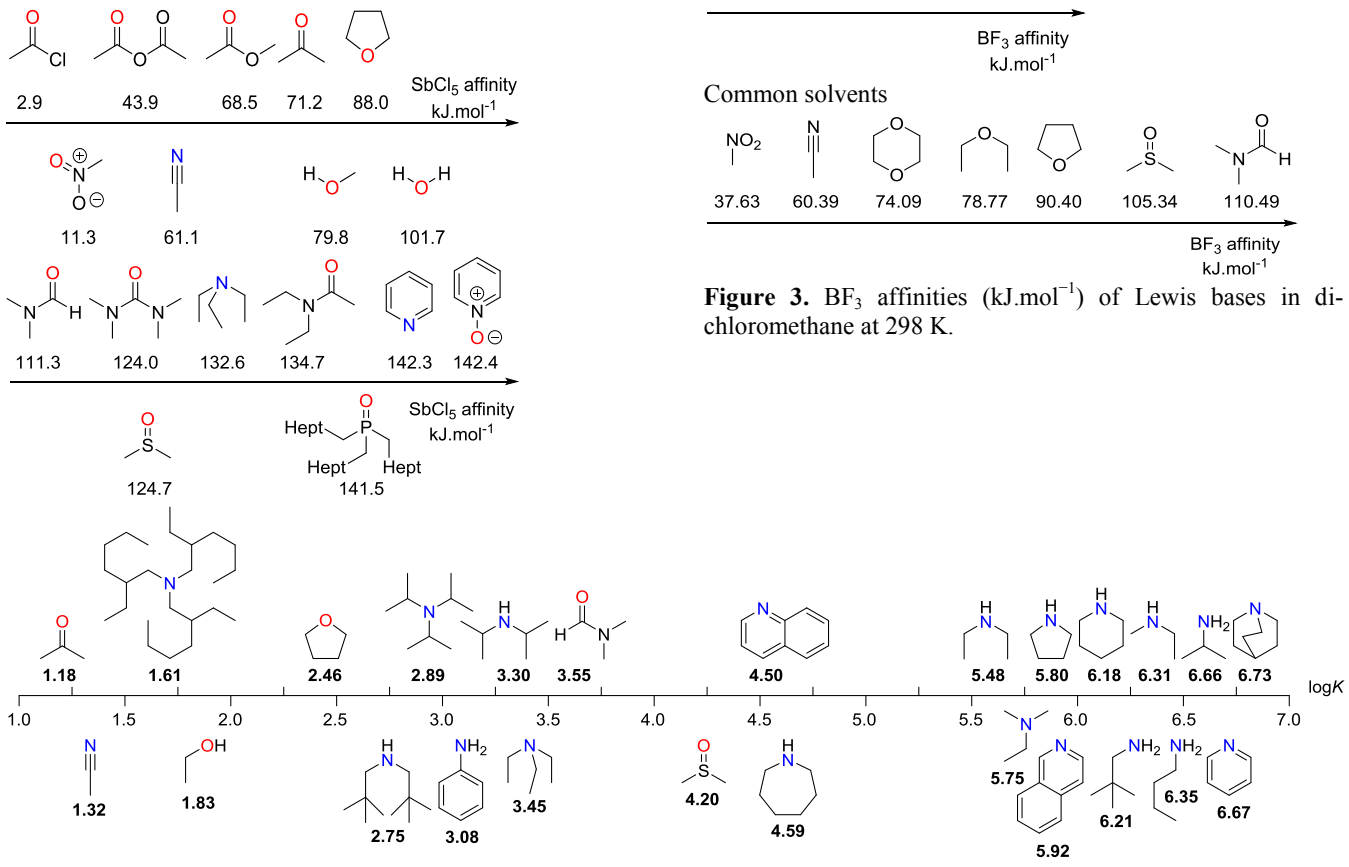
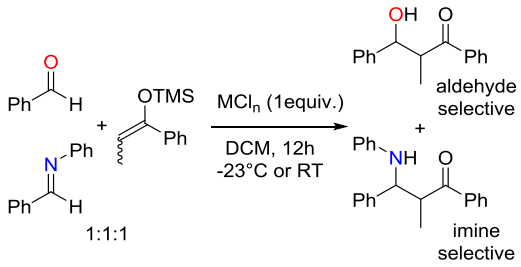


Figure 4. Equilibrium constants for various Lewis bases towards (salen)Zn in DCM (log *K*).

This ranking of affinities is unfortunately not absolute, especially because drastic modulation occurs by changing the nature of the metal, with specific affinities for oxygen or nitrogen atoms for instance. This was not investigated with salen complexes, but a study by Kobayashi *et al.*[11] classified a large range of unliganded metal ions as Lewis acids. They elegantly used competitive Mukaiyama reactions with aldehydes and imines, to identify oxophilic versus azaphilic Lewis acids, or unselective ones (see Table 1).

Table 1. Benchmark reaction to classify oxo/azaphilic Lewis acids



	Active LA Yield > 40% at -23°C	Weak LA Yield < 40% at -23°C Yield > 40% at RT	Inactive LA Yield < 40% at RT
Aldehyde selective	**BCl_3, $TiCl_4$, $GaCl_3$, $ZrCl_4$** $AlCl_3$, $NbCl_5$, $SnCl_2$, $SbCl_5$, $HfCl_4$, $ReCl_3$	none	PCl_5 VCl_3 $CrCl_3$ $MnCl_2$ $NiCl_2$ $RhCl_3$ $PdCl_2$ $AgCl$ $CdCl_2$ $IrCl_3$ $AuCl$ $HgCl_2$ $PbCl_2$
Imine selective	**$ScCl_3$** $FeCl_3$, $InCl_3$, $BiCl_3$	**$CoCl_2$, $CuCl$, $CuCl_2$, YCl_3, $YbCl_3$** $SiCl_4$, $FeCl_2$, $GeCl_4$, $OsCl_3$, $PtCl_2$	
Non-selective	$MoCl_5$, $MoCl_3$, $SnCl_3$, $TaCl_5$, WCl_6, WCl_5, $ReCl_3$, $TiCl_3$	$ZnCl_2$, $RuCl_3$	

In bold: Selectivity > 9/1

Although not quantitative, this table allows one to perceive the general preferences of these cations in the presence of nitrogen and oxygen substrates or additives. One should also be aware that ligand effect exerted by the salen would modulate the results of this classification; clearly, measurements that are more specific are required from the physical organic chemistry community about this very important class of catalyst.

As only a limited array of Lewis bases were investigated in these affinity scales, it is interesting to consider a closely related thermodynamical property, the hydrogen-bond affinity, as measured by pK_{BHX} on a far larger range of compounds and which allow an approximate ranking of Lewis basic catalysts.[10]

What are the different co-catalysis modalities? When mixed with a salen-metal, an organic molecule can serve multiple roles:
1. The additive serves as an axial ligand for the metal, modifying its electron density, and changing the overall geometry of the complex. Salen complexes with a general formula presented in Figure 5A can adopt mainly two stepped conformations and an 'umbrella' conformer,[12] this equilibrium is modulated by the presence of the chiral centers, Figure 5B.

The steeped geometry is also strongly modulated by the nature of axial ligands, as shown by the group of Fujii[13] with (salen)Mn^{IV} complexes in the solid state (Figure 5C).

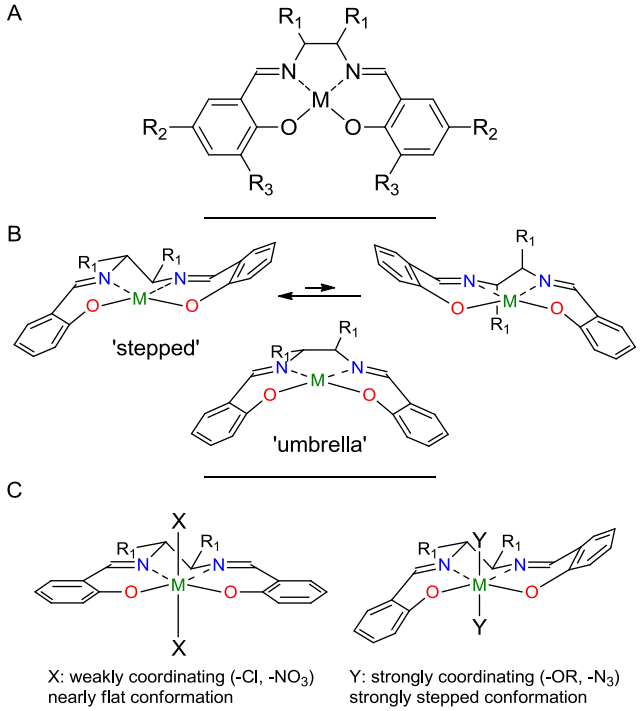


Figure 5. A: general formula of (salen) complexes; B: possible conformations; C: influence of axial ligands on the conformation of (salen)MX_2.

Hence in the respective crystals, the dichloride complex (salen)$MnCl_2$ is almost flat, while more strongly coordinating ligands, like alcoholate or azide, lead to highly twisted complexes with a 'stepped' conformation. This finding was confirmed in solution by circular dichroism measurements and was explained by an important steric repulsion between these strongly coordinating axial ligands and the two axial hydrogen atoms located at the chiral centers of the cyclohexane diamine moiety.
2. The additive can be a Lewis base, generating a nucleophile by the attack of an inert pro-nucleophile substrate, while the salen-metal activates in parallel an electrophilic reactant.
3. The additive can be a Brønsted base, producing a nucleophile by deprotonation, and serving as a reprotonation agent at the end of the mechanistic process.

These complementary roles are controlled by the balanced characters of each additive, mixing thermodynamic parameters, Lewis and Brønsted basicities, with nucleophilicity, a kinetic parameter. Optimization studies thus identify the most suitable additive, with the well-tuned set of parameters for the considered reaction. For instance, if we examine a small set of amines, one can realize that comparison of quantified parameters obtained by physical-organic chemistry measurements shows very dissimilar behaviors. Nowadays we can access a fair variety of such parameters, with the p*K*a in acetonitrile as

a model of organic solvent,[14-18] the Lewis basicity reflected in the Methyl Cation Affinity (MCA),[19] as the affinity for the simplest carbon electrophile. Finally, the nucleophilicity parameter *N*, depending on the rate of attack of a nucleophile onto a set of reference electrophiles, as conceptualized by Mayr and collaborators (Figure 6) is giving a semi-quantitative kinetic ranking of the considered catalysts.[20, 21]

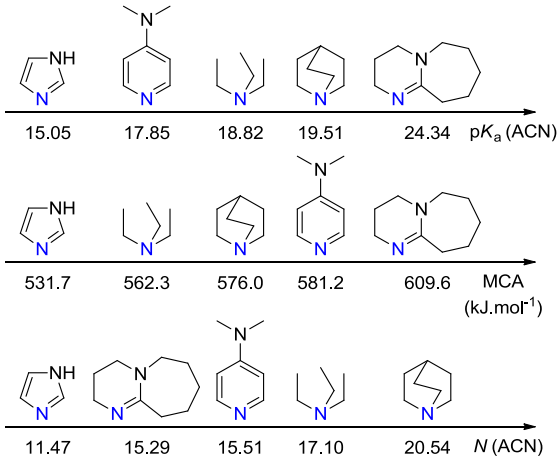


Figure 6. Relative rankings of five amines, according to their Brønsted basicity, Lewis basicity (Methyl Cation Affinity) and Nucleophilicity *N*.

More generally, intuition can be misleading, and exceptions are common, as very basic compounds can be poor nucleophiles, and others can be extremely nucleophilic while moderately basic. In Figure 7, a selection of classical bases is presented, with their nucleophilicity *N* plotted against the Lewis basicity MCA (ΔH in kJ.mol^{-1}).

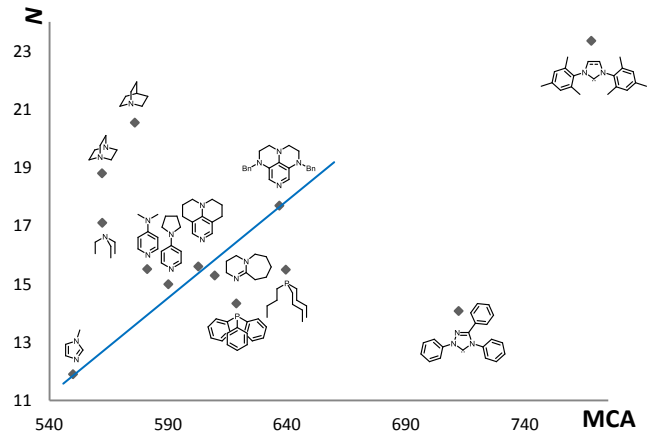


Figure 7. Nucleophilicity *N* against Lewis basicity MCA, for a selection of organocatalysts.

Hence, if a general trend logically links the basicity and the nucleophilic character, with imidazoles as weak catalysts in both parameters, and NHCs as the strongest, some catalysts deviate, like quinuclidine, which is far more nucleophilic than basic, or, on the contrary, tributylphosphine, sensibly more basic than nucleophilic.

4. The additive is a Brønsted acid, increasing the electrophilicity of the substrate by protonation, thus directly linked to the pK_a of the two species.

5. The cocatalyst bears an onium salt, with a permanent cation that can anchor a reaction anion that serves as nucleophile in the mechanism and is hence controlled by electrostatic interactions.

6. In the opposite scenario, the additive is anionic, and can then interact by ion-pairing with a cationic salen-metal complex and hence tune its electronic and geometrical properties.

7. Finally, cocatalysts with H-bonding moieties can activate a substrate by increasing its electrophilicity and controling its position in the transition-state.

The various scenarios of multicatalysis[22] led to introduce different terms to describe them, in this review each reaction will be defined according to the following classification:

Multifunctional Catalysis (bi-, tri-, etc) [**MF Cat.**] when a single species includes multiple catalytic (metallic or organic) active sites.

Co-Catalysis [**Co Cat.**] when several catalytic species are acting in synergy. It is similar to *dual catalysis* for some authors.

Catalysis with Additive [**Add Cat.**] when an active species is a modifier of the main catalyst, specifically in this review when an organic molecule acts as a ligand of the metal center.

This classification will be schematized in each example as a stamp, with in some cases possible combination of these scenarios.

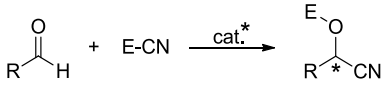
For historical reasons, cyanation reactions are exceptionally well represented among the transformations considered here; we thus decided to treat these reactions in a separate and independent chapter to make specific comparisons within this homogeneous subfield, and show the relative advantages brought by the different dual, and even triple, catalytic systems used to cyanate carbonyl compounds.

2. Cyanation of Carbonyl Compounds and Imines

The topic of asymmetric cyanation reactions was reviewed in 2020 by Zhou and Yu,[23] focusing on the most recent strategies (Scheme 1). We aim here at giving an in-depth look into the intimate machinery of dual catalytic systems exploiting the synergistic combination of a salen complex with a Lewis base to promote carbonyl cyanation.

2.1. Acylcyanation with Amines

Asymmetric organometallic catalysis has proven to be an essential tool for the synthesis of enantioenriched cyanohydrins, as valuable synthons for various derivatizations towards biologically active compounds (Scheme 1).[24]

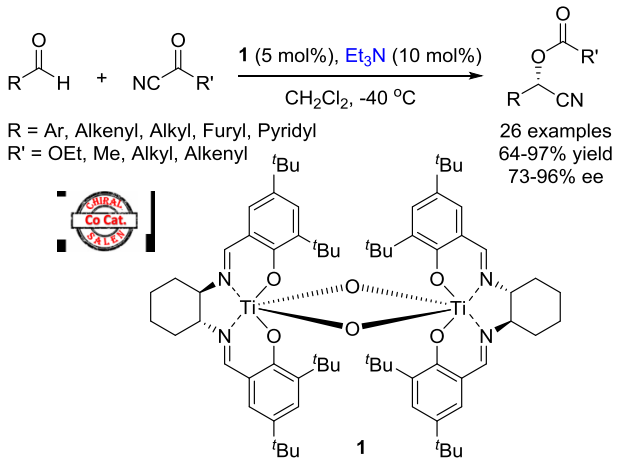


Scheme 1. Enantioselective cyanation of aldehydes

The base-catalysed benzoylcyanation of aldehydes was reported as early as 1949.[25] Since then, acceleration in the presence of Lewis acids was demonstrated. Among the numerous metal complexes incorporating chiral ligands used to promote this reaction as chiral Lewis acids,[26] salen complexes played a major role affording the target products in high yield and

enantioselectivity values. For instance, the groups of North[27] and Belokon,[28] demonstrated the efficiency of (salen)Ti or (salen)V derivatives, and performed mechanistic studies highlighting the formation of bimetallic complexes as active species. Even if trimethylsilyl cyanide is most often used for this transformation, acetyl cyanide and cyanoformate are valuable alternatives as both less toxic and inexpensive reagents, delivering interesting *O*-functionalized derivatives. This completely atom economical reaction furthermore avoids any eventual reversibility of the cyanide addition, as equilibration is leading to important erosion in enantioselectivity of the cyanohydrin.

A typical procedure with acylcyanides relying on the sole organometallic catalysis is as follows.[29] In the asymmetric addition of ethyl cyanoformate to aldehydes providing enantiomerically enriched cyanohydrin carbonates, 5 mol% of the bimetallic titanium complex $[(salen)TiO]_2$ are necessary to achieve complete conversion within 18 hours, performing the reaction at -40 °C to access high ee values (up to 95%). This catalyst loading is however 50 times higher than that required when TMSCN is employed. Furthermore, 2 equivalents of EtOCOCN are needed, antagonizing the atom economy of the process. In this context, Moberg and her group reported in 2005 an upgrade of this catalytic system, while studying the use of acetyl cyanide in this cyanation reaction (Scheme 2).[30,31]



Scheme 2. Enantioselective cyanation of aldehydes using ethyl cyanoformate or α-ketonitriles with 1 and Et_3N

As the use of catalyst **1** alone proved unsuccessful to promote the reaction between benzaldehyde and acetyl cyanide, the group explored a dual activation setting, including **1** as active Lewis acid together with an additional Lewis base. Initially, addition of DMAP allowed the formation of the desired product; screening of different amine bases showed the superiority of triethylamine. Hence, complete conversion was obtained in 8 h with 5 mol% **1** and 10 mol% NEt_3 delivering the *O*-acetylated cyanohydrin from benzaldehyde in 94 % ee with 96% conversion (Table 2). Use of chiral bases such as quinine derivatives did not lead to usefully improved results and marginal matched/mismatched effects between the two chiral promoters.

Table 2. Effect of amines as additives to catalyst **1** for the cyanation of benzaldehyde

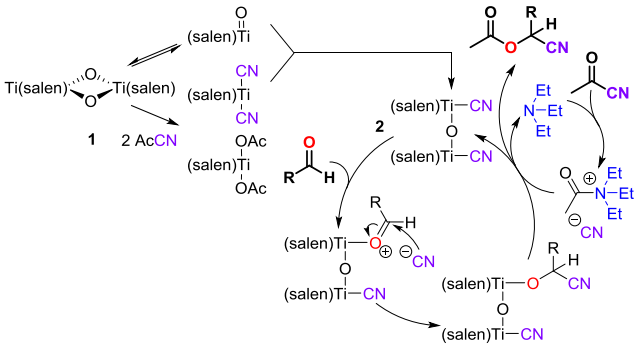
Base	Conv. (%)	ee (%)	pK_{BHX}	*N*	MCA
DMAP	57	94	2.80	15.51	581.2
DABCO	67	92	2.33	18.80	562.2
NEt_3	96	94	1.98	17.10	562.3
DIPEA	97	81	1.05		(557.3)
Sparteine	93	65			
Quinine	80	92		(15.6)	(580.6)
cinchonidine	78	96		(15.6)	(580.6)

Conditions: $[(salen)TiO]_2$ 5 mol%, base 10 mol%, -40°C for 6-9 h. *N*: nucleophilicity parameter according to Mayr, in ACN, MCA: Methyl Cation Affinity in $kJ.mol^{-1}$ as calculed by Zipse, see introduction. (bracketed values are estimated from very similar compounds)

This dual Lewis acid/Lewis base activation allowed the cyanation of benzaldehyde with EtOCOCN to occur under milder conditions, since the amount of the acylating agent was reduced to 1.2 equivalents, and the reaction duration to 3 h. This procedure was successfully extended to the reaction of various aldehydes (aromatic, heteroaromatic, unsaturated and aliphatic) with different α-ketonitriles.[32]

Some control experiments were performed to furnish insight into the reaction mechanism. ^{13}C-labelling tests ruled out a cyanation by cyanide ions from HCN, conceivably present in trace amounts in the ketonitriles. Furthermore, acetyl cyanide is already known as an acylating agent; therefore, the Lewis base is proposed to attack the carbonyl group of the acyl cyanide to generate an acylating agent and to liberate a cyanide ion. Both species are then required to react with the Lewis-acid activated aldehyde at low temperature. The mechanism was recently studied in more detail.[33] Competitive experiments with various substituted aryl-aldehydes were performed and allowed a Hammett correlation study. The results indicated a nucleophilic attack as the rate-determining step for aldehyde substrates bearing electron-donating or halogen substituents, whereas the acylation step was limiting for those with highly electron-withdrawing groups. A detailed mechanism was suggested, which is simplified in Scheme 3 below, with omission of several important resting-states that were characterized.

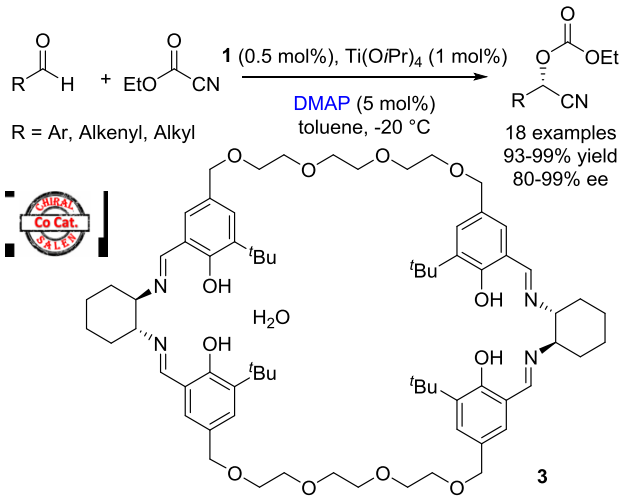
Variation of the enantiomeric excess along with the reaction time, and observation of a period of induction indicate that the dimeric titanium precatalyst is initially converted into the active species, the dicyano-dimetallic structure **2**, formed by reaction of **1** with acetyl cyanide and disproportionation/recombination. This dicyano **2** can then activate the aldehyde reactant by coordination and release of a cyanide anion. Nucleophilic attack delivers the coordinated cyanohydrin, which reacts with the acylammonium, itself formed through a parallel cycle with cyanide displacement by the tertiary amine onto acetyl cyanide. Acetylation of the cyanhydrin moiety gives the final product, while alcoholate substitution by the cyanide anion regenerates the dicyano-dimetallic species **2**, closing the primary catalytic cycle.



Scheme 3. Proposed mechanism for the enantioselective cyanation of aldehydes with 1 and Et_3N (all intermediates are Ti^{IV} species)

This proposition is in accordance with the mechanism reported by North *et al.* for the asymmetric addition of ethyl cyanoformate to aldehydes in the absence of a base.[34]

In 2013, aiming at facilitating the formation of μ-oxo-bridged titanium dimers in an intramolecular way, Khan *et al.* synthesized chiral macrocyclic (salen)Ti^{IV} complexes and evaluated their efficiency in the asymmetric cyanoethoxycarbonylation of aldehydes (Scheme 4).[35] Macrocycle **3**, with two flexible polyether linkages, led to a highly active catalytic system, which could be used with catalytic loading as low as 1 mol%, when the reaction was performed at -20 °C, in toluene, in the presence of DMAP as Lewis base. Aromatic or aliphatic aldehydes underwent cyanoethoxycarbonylation with up to full conversion and nearly perfect enantioselectivity (see Scheme 4). This emphasizes the benefits brought by the cooperative action of two salen species in achieving very high levels of enantioselectivity, as seen previously in other transformations.[36] Recovery of the catalyst was interestingly feasible, and its reuse was performed successfully in three recycling experiments without loss of activity or enantioselectivity. The authors further demonstrated the viability of their procedure on large scale by the preparation of two pharmaceutically important chiral drugs, (*R*)-Proethalol and (*R*)-phenylephedrine.



Scheme 4. Asymmetric cyanoethoxycarbonylation of aldehydes with an *in situ* generated macrocyclic Ti-catalyst and DMAP

It is interesting to observe that during optimizations, the Lewis base nature had only a marginal influence on the final conversions, although with various kinetics, but had a drastic impact on the measured enantioselectivities, Table 3.

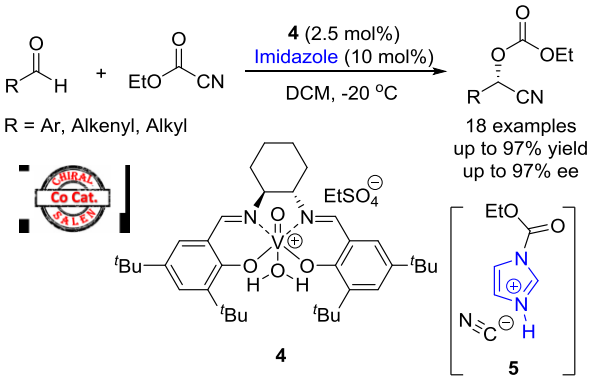
Table 3. Effect of amines as additives in the cyanoethoxycarbonylation of benzaldehyde catalyzed by Ti-salen macrocyclic **3** catalyst.

Base	t (h)	Yield (%)	ee (%)	pK_{BHX}	*N*
NEt_3	1	99	69	1.98	17.10
iPr_2NH	3	97	65	2.00	
KCN	3	99	41		16.27
DMAP	3	99	74	2.80	15.51
DBU	4	98	70	3.85	15.29
Cinchonine	5	95	72	(2.7)	(15.6)
Quinine	5	98	73	(2.7)	(15.6)
ImH	12	88	20	2.42	11.47
NMI	16	82	15	2.72	11.90
Pyridine	18	95	33	1.86	(12.9)
2,6-lutidine	24	72	17	2.14	(< 10)

Conditions: Ti catalyst 0.5 mol%, base 5 mol%, toluene, RT.

We can furthermore note that the reaction rate is directly proportional to the amine nucleophilicity (a kinetic parameter), probably because the most nucleophilic amine co-catalysts can lead to large amounts of acyl-ammonium intermediate all along the reaction course by rapid regeneration. In contrast, the Lewis basicity, as roughly reflected in the hydrogen-bond affinity pK_{BHX}, does not correlate at all with the reaction speed.

Previously, in 2008, the activity of monomeric vanadium-based catalysts was investigated by the group of Khan[37] using the (salen)V^{V} complex **4** to promote the same transformation. The study again proved the crucial role of additional bases, as the reaction did not proceed in the absence of a co-catalyst (see Scheme 5).



Scheme 5. Asymmetric cyanoethoxycarbonylation of aldehydes with a (salen)V^{v} complex and imidazole

In this case, imidazole was the best Lewis base, and led to the efficient asymmetric addition of ethyl cyanoformate to benzaldehyde at -20 °C, with a (salen)V^{V} **4** loading of 2.5 mol% and 10 mol% of base. As depicted in Scheme 5, the procedure was applied successfully to a range of aromatic and aliphatic aldehydes delivering the target products in high isolated yields (80-97%) and enantioselectivity values (76-97%).

Table 4. Effect of amines as additives with (salen)V^V **4** catalyst.

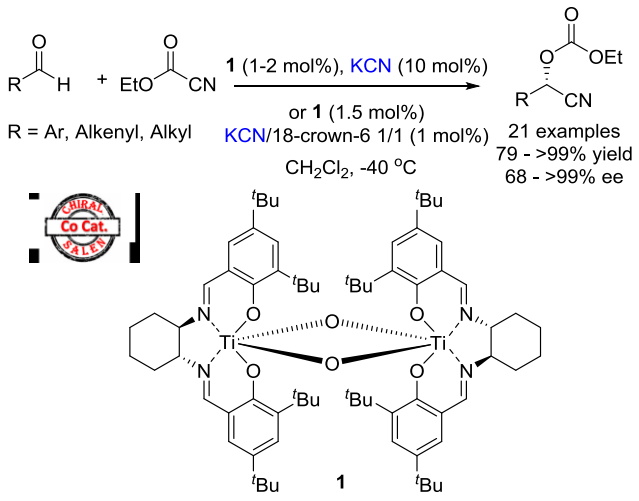
Base	t (h)	Yield (%)	ee (%)	pK_{BHX}	*N*
NEt_3	8	95	9	1.98	17.10
KCN	18	91	92		16.27
ImH	18	96	93	2.42	11.47
NMI	12	95	90	2.72	11.90
Pyridine	24	0	0	1.86	(12.9)
2,6-lutidine	36	89	93	2.14	(< 10)

Conditions: Catalyst **4** 2.5 mol%, base 10 mol%, DCM, -20 °C.

Insight into the mechanism was provided by NMR spectroscopy and UV-Vis monitoring of the reaction, proving the formation of intermediate species **5** (in Scheme 5) resulting from the reaction of the cyanoformate with the base. The fact that the virtually non-nucleophilic lutidine is however able to promote this transformation efficiently, and in contrast, the fairly nucleophilic pyridine is incompetent in doing so (see Table 4), suggests a more complex reaction mechanism with amine-metal interactions tuning its activity, in concurrence with amine/cyanoformate addition.

2.2. Acylcyanation with Cyanide Ion Catalysis

As previously seen, amine derivatives are not the sole efficient catalysts for accelerating and enhancing selectivity in asymmetric cyanohydrin carbonate synthesis. North and coworkers indeed reported the valuable use of the cyanide ion as a co-catalyst. Although the cyanide ion is not strictly speaking an organic entity, however, we include this additive as providing an interesting effect on the reaction of interest in this review. This later is known as a reagent in the synthesis of racemic cyanohydrins; but its introduction in a catalytic amount (10 mol%) into the reaction mixture containing the chiral (salen)Ti dimeric species **1** (2 mol%) resulted in a significant increase in both reaction rate and enantioselectivity value.[38] The reaction between benzaldehyde and ethylcyanoformate could occur at –40 °C affording complete conversion and up to 95% ee in 26 h. These conditions remained valid with different aromatic or aliphatic aldehydes and various cyanoformates, including chiral ones, but remained ineffective for ketones (see Scheme 6).

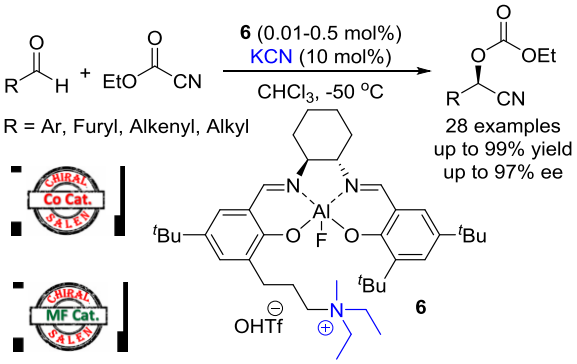


Scheme 6. Asymmetric cyanoethoxycarbonylation of aldehydes with a dimeric (salen)Ti complex and cyanide ion as co-catalyst

Since the catalytic reactions were performed in dichloromethane using solid, insoluble KCN as catalyst, the mixture remained heterogeneous. The authors could further improve their procedure by employing a 1:1 complex made from KCN and 18-crown-6, freely soluble in DCM. With only 1 mol% of this complex and 1.5 mol% of the (salen)Ti derivative, the reactions could be performed in the same way as in the previous conditions employing 10 mol% of KCN. The authors monitored the reaction kinetics of this last procedure by ^1H NMR, and emphasized the major role played by the cyanide anion[39] in the conversion of precatalyst **1** to the bis-cyanide titanium complex **2** which is key in the catalytic cycle (see Scheme 3).

2.3. Acylcyanation with Quaternary Ammoniums

The group of Peters[40] employed in 2017 bifunctional catalysts, combining a (salen)Al^{III} complex with an ammonium salt **6** as ion-pairing already proved highly effective in other asymmetric transformations.[41] Here, the authors reasoned that a salen complex bearing a linked ammonium unit could activate both the aldehyde via the Lewis acidic metallic site and control the face-selective attack of the cyanide anion through electrostatic interactions with the cationic functionality. The ligand structure was optimized, tuning the spacer length and the ammonium structure, as well as the metal precursor (see Scheme 7).



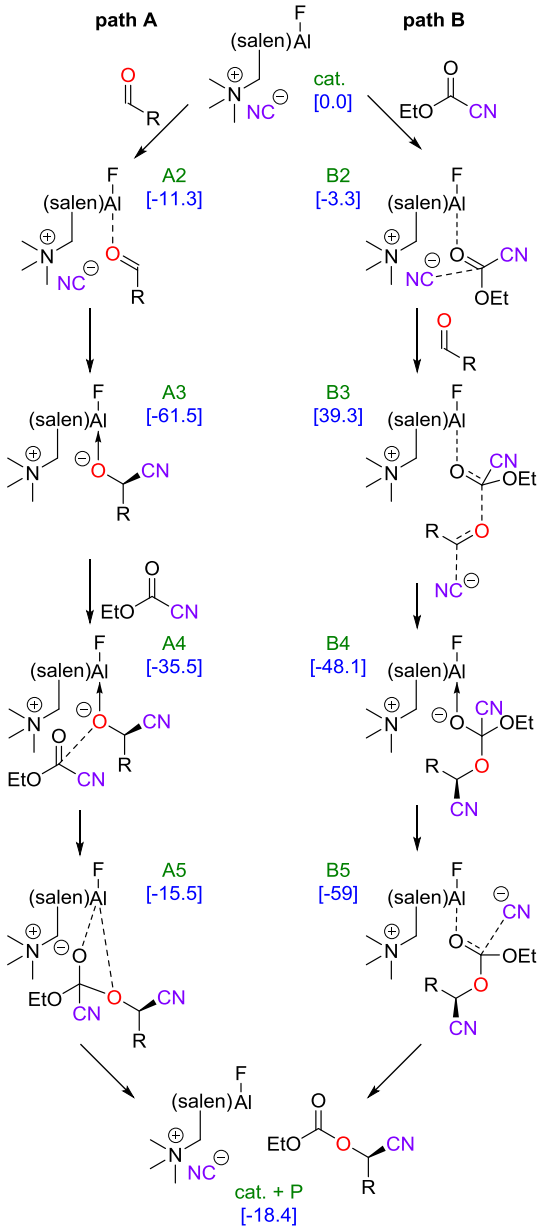
Scheme 7. Asymmetric carboxycyanation of aldehydes with a (salen)Al fluoride complex with an appended ammonium salt

Control experiments proved that covalent link between both active moieties were necessary to access high reactivity and enantioselectivity. The use of an aluminum fluoride associated with the ammonium bearing a non-coordinating anion proved essential for this exceptional activity. Catalyst loading could be reduced to 0.01 mol% corresponding to TON values of 9800. Here again, the addition of catalytic quantities of KCN was beneficial for the reaction rate. Authors attributed this high activity to the robustness of the Al-F bond leading to a stable catalyst with an increased Lewis acidity.

DFT studies were conducted by the same group[42] in 2019, on the base of which the classical mechanism (path A in Scheme 8) implying the direct activation of the aldehyde by the Lewis acid site was put aside owing to an energetically difficult

carboxylation step. In this, the most stable intermediate is **A3** (at -61.5 kJ.mol^{-1}) and the **A4**->**A5** transition state is located at 16.7 kJ.mol^{-1}, corresponding to an activation barrier of 78.2 kJ.mol^{-1}. Thus alternative path B was proposed, calculations showing a less energy-demanding profile, the largest gap being 42.7 kJ.mol^{-1} in the **B4**->**B5** step.

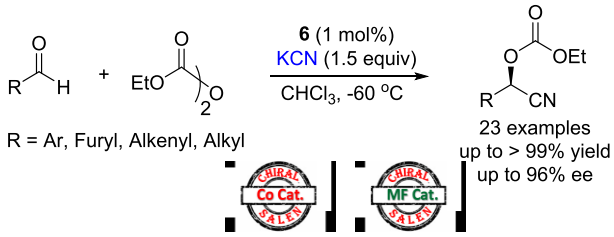
In this hypothesis, the reaction proceeds with initial coordination of the cyanoformate onto the aluminum center, the ammonium moiety maintaining the cyanide ion in close proximity after anion metathesis of the triflate, delivering intermediate **B2**. Then the aldehyde substrate inserts between the cyanide and the cyanoformate carbonyl via transition state **B3** in a trimolecular reaction, to give coordinated cyano-alcoholate intermediate **B4**. Cyanide elimination via a TS located at -5.4 kJ.mol^{-1}, leads to the coordinated product as intermediate **B5** (activation barrier of 42.7 kJ.mol^{-1}, and final decomplexation releases the product with catalyst regeneration.



Scheme 8. DFT calculations for the carboxycyanation in the presence of KCN and complex 6

As recognized by the authors themselves, the major concern about this mechanistic proposal resides in the difficult rationalization of the stereocontrol. Facial differentiation occurs within TS **B3** during cyanide addition, which takes place at quite a remote distance from the chiral salen scaffold. Enantioselection results could thus be explained by considering a very compact pocket ensuring long-distance transmission of chiral information.

In this mechanistic article, the authors also explored an elegant procedure, using potassium cyanide as the source of the cyano group, to replace the cyanoformate reagent, carbonatation of the cyanohydrin being assured by diethyl pyrocarbonate, with the cyanide anion additionally assuming an ancillary catalyst role, (see Scheme 9).

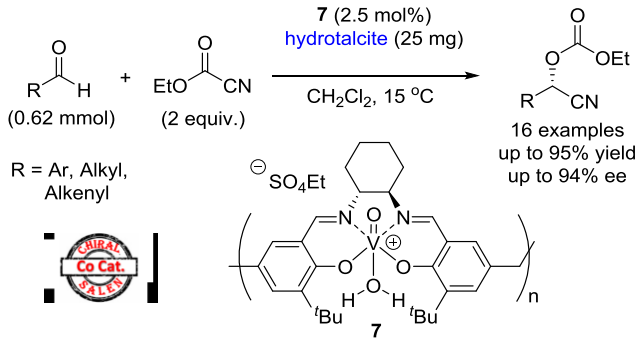


Scheme 9. Carboxycyanation catalysed by 6 with stoechiometric KCN and pyrocarbonate

This new procedure led to similar results than the first protocol employing ethylcyanoformate, albeit with some reduced activity, possibly due to temporary inhibition of the Lewis acid center by $EtOCO_2^-$ or EtO^-, as proposed by the authors.

2.4. Acylcyanation with Heterogenous Bases

The group of Khan[43] tackled the challenge of working out a procedure leading to the efficient and easy recovery of the bicatalytic system for its reuse. They thus prepared a polymeric vanadium salen catalyst **7** from an enantiopure salen polymeric ligand possessing methylene spacers that was already shown to be easily recoverable by simple precipitation in hexane (Scheme 10).[44] The use of solid bases such as hydrotalcite or alumina was further explored as recoverable co-catalysts. The authors optimized the reaction parameters, and particularly the amount of both the Lewis acid and the Lewis base catalysts, showing that 2.5 mol% of the V-salen complex and hydrotalcite as base (25mg/mmol of aldehyde substrate), delivered the target product from benzaldehyde in 94% yield and 88% ee, at 15°C.



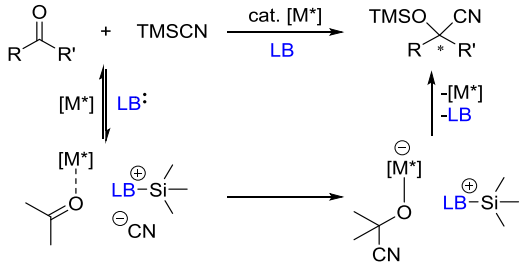
Scheme 10. Enantioselective addition of ethyl cyanoformate to various aldehydes using a polymeric (salen)V^{V} complex together with hydrotalcite

This combined system was successfully applied to the transformation of a variety of aldehydes (see Scheme 10) with excellent yields and enantioselectivities, with minor electronic effects from the substrates substituents.

Noticeably, the authors verified the recyclability of the catalytic system by addition of hexane causing the precipitation of the polymeric (salen)V complex **7**, which was recovered after filtration, together with the insoluble hydrotalcite powder. This mixture was reengaged in three successive runs without marked loss of selectivity, even if reaction times had to be slightly prolonged to maintain full conversion. Although not strictly speaking an organocatalyst, hydrotalcite plays the role of a Lewis base, activating the cyanoformate with nucleophilic M-OH groups, liberating a cyanide anion, while the aldehyde interacted with the Lewis acidic site for a concerted nucleophilic attack of CN and carboxylation of the aldehydic oxygen, to produce the desired product in high optical purity.

2.5. Cyanosilylation of Carbonyl Compounds

One of the earliest examples of asymmetric cyanation reactions of carbonyl compounds was cyanosilylation. Dual activation combining a Lewis acid that activates the carbonyl substrates, with a Lewis base additive, which liberates cyanide anions by nucleophilic displacement, ensures a very efficient conversion. Intermolecular attack of the cyanide to the coordinated aldehyde or ketone forms the liganded cyanohydrins. Final capping of this alcoholate delivers the silylcyanohydrin, hence protected from any reversion to the starting materials (Scheme 11).



Scheme 11. General mechanism of cyanosilylation under co-catalysis

From the very first studies, oxygen nucleophiles demonstrated their efficacy, with numerous examples using *N*-oxides and phosphine oxides, and an example relying on acylphosphoranes. This predominance probably stems from the high oxophily of the TMS group making these classes of Lewis base prime promoters for cyanide displacement. The authors in this field seem to have privileged the association of *N*-oxides with (salen)Ti^{IV} catalysts, and of phosphine oxides with (salen)Al^{III} ones, although exceptions are present.

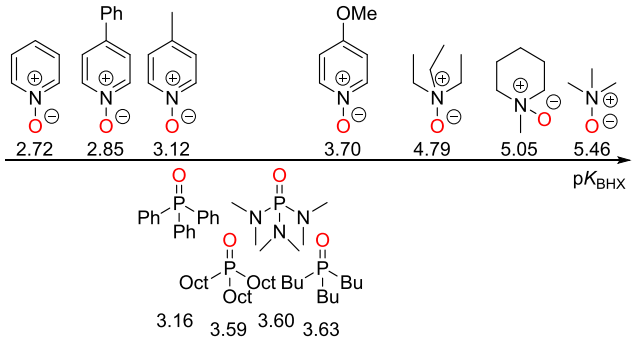


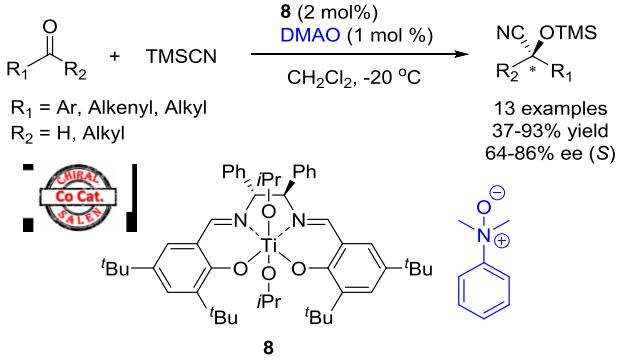
Figure 8. Hydrogen-bond affinity (pK_{BHX}) of various *N*-oxides and phosphine oxides.

We will review these two additives separately, while we can note that *N*-oxides cover a far larger range of Lewis acidity, offering broader optimization opportunities when fine-tuning of the nucleophily is required.

2.5.1. Cyanosilylation with *N*-Oxides

Enantioselective cyanosilylations in the presence of *N*-oxides were investigated with titanium and aluminum complexes, which will be presented in this order. A unique bifunctional catalyst was reported, using both metals, which will be discussed at the end of the chapter.

Beginning by catalytic systems based on titanium, Feng *et al*,[45] explored this cyanation with ketones in 2003, demonstrating that a (salen)Ti^{IV} derived from 1,2-diamino-1,2-diphenylethane **8** offered good conversions and selectivities in combination with dimethylaniline *N*-oxide (DMAO) (Scheme 12).



Scheme 12. Catalytic enantioselective cyanosilylation of ketones developed by Feng *et al*.

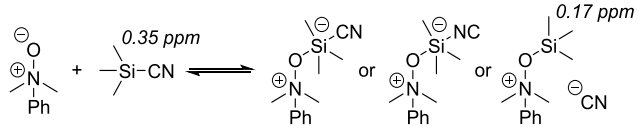
Among the additives tested,[46] this particular *N*-oxide clearly stood out in terms of activity and selectivity (see Table 5).

Table 5. Effect of amines as additives with (salen)Ti^{IV} **8** catalyst.

Lewis base	Yield (%)	ee (%)	pK_{BHX}	$SbCl_5$ affinity (kJ mol^{-1})
PyrNO	0	0	2.72	142.4
Me_3NO	26	65	5.46	
HMPA	30	34	3.60	(140)
NMNO	32	60	(4.9)	
Et_3NO	53	66	4.79	(218)
$CyMe_2NO$	63	51	-	
$PhNMe_2O$	95	67	-	

Conditions: acetophenone+TMSCN, (salen)Ti 20 mol%, Lewis base 20 mol%, DCM, 0 °C, 84 h. Bracketed Values are extrapolated from very similar compounds.

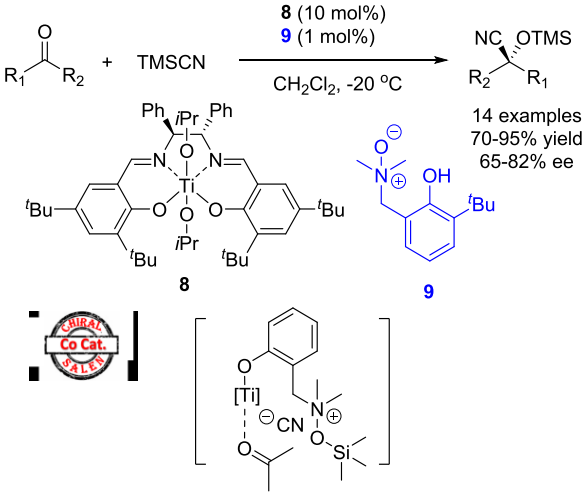
To explain this optimal combination metal complex/*N*-oxide, the authors suggested that strongly nucleophilic *N*-oxides (like Me_3NO) quickly activate the silyl derivative but also strongly coordinate the metal center with formation of a non-active Lewis pair that cannot serve to activate the ketone substrate. DMAO thus represents the optimum balance in nucleophilicity/coordination behaviors. It was noted that upon mixing of TMSCN with the *N*-oxide additive in $CDCl_3$, the chemical shift of the methyl groups of the former went from 0.35 to 0.17 ppm; this shielding effect was attributed to the 'coordination' of the oxygen atom to the silyl group (Scheme 13).



Scheme 13. Potential structures resulting from nucleophilic attack of TMSCN with DMAO

No indication about the 'coordinating' pattern was given by the authors; the product of this interaction could be either a pentavalent siliconate with a cyano group or an isonitrile moiety, or a silyl ether (see Scheme 13), the proton NMR value obtained for the methyl group being fully consistent with the latter (0.15 with a similar N^+-O-TMS triad,[47] a reported siliconate[48] being around -0.18 pm).

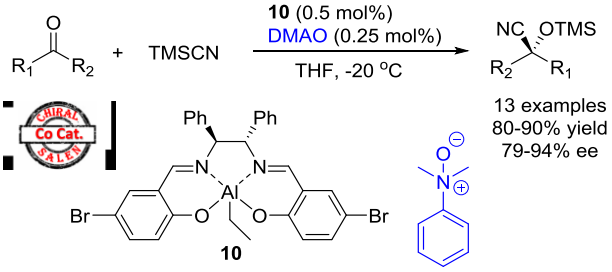
Around the same time, Feng and collaborators[49,50] explored the potential offered by the use of a bifunctional additive **9** combining an *N*-oxide as Lewis base activator with a phenolic moiety that could anchor to the Lewis acidic co-promoter as a phenolate ligand (see Scheme 14).



Scheme 14. Enantioselective cyanosilylation of ketones in the presence of a bifunctional phenol/*N*-oxide additive

The synergistic activation was effective, and the authors proposed an *in situ* generation of a bifunctional catalyst depicted in Scheme 14. However, we can note that after careful optimization studies, the final conditions employed 10 mol% of the (salen)$Ti(OiPr)_2$ Lewis acid with 1 mol% of phenol **9**, while the previously reported system relying on a simple *N*-oxide required only 2 mol% of (salen)$Ti(OiPr)_2$ to attain sensibly identical activities and selectivities.

Then, when examining the aluminum-based systems, the group of Feng[51] conducted in 2004 an in-depth investigation of the cyanosilylation reaction by varying all parameters of the dual system: nature of the metal, salen ligand, apical ligand on the metal, Lewis base additive, solvent, loading and Lewis acid/base ratio. The most efficient system employed the complex **10** at a very low catalyst loading with half the quantity of DMAO (Scheme 15).



Scheme 15. Enantioselective cyanosilylation of ketones catalyzed by 10 / DMAO

This study is notably interesting because it highlights the drastic effect of each parameter of the catalytic conditions on the reaction efficacy, conversely showing that the previously employed titanium complex was far from being optimal in terms of activity, while DMAO, as previously selected, was indeed the best co-catalyst (Table 6).

Table 6. Lewis acid effect on the enantioselective cyanosilylation of ketones with DMAO as co-catalyst.

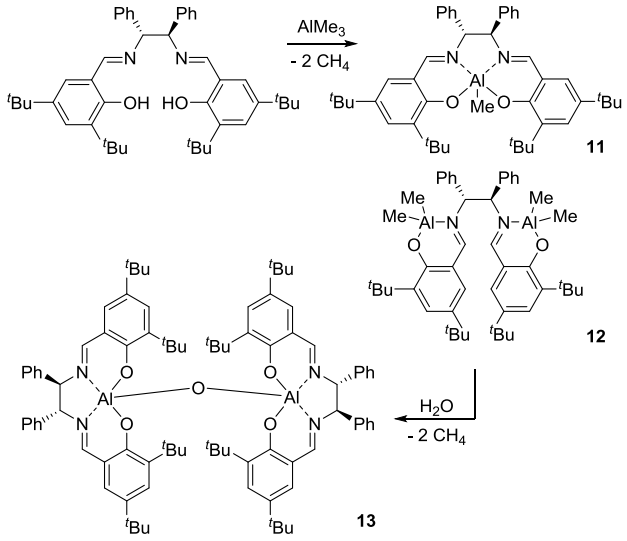
Lewis acid	Yield (%)	ee (%)

(salen)AlCl	trace	87
(salen)Zn	trace	72
(salen)Ni	trace	0
(salen)Ti(O*i*Pr)$_2$	11	74
(salen)Al(O*i*Pr)	17	14
(salen)AlCN	36	56
(salen)AlEt	45	83
(salen)Cu	80	0

Conditions: Jacobsen catalysts of type **8** with variation of the metal (salen)M 2 mol%, dimethylaniline *N*-oxide (DMAO) 1 mol%, DCM, -20 °C, 78 h.

It was shown, for the most active aluminum catalyst, that the pendant ethyl group remained unchanged under catalytic conditions. In the same way, modulation trials with various phenolates to coordinate the metal had little impact on its activity.

Then in 2008, the group of Carpentier[52] reported very interesting results of a thorough investigation on these complex dual systems based on aluminum. First, a very important issue addressed the true nature of the organometallic catalysts, as all previous authors employed *in situ* generated (salen)Al complexes without precise knowledge of the species formed in the reaction mixture. It was shown that in all the protocols tested, reaction of aluminum precursors with salen ligands always generated mixtures of mono-metallic 'closed' complex **11** and bimetallic 'open' complex **12** (scheme 16).



Scheme 16. Mono-metallic and bi-metallic complexes developed by Carpentier *et al.* for enantioselective cyanosilylation of ketones

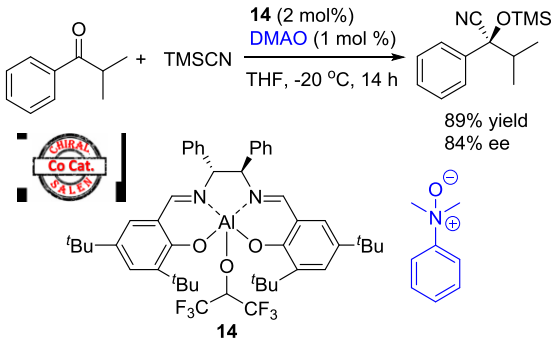
At best, the usual protocol led to an unfavorable 27:73 ratio between **11**:**12**. Only when high temperatures were employed, to drive the equilibrium towards the expected mono-metallic **11**, could favorable mixtures be obtained, however not quantitatively, as a 91:9 ratio was the maximum attainable. Furthermore, it was demonstrated that in the presence of even traces of water, a third organobimetallic species **13** was easily generate, a compound first characterised by Barron *et al.* in 1991.[53] This triple concomitance of **11**/**12**/**13** species holds true also for complexes generated from aluminum alkoxides. This unavoidable presence of a bimetallic structure **12** and dimeric structure **13** is not at all inconsequential, as demonstrated by the next experiments, showing the differential reactivities of these species in cyanation reactions (Table 7).

Table 7. Lewis base effect on the enantioselective cyanosilylation of acetophenone with DMAO co-catalyst

Lewis acid	Yield (%)	ee (%)
(salen)H$_2$ + AlMe$_3$	52	80
(salen)AlMe	81	84
(salen)(AlMe)$_2$	8	81
[(salen)Al]$_2$O	98	80
(salen)H$_2$ + Al(O*i*Pr)$_3$	17	14
(salen)AlO*i*Pr	71	81

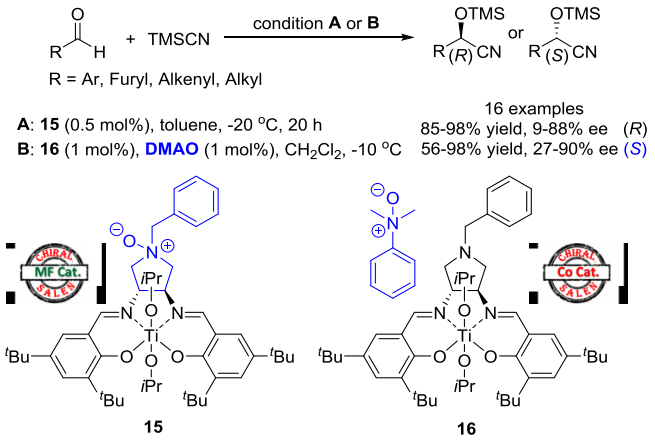
Conditions: Acetophenone+TMSCN 2 equiv., THF, Lewis base 2 mol% (1,2-Diamino-1,2-diphenylethane salen), DMAO 1 mol%, -20 °C, 48 h.

Hence, well defined species behave with various activities and stereocontrol, the mono-metallic **11** being the most active, while the bi-metallic **12** was almost inactive. Notably, the dimeric complex **13** was nicely active and selective. In a third part, the influence of the pendant group on the aluminum center was investigated, by varying the alkoxide moiety. While moderate differences were generally noted, very bulky alkoxides led to lower rates, while inversely electron poor groups led to more active catalysts (see Table 7). It was additionally observed that chiral alkoxides did not greatly influence the selectivity, with limited matched/mismatched effects in relation to the salen chirality. Finally, the knowledge gathered allowed the efficient cyanosilylation of very encumbered ketones, with rapid and excellent conversions and enantioselectivity values using hexafluoro-2-propoxide-Al-salen catalyst **14** and DMAO as co-catalyst (Scheme 17).



Scheme 17. Enantioselective cyanosilylation of ketones with hexafluoroisopropoxide catalyst 14

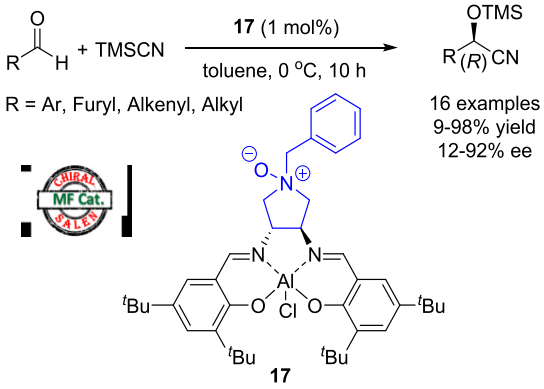
Bifunctional catalysts were also examined, as by the group of Sun who designed bifunctional catalysts incorporating a metal salen-complex and a pyrrolidine *N*-oxide on the same scaffold, which they called a 'two-center catalyst'. Methodologies were explored with both titanium and aluminum complexes, notably for the cyanation of aldehydes, and not ketones, as was the case in previous studies. Here, the diamino core of the Jacobsen catalyst was replaced by a chiral, *C*2-symmetrical diaminopyrrolidine, whose nitrogen atom was then oxidized to give the corresponding *N*-oxide. Both ligands were converted into their respective titanium isopropylate complexes **15** and **16** (see Scheme 18).[54]



Scheme 18. Catalytic enantioselective cyanosilylation with the 'two-center catalyst' developped by Sun's group

Methodological optimizations then identified the best conditions to perform the cyanation with the bifunctional catalysts **15** in comparison with the duet of catalysts, 'unoxidized' catalyst **16** together with external DMAO. Both systems were effective, although bifunctional promoter **15** was generally more active; but most interestingly, the system delivered opposite enantiomers of the cyanhydrins, with good selectivities in either case. This switching phenomenon was not explained but arises from the differential transition states when dual intramolecular or separate parallel activations take place.

The same methodology was applied with the corresponding aluminum complexes by the same group[55] in 2012 (Scheme 19).

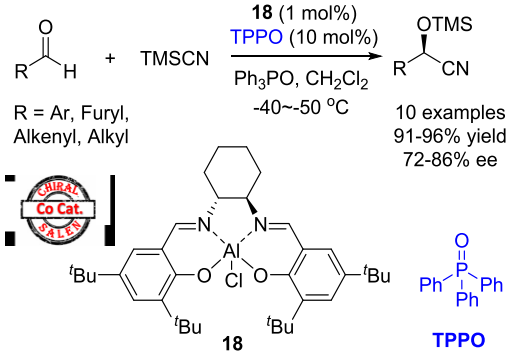


Scheme 19. Enantioselective cyanosilylation of aldehydes catalysed by Al salen bifunctional catalyst 17

This metal switch from titanium to aluminum brought a notable boost in selectivity, allowing the bifunctional catalytic system to perform with better selectivities even at 0 °C, when titanium catalyst 15 was at its optimum at -20 °C.

2.5.2. Cyanosilylation with Phosphine Oxides

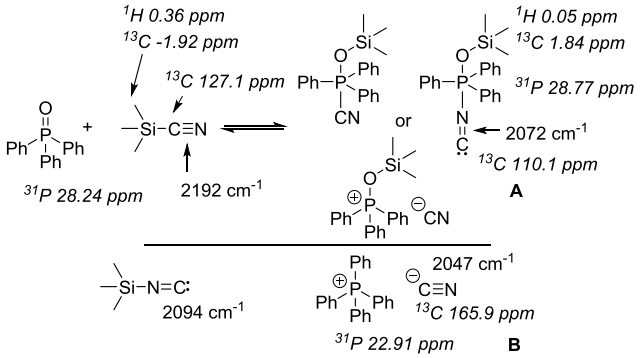
In parallel with the use of *N*-oxides by the group of Feng as seen before, the group of Kim explored the utility of phosphine oxides in co-promoting the reaction of cyanosilylation (Scheme 20). The first report appeared in 2005, with the dual system associating a (salen)AlCl catalyst **18** with triphenylphosphine oxide (TPPO, see Scheme 20).[56]



Scheme 20. First example of (salen)AlCl catalysed enantioselective cyanosilylation of aldehydes with TPPO as co-catalyst

In this initial report, the authors made no mention about the choice of TPPO as co-catalyst, only stating that switching to tris-*tert*-butylphosphine oxide gave a similar conversion but with a lower selectivity (which fell from 69 to 44% ee under the same conditions). Interestingly, at this low temperature, neither of the two catalysts alone could promote a detectable conversion, showing the synergistic effect of the Lewis acid/base pair. Without experimental arguments, they hypothesized, in a similar way to the reactivity of *N*-oxides, that the co-catalyst was activating TMSCN by nucleophilic attack in parallel to the electrophilic activation of the carbonyl substrate by the aluminum Lewis acid.

At this stage, it is useful to examine in more detail the exact role of TPPO. From experiments of the different contributors to this chapter, and from additional data, it is clear that TPPO interacts with TMSCN to form an active species that can quickly transfer a cyano group onto the carbonyl substrate. The nature of this intermediate is not unambiguously determined, but should be among the plausible structures represented in Scheme 21.



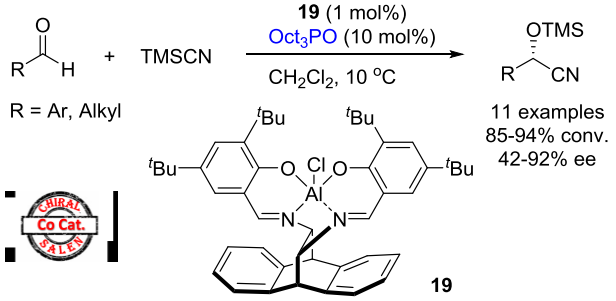
Scheme 21. Potential structures resulting from nucleophilic attack of TMSCN by TPPO (IR in cm^{-1} and ^{1}H NMR in ppm)

In a different context, Corey[57] had investigated the novel compound obtained upon mixing TPPO with TMSCN and attributed, on spectroscopic grounds, the structure **A** to it, with a pentavalent phosphorus and an isocyanide moiety, still being

very cautious on this attribution. It seems however certain that there is no formation of a simple phosphonium cyanide salt as shown by comparison with the known salt **B**.[58]

Turning back to methodological studies on the topic, the previously employed conditions were applied to the cyanation of ketones by Kim in 2006,[59] providing that TPPO loading was increased to 30 mol% and the temperature increased to 25 °C in order to keep a good conversion. Under these conditions, yields ranged between 75 and 98%, while ee's were from 60 to 91%. Both works on aldehydes and ketones were reviewed by Kim in 2006.[60]

In 2008, the group of Zhou[61] explored the use of a chiral diaminoethanoanthracene-based salen ligand, again with an Al^{III} Lewis acidic center **19**, Scheme 22.



Scheme 22. (Salen)AlCl catalyst 19 based on an anthracene-derived diamine

In this study, the authors compared three different phosphine oxides in addition to the (anthra-salen)AlCl catalyst (see Table 8 and Figure 9). They identified tri-octylphosphine oxide (Oct_3PO) as the best co-catalyst, performing better in terms of activity and selectivity. Optimization led to the use of DCM at 10°C with 1 mol% of (anthra-salen)AlCl with 10 mol% of Oct_3PO. Exemplification resulted in the preparation of eleven cyanohydrins derived from aldehydes, with yields ranging from 85 to 94%, and enantioselectivities from 42 to 92%, but with, on the average, slightly better selectivities than those observed with the classical diaminocyclohexane salen employed by Kim.[59]

Table 8. Effect of various phosphine oxides as co-catalysts on the (anthrax-salen)AlCl **19** catalyzed cyanosilylation of aldehydes

Phosphine Oxide	Yield (%)	ee (%)	pK_{BHX}
Ph_3PO	89	81	3.16
nBu_3PO	93	64	3.59
$nOct_3PO$	93	86	3.63

Conditions: (anthrax-salen)AlCl **19** 1 mol%, DCM, 10°C, 16 h.

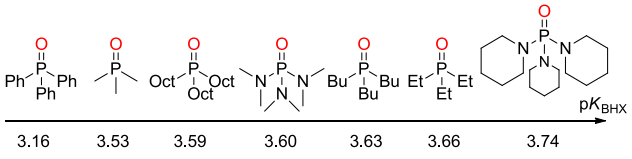
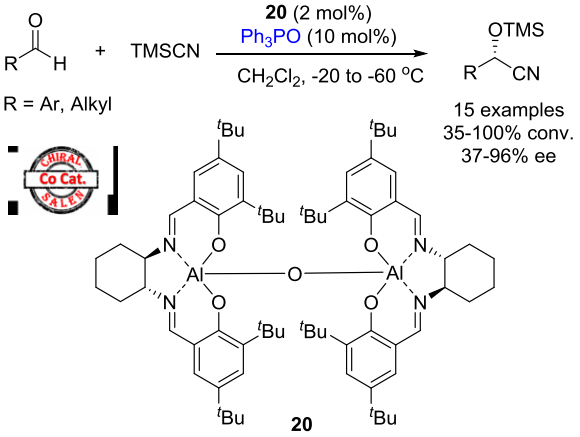


Figure 9. Hydrogen-bond affinity (pK_{BHX}) for a range of phosphane oxides.

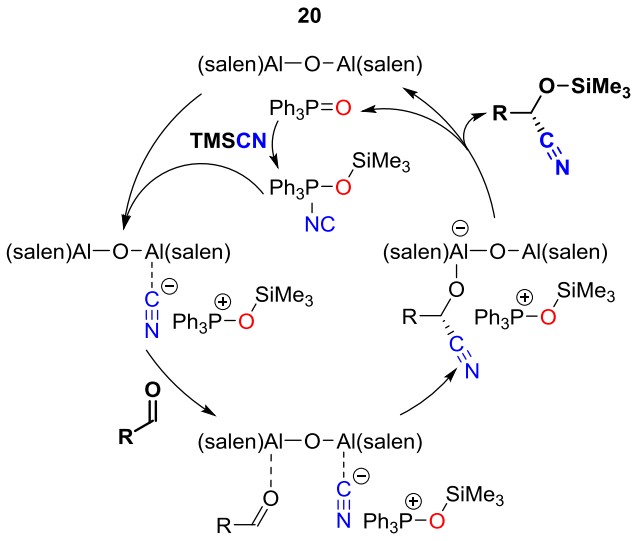
North and coworkers[62] studied in 2009 the bimetallic aluminum catalyst **20**, always in conjunction with TPPO as co-catalyst to carry out the cyanation of aldehydes (Scheme 23).



Scheme 23. Cyanosilylation of aldehydes with bimetallic catalyst 20 and TPPO as co-catalyst

A large array of aldehydes could be converted, even challenging encumbered alkyl ones, although with mediocre selectivity. Kinetics experiments revealed a triple first-order dependence of the reaction, on TMSCN, the bimetallic catalyst **20** and on the TPPO co-catalyst. This suggests a trimolecular process in the rate-determining step of the reaction.

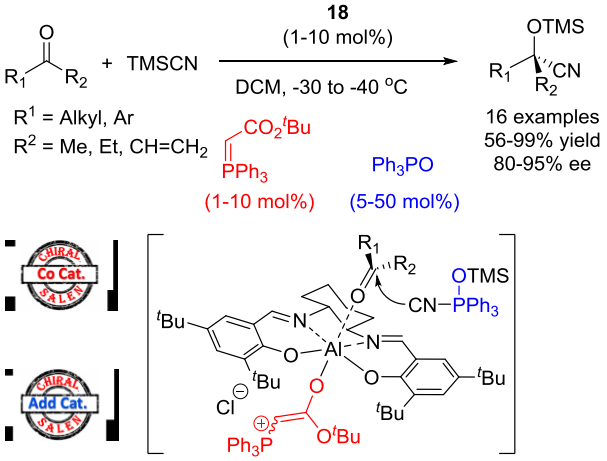
This was further substantiated by the same group[63] in 2010 by performing thorough and meticulous kinetic studies, comparing dimeric $[(salen)TiO]_2$, $(salen)V^V$ catalysts without added Lewis base, and dimeric (salen)Al-O-Al(salen) promoter with added TPPO. By varying the aldehyde and ketone substrates, the authors could draw Hammett plots for these three systems, and concluded that titanium catalyst **1** and aluminum catalyst **20** were acting as pure Lewis acidic activators, (**20** being weaker than **1**) while the vanadium catalyst **4** had a minor contribution of Lewis basicity, arising from the slightly nucleophilic character of V=O, and from the basicity of the counteranion. Finally, and of great importance in this chapter, the dual system aluminum and TPPO is most largely driven by the Lewis basic action of TPPO, the feeble Lewis acidity of the aluminum center being just enough to ensure asymmetric induction by carbonyl coordination, without much electrophilic activation. This coordination insures a facial shielding of the carbonyl and thus orientates the preferential cyanide attack to it. Consequently, a mechanistic course was proposed as shown in Scheme 24.



Scheme 24. Proposed mechanism for the cyanosilylation of aldehydes catalyzed by bimetallic catalyst 20 and TPPO

We can note that no precise or spectroscopically proven structure for the activated form of TMSCN upon interaction with TPPO has been given or commented upon. In any case, nucleophilic attack on TMSCN leads to a cyanide-phosphonium species, which could it be an ion pair or a pentavalent phosphorus derivative. Coordination of the cyano group by one aluminum center is followed by weak coordination of the carbonyl substrate on the other. An internal nuclephilic attack then takes place, in the chiral environment exerted by the two salen ligands, favoring the formation of one cyanoalcoholate enantiomer. The counter cation, silyloxyphosphonium finally serves as silylating agent to deliver the TMS cyanohydrin with regeneration of both catalysts.

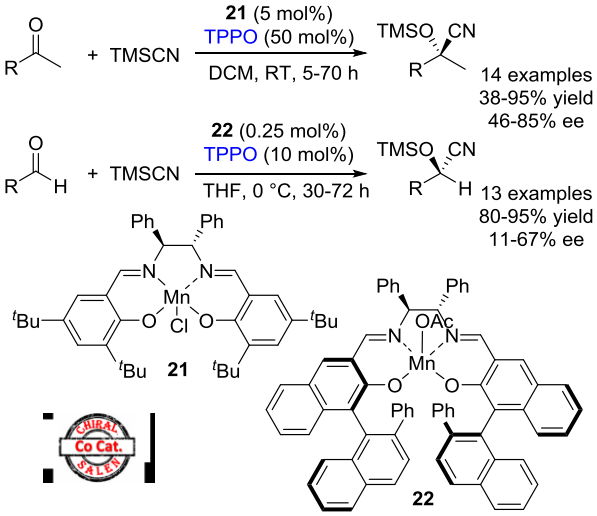
The group of Zhou,[64] developed in 2016 a cyanation protocol relying on a ternary system, (salen)AlCl **18** (see Scheme 20), with TPPO and a phosphorane. After the serendipitous discovery of an exceptional activity in cyanation of a compound resulting from a tandem Wittig reaction/cyanation process, the authors realized that remaining traces of the phosphorane reagent were responsible for the observed activation of the metallic catalyst. Careful screening went on to identify the most efficient catalytic combination with a 1:1 ratio between the aluminum promoter and the ester-functionalized Wittig reagent (thus considered as an additive), plus five times this catalyst loading of TPPO (a true cocatalyst), see Scheme 25.



Scheme 25. Cyanosilylation catalyzed by (salen)AlCl 18, TPPO and phosphorane as co-catalysts

With this very active catalytic triad, a large selection of ketone could be cyanated at low temperature with good conversions and excellent selectivities. Mechanistic studies were then conducted, and an elegant conductimetric approach showed the dramatic effect of the phosphorane, which strongly coordinates the (salen)AlCl complex and led to a cationic species, by release of a chloride anion. The resulting aluminum complex is highly electrophilic and can thus strongly activate the ketone moiety by tight coordination.

If we return to 2006, the group of Kim, also explored the use of manganese complexes **21** and **22** in the cyanosilylation of carbonyls, firstly of ketones[65] and then of aldehydes (Scheme 26).[66]

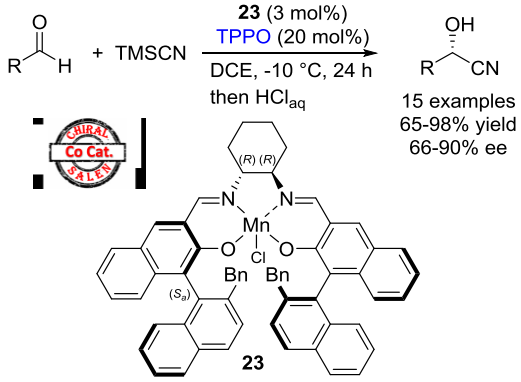


Scheme 26. Enantioselective cyanosilylation of ketones and aldehydes with (salen)Mn^{III} catalysts

Best results were reported with the diphenyldiamine-salen ligand, together with TPPO, both at relatively high loadings, for cyanation of ketones. The Katsuki catalyst **22** was preferred with aldehydes, which, intrinsically more reactive, required far lower catalyst loadings but afforded cyanohydrins with only modest selectivities (11-67% ee), probably through the occurrence of unselective background reaction. The au-

thors again reported the formation of an unidentified species upon mixing TPPO and TMSCN, with similar spectroscopic signatures.

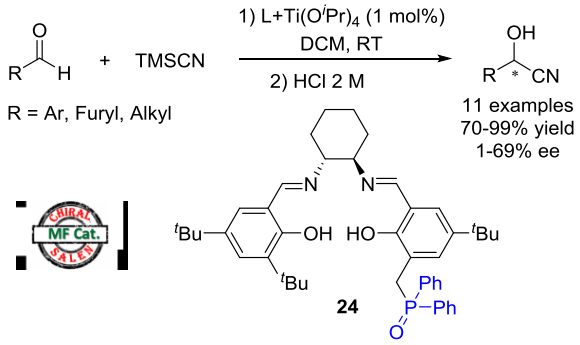
Almost a decade later, the group of Xu,[67] reopened the manganese/TPPO file in cyanations of aldehydes, by exploring the potential of modified Katsuki catalysts. Within the array of ligands tested, screening the matched/mismatched pairs of centered/axial chiralities, the most efficient catalyst possessed benzyl groups at the BINOL tip (see **23** in Scheme 27), bringing chiral information around the metal center, and combines (*R*,*R*) and (S_a) configurations.



Scheme 27. Cyanosilylation of aldehydes catalyzed by salen complex 23 and TPPO

A large variety of aromatic aldehydes could be cyanated in good yield and selectivity, while four alkyl aldehydes were nicely converted, but without measurable enantioselectivity. One would also note with this system that a fairly large loading of TPPO (20 mol%) was necessary to achieve good conversions.

Cyanation reactions with phosphine oxide activators were developed with salen complexes of aluminum and manganese as just seen; the group of Lu,[68] demonstrated in 2011 the potential of (salen)Ti^{IV} in cyanations, moreover with a bifunctional catalyst (Scheme 28). Catalyst **24** proved nicely active, far more than the classical (salen)Ti(O*i*Pr)$_2$ with added TPPO, capitalizing on the improvement brought by the synergistic effect of having both promoters on the same catalyst.

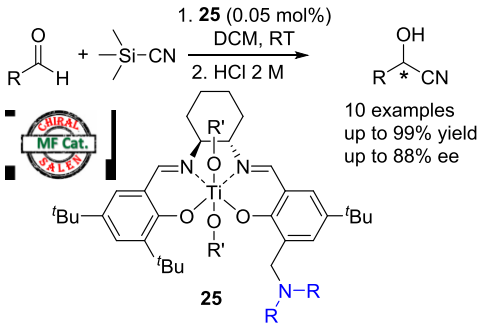


Scheme 28. Cyanosilylation of aldehydes with bifunctional (salen)Ti/TPPO catalyst 24 (unspecified absolute configuration)

If the great acceleration of cyanation in the presence of the bifunctional catalyst by internal Lewis basic assistance is undeniable, this system does not compare well with the aluminum and manganese complexes, reaching only modest enantioselectivities.

2.5.3. Cyanosilylation with Amines

In a 2011 study, the group of Lu[69] studied the cooperative catalytic performances of bifunctional (salen)Ti^{IV} complexes bearing various active moieties, phosphine oxides, quaternary ammoniums and tertiary amines. Among the latter, the diethylaminomethyl catalyst **25** showed an exceptional activity at 1 mol% compared to the other tested complexes in the cyanation of benzaldehyde with TMSCN. Optimizations allowed the use of 0.05 mol% of this bifunctional promoter with a small array of aldehydes, showed a strong substrate dependence in terms of activity/enantioselectivity (Scheme 29 and Table 9).



Scheme 29. Cyanation with amine-fonctionalized catalysts 25

Table 9. Effect of amines as co-catalysts on the cyanosilylation of benzalaldehyde with **25**

-NR$_2$	mol%	Time (min)	Yield (%)	pK_{BHX}	*N*
Morpholine	1	180	< 5	1.56	16.50
Imidazole	1	180	98	2.72	11.90
Piperidine	1	60	97	2.11	18.90
TBD	1	40	99	3.48	14.43
-NEt$_2$	1	10	99	1.98	17.30
-NEt$_2$	0.5	10	99		
-NEt$_2$	0.1	10	97		
-NEt$_2$	0.05	10	97		
-NEt$_2$	0.02	90	99		
-NEt$_2$	0.002	1440	58		

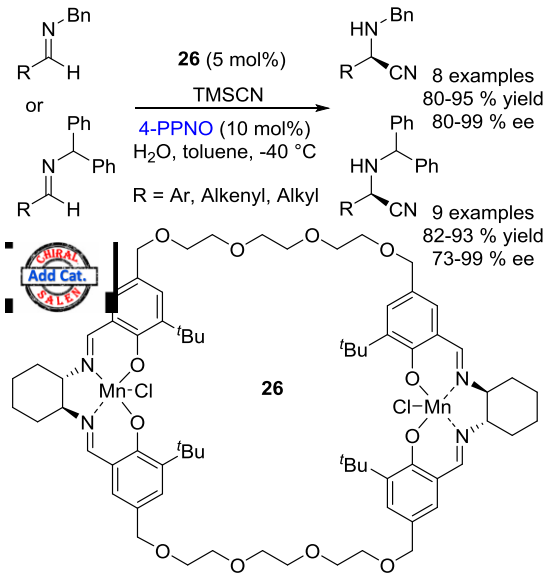
Conditions: Ligand + Ti(OiPr)$_4$, PhCHO, DCM, RT, (TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene).

The authors did not comment on the monomeric or dimeric nature of the catalyst, as in the presence of traces of water, such (salen)Ti^{IV} tend to form a cyclic (Ti-O)$_2$ dimer with markedly different behavior from the monomer. The very irregular activity pattern is not correlating with neither nucleophilicity (*N*, kinetic parameter), nor Lewis basicity (pK_{BHX}, thermodynamic parameter) indicating a complex reactivity setting where concurrent interactions are at play. It is thus probable that the nitrogen Lewis base interacts both with TMSCN and with the electrophilic metal center, these

activating/deleterious interactions being best balanced in the case of the diethylamino group.

2.6. Strecker Reactions-Cyanation of Imines

Imines are usually less electrophilic carbonyl derivatives compared to aldehydes and ketones and are thus more challenging substrates in cyanation reactions. Having reached high activity/selectivity results in cyanoformylation reactions with a bimetallic macrocyclic catalyst with titanium, the group of Khan[70] exploited the same ligand in the cyanosilylation of *N*-benzylimines and *N*-benzhydrylimines using the bimetallic macrocyclic manganese^{III} complex **26**.



Scheme 30. Asymmetric Strecker reaction of benzyl- and benzhydrylimines with TMSCN catalysed by 26 and 4-PPNO as co-catalyst

Optimizations studies identified catalyst **26** with PEG-3 linkers as the most selective in combination with 4-phenylpyridine *N*-oxide (4-PPNO) as co-catalyst. A small array of benzyl- and benzhydryl-imines were reacted, preparing aminonitriles in enantioenriched forms with excellent yields and selectivities (Scheme 30).

Kinetic measurements showed a first order dependence on both susbtrates, imine and TMSCN, and catalyst. Order determination was not performed with the co-catalyst 4-PPNO, which could have given some insight into its role(s). The authors assume a unique interaction with the manganese, thus acting as an apical ligand, inducing a strongly stepped conformation as shown in Figure 5, thus ameliorating facial differentiation, classifying it as an additive. However, they did not comment on its eventual role as nucleophile displacing the cyanide anion from TMSCN, although this eventuality was exposed in the introduction, defining a role of co-catalyst. This secondary action can be partially substantiated, as one might note that in optimization tables, yields increase proportionally to the 4-PPNO loading from 2.5 to 10 mol%, a fact explained by the larger quantity of cyanide ion then released in the solution.

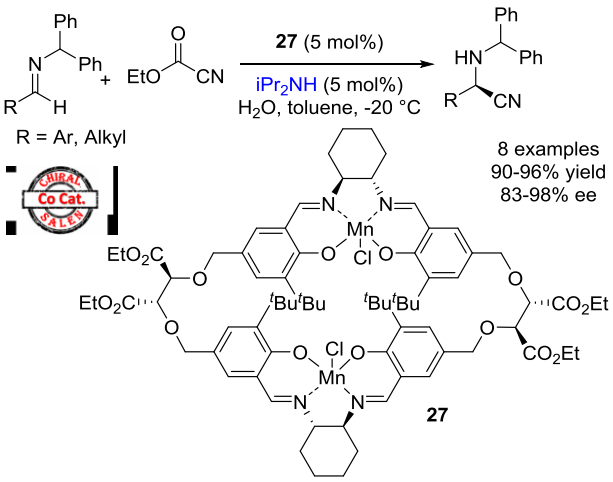
Table 10. Effect of *N*-Oxide co-catalysts on the asymmetric Strecker reaction with complex **26**

Lewis base	Yield (%)	ee (%)	pK_{BHX}	
none	73	70		
PyrNO	70	74	2.72	
4-PPNO	80	79	2.85	
Ph_3PO	62	61	3.16	
4-Pr-PyrNO	59	62	(3.12)	

Conditions: (salen)Mn^{III} catalyst **26** 10 mol%, toluene, -20 °C, 6 h.

It can be noted that among the co-catalysts tested, the most Lewis basic (according to its pK_{BHX}) seems detrimental for both activity and enantioselectivity (Table 10). It can be hypothesized that with strongly basic ligands, the manganese can be fully coordinated by two molecules of co-catalyst, excluding coordination of the imine substrate, hence deprived of electrophilic activation and facial discrimination.

In the same publication, the group of Khan also explored the Strecker reaction using ethyl cyanoformate as the cyanide source. Optimization investigations in that case identified the macrocyclic bimetallic complex **27** as the most efficient catalyst, in conjunction with diisopropylamine as co-catalyst (Scheme 31).



Scheme 31. Asymmetric Strecker reaction with benzhydrylimines and ethyl cyanoformate catalysed by complex 27

Excellent conversions and enantioselectivities could be obtained with various *N*-benzhydrylimines, efficiently delivering chiral aminonitriles if a "matched" pair is employed (tartrate linker and diamine configurations). One must realize that under these conditions, with water intentionally introduced in the medium, the product does not incorporate the ethyl formate moiety to form a carbamate as seen in chapters 2.1-2.4. The water slowly hydrolyses the cyanoformate reactant to liberate cyanide anions, probably with Brønsted-base assistance from the amine (Table 11).

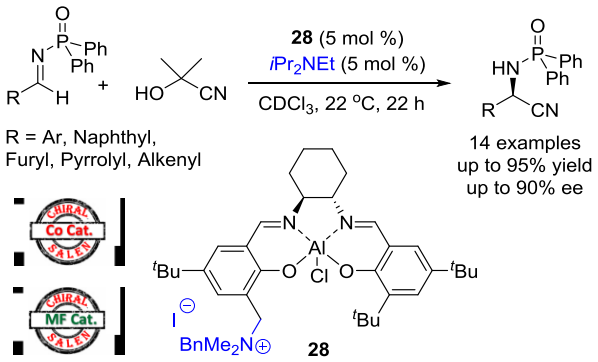
Table 11. Effect of Brønsted bases as co-catalysts in the asymmetric Strecker reaction with bimetallic complex **27**

Base	Yield (%)	ee (%)	pK_{BHX}	pK_a

None	57	79	-	-
ImH	83	73	2.42	15.05
2,6-lutidine	95	62	2.14	13.92
iPr_2NH	95	87	2.00	18.81
NEt_3	98	65	1.98	18.82

Conditions: (salen)Mn catalyst **27** 10 mol%, toluene, -20 °C, 8 h.

The cooperative Lewis acid/onium salt/Brønsted base catalysis developed by Peters was also efficiently applied to the enantioselective hydrocyanations of aldimines.[71] This group performed the Strecker reaction by the addition of acetone cyanohydrin (an attractive cyanation agent releasing only acetone as by-product) to phosphinoyl aldimines (as storable and easily deprotected imine precursors). After optimization of the catalytic system, *i.e.* the structure of the ammonium unit linked to the aluminum-complex **28** and the nature of the catalytic base used to liberate a cyanide anion from acetone cyanhydrin, the reaction occurred efficiently with various *N*-phosphinoyl aldimines to deliver the targeted enantioenriched α-amino acid precursors in good to excellent yields and up to 90% ee (see Scheme 32).



Scheme 32. Catalytic asymmetric hydrocyanation of *N*-phosphinoyl aldimines with complex 28 bearing an appended ammonium salt

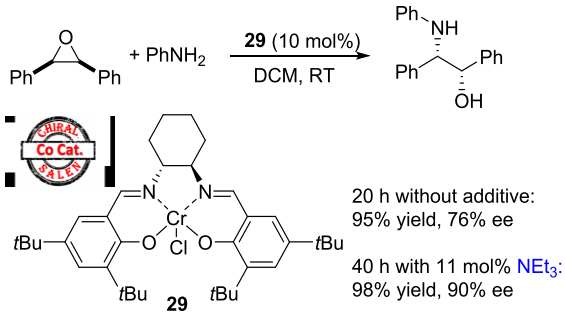
The authors proposed here again that the imine electrophile was activated by the Lewis acidic aluminum centre and the cyanide anion by the ammonium moiety, allowing for an efficient control of its attack on the imine thus leading to enantiofacial differentiation. They also proved that the generated conjugated acid of the Hünig's base was the proton source for the product release.

3. Catalysis with a Metallo-Salen and a Lewis Base

3.1. Metallo-Salen and Amines

3.1.1. Epoxide Ring-Opening

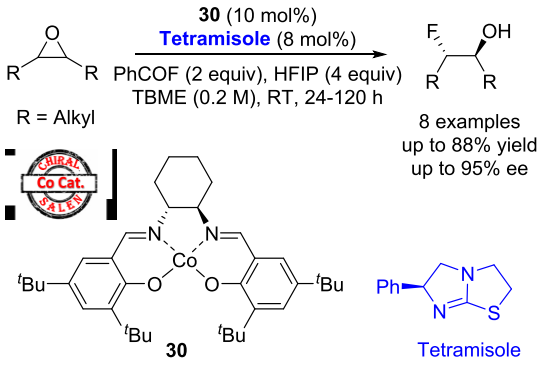
While studying the aminolysis of epoxides with anilines in the presence of (salen)Cr^{III} complex 29, Bartoli and Melchiorre[72] noted that in the case of *meso*-stilbene, catalytic amounts of triethylamine dramatically increased the selectivity, at the expense of a prolonged reaction time (Scheme 33).



Scheme 33. Anilinolysis of epoxides catalysed by complex 29

The exact role of the base was not investigated, however, as is classically observed in such chromium-based systems,[36] an important non-linear effect is observed, indicating that more than one chromium center is involved in the rate-determining step.

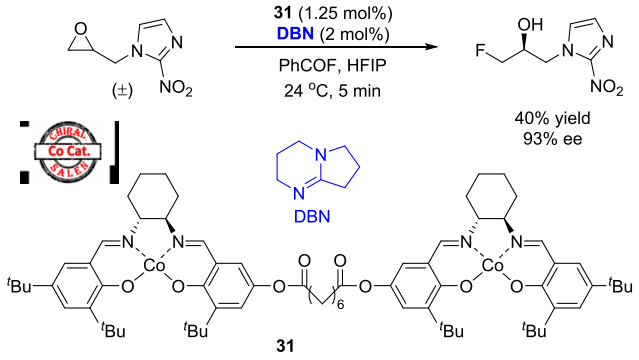
In 2010, Doyle *et al.*[73] then developed a highly enantioselective fluoride ring opening of meso epoxides using the dual-catalyst system where (salen)Co^{II} **30** acts as the Lewis acid and (-)-Tetramisole acts as the Lewis base. Commercial benzoyl fluoride was used as a latent source of fluoride (Scheme 34). In applying this effective method to the ring opening of various *meso* epoxides, a series of products can be obtained in excellent yields and ee values.



Scheme 34. Enantioselective fluoride ring opening of *meso*-epoxides using a cooperative dual-catalyst system

In 2011, the same group[74] reported the mechanistic studies of this transformation. The authors investigated the kinetics, substituent effects, nonlinear effects, and reactivity of this system. Interestingly, they observed a strong match/mismatch effect; as the combination of (salen)Co^{II} **30** with (-)-Tetramisole gives very high conversion and ee on a model cyclic *meso*-epoxide (88% conv, 95% ee) while the use of the (*S*,*S*)-analogous cobalt complex with the same chiral base leads to 8% conversion and -32% ee. This indicates that both chiral promoters are important to achieve high selectivity. Indeed, they revealed that Tetramisole also serves as a ligand for the (salen)Co^{II} (an additive), in parallel to its primary role of nucleophile to liberate a fluoride anion after attack of the

acylfluoride (a co-catalyst). It was also shown that rates, turnover numbers, and substrate scope could be significantly improved by the use of a linked salen framework **31**, probably again by cooperative action of two metal centers.[36] An application was developed with the linked salen catalyst and DBN for the production of a known PET tracer, fluoromisonidazole (FMISO) with a high ee value of 93% in only 5 minutes (Scheme 35).

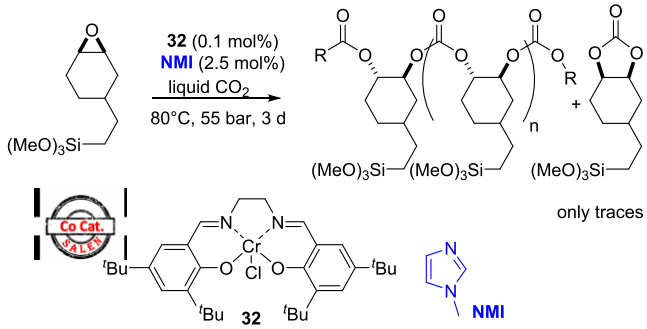


Scheme 35. Synthesis of fluoromisonidazole using dimeric catalyst (*R*,*R*,*R*,*R*)-31 and DBN

3.1.2. Reaction of CO_2 with Epoxides

In recent years, carbon dioxide (CO_2) has attracted widespread attention as a non-toxic, non-flammable, highly abundant and renewable C1 feedstock for organic synthesis.[75,76] Because carbonate products are widely used as electrolytes for lithium-ion batteries, fine chemical intermediates and aprotic high-boiling polar solvents,[77-79] their synthesis by performing a 100% atom-economic cycloaddition reaction between epoxides and CO_2 is one of the most promising reactions for the simple and economical fixation of CO_2. In this context, the development of efficient enantiopure catalytic systems for their enantioselective preparation is currently very timely.

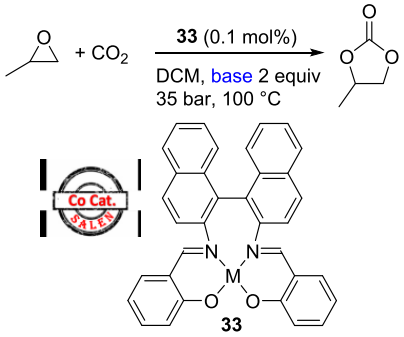
The first use of a combined catalytic system was reported by Darensbourg[80] with the copolymerization of an epoxide with carbon dioxide in the presence of an achiral (salen)Cr^{III} complex **32** and *N*-methylimidazole (Scheme 36).



Scheme 36. (salen)Cr^{III}/ *N*-methylimidazole catalyzed copolymerization of epoxide with CO_2

Although chirality was not considered since an achiral salen ligand was employed, the chemoselectivity was remarkable, since the dual catalysis induces the intermolecular attack of the transient carboxylic anion, and not the intramolecular formation of a cyclic carbonate.

The same year, the group of Shi[81] investigated several bicatalytic systems for carbon dioxide incorporation with propylene oxide to give propylene carbonate. Diverse nitrogen bases were studied together with (salen)Zn^{II}, Cu^{II} or Co^{II} complexes derived from *rac*-Binam (see **33** in Scheme 37 and Table 12 for the structures of the bases that were investigated).



Scheme 37. Carbonate formation from propylene oxide catalyzed by *rac*-Binam salen complex 33 and nitrogen bases

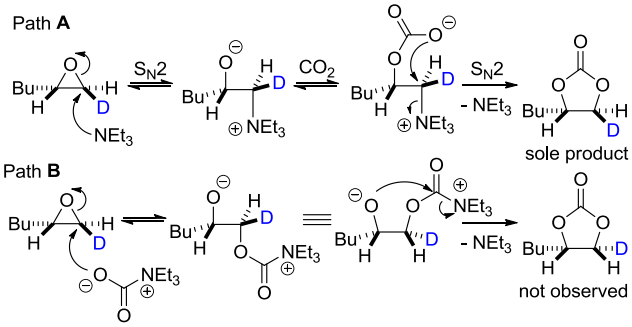
First, it was shown that the sole Lewis acid, or the sole base could not promote the transformation. In all the tested combinations, triethylamine appeared as the most potent base, together with the zinc or the cobalt complex, DMAP being just below (see Table 12).

Table 12. Effect of base co-catalyst on carbonate formation from propylene oxide and CO_2

Base	Zn^{II}		Cu^{II}		Co^{II}	
	Yield	*TON*	Yield	*TON*	Yield	*TON*
none	0		0		0	
DABCO	30	*30*				
NEt_3	86	*856*	51	*510*	91	*913*
DBU	80	*803*				
pyridine	83	*833*				
DMAP	70	*702*	40	*397*	80	*800*

Conditions: 0.1 mol% for the catalyst, 0.2-1.0 mol % organic base, CH_2Cl_2, RT.

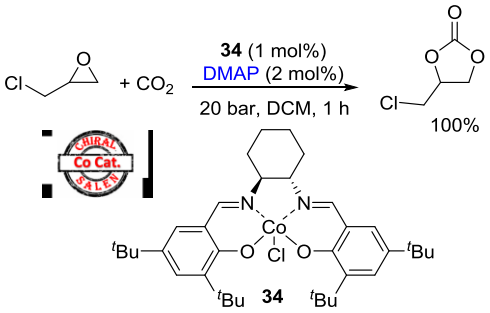
Then, mechanistic studies with a deuterated epoxide indicated a plausible course for this transformation, clarifying the exact role of each catalyst (Scheme 38).



Scheme 38. Carbonate formation from a deuterated epoxide

Hence, between the two possible reaction scenarios, only path **A** matches the experimental result, that is global retention of configuration. The reaction would thus occur with initial nucleophilic attack of the base onto the epoxide to form an ammonium-alcoholate, followed by addition of the latter onto carbon dioxide, a second intramolecular substitution giving the final cyclic carbonate with the observed stereochemistry, (the same outcome is also valid if the attacks take place at the most substituted epoxide carbon). Unfortunately, the use of an enantiopure catalyst did not provide any kinetic resolution of racemic propylene oxide with ee's up to 5% observed for the obtained propylene carbonate.

In 2004, Nguyen *et al.*[82] prolonged this study using a chiral (salen)Co^{III} complex **34** and a small series of nitrogen bases (Scheme 39).



Scheme 39. Carbonate formation from epichlorhydrin with CO_2 promoted by complex 34 and DMAP

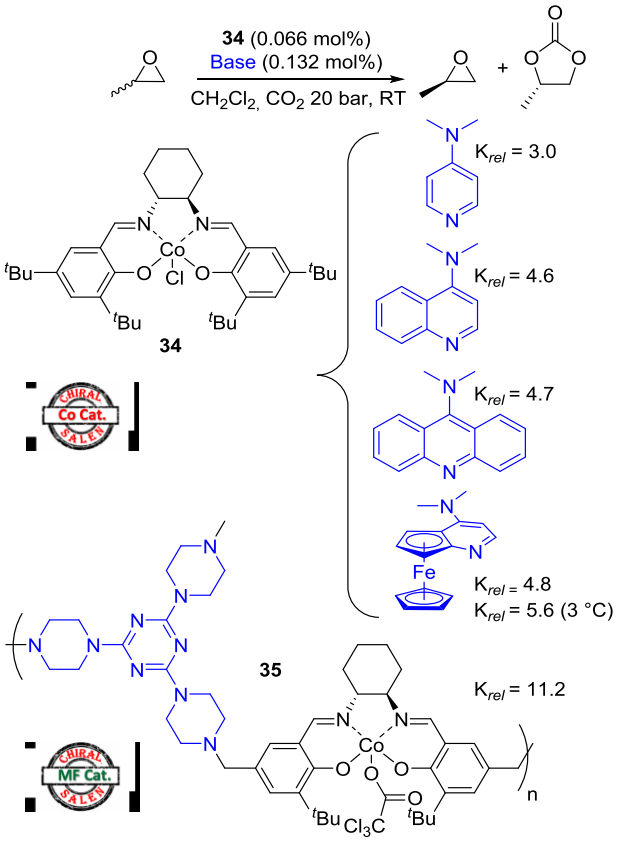
Among the bases screened, DMAP resulted in high TOFs at 100°C since very low metal catalyst loadings were effective, and we can observe that within the series, the activity almost perfectly correlates with the thermodynamic Lewis basicity of the catalyst, except with triethylamine for which steric hindrance could moderate its inherent basicity, Table 13. In this part of the study, the potential kinetic resolution of racemic epoxides was not examined.

Table 13. Effect of bases as co-catalysts on carbonate formation from propylene oxide and CO_2

Base	TOF (h^{-1})	*N*	MCA ($kJ.mol^{-1}$)
DMAP	1200	15.80	581.2
NMI	506	11.90	550.0
NEt_3	99	17.30	562.3
Pyridine	25	12.90	518.7

Conditions: catalyst **34** 0.066 mol%, 2 equiv of organic base, DCM, 100 °C, 1 h.

When an enantiopure epoxide was used, the corresponding cyclic carbonate was obtained with complete retention of the original stereochemistry. The use of a chiral base ((*R*)-(+)-4-dimethylaminopyridinyl-(pentaphenyl-cyclopentadienyl)iron, the chiral DMAP developed by Fu, led to an increase in selectivity. By testing other bases, the authors determined that their chiral nature was not essential to the overall selectivity of the reaction; whereas their steric bulk and electronic properties were determining factors (see Scheme 40). They were furthermore able to perform the kinetic resolution of racemic propylene oxide with CO_2, by running the reaction at low temperature with chiral DMAP, with selectivity factors of up to s = 5.6 were obtained, but at the cost of a dramatically reduced TOF.



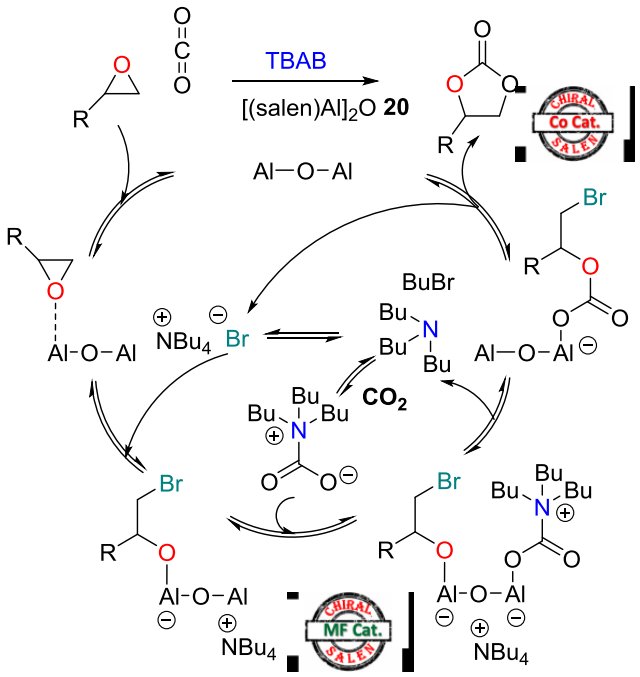
Scheme 40. Kinetic resolution of propylene oxide with CO_2 promoted by complexes 34 and 35 with various bases

As shown by the authors, two equivalents of base are mandatory, one to coordinate the Lewis acid resulting in a stronger coordination of the epoxide onto the cobalt center and a second DMAP to act as a nucleophile to ring open the epoxide.

Almost ten years later, Kureshy's group[83] employed for the same reaction a polymeric (salen)Co^{II} complex **35** linked by triazine-piperidine moieties, hence constituting a bifunctional and chiral catalyst, containing the Lewis acid and Lewis basic centres (see Scheme 40). The best selectivity value was obtained with CCl_3COO^- as a bulky axial ligand when the reaction was run at low temperatures and atmospheric pressure of CO_2. The catalyst was furthermore recovered and reused very effectively for ten runs without any performance decrease.

The use of bimetallic $[(salen)Al]_2O$ complex **20** (see Scheme 23) has also been investigated by Pasquale and coll.[84] to promote the same kinetic resolution at room temperature, under atmospheric pressure of CO_2 in the presence of tetrabutylammonium bromide (TBAB) as co-catalyst (Scheme 41). Although TBAB is not *per se* a Lewis base, a precise analysis of the reaction kinetics showed that part of the quaternary ammonium is in equilibrium with tributylamine and bromobutane, the former acting as a nucleophile to activate the

carbon dioxide and form a carbamate zwitterion. It then attacks the aluminum bromoalcoholate arising from the ring opening of the epoxide by the bromide anion after Lewis acidic activation by the (salen)Al complex. It was proven that in the absence of tributylamine in the system, almost no conversion was observed.

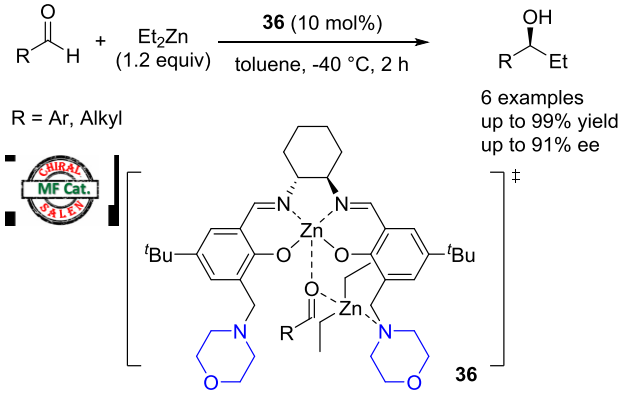


Scheme 41. Kinetic resolution of propylene oxide with CO_2 promoted by a bimetallic (salen)Al complex 20 in the presence of TBAB

This results in a far more complex setting than anticipated by the authors. In fact, the reaction relies on a triple catalysis: nucleophilic amine and bromide anion activate both reagents, the resulting activated forms being merged together on the double Lewis acid catalyst.

3.1.3. Organozinc Addition onto Carbonyl Compounds.

Over the past few decades, catalysts containing chiral ligands with two or more reactive sites have successfully achieved asymmetric C-C bond formation.[85-88] We will now concentrate on salen-derived catalysts which contain both a Lewis acid center and Lewis basic moieties that showed a powerful effect, especially for organozinc addition onto carbonyl compounds.
In 2001, Kozlowski *et al.*[89,90] developed a new class of catalysts that demonstrate excellent reactivity and good enantioselectivity for the addition of diethylzinc to aldehydes. In applying the modular bifunctional (salen)Zn catalyst **36** to this reaction, an apical coordination site on the salen metal center could act as a Lewis acid site to activate the aldehyde while the tethered base could independently activate the Et_2Zn nucleophile (Scheme 42).



Scheme 42. Enantioselective catalytic addition of diethylzinc to aldehydes using catalyst 36 containing morpholine groups, and proposed transition state

Among a variety of catalysts with appended nitrogen bases tested, the authors demonstrated that the morpholine group was the most efficient (see Table 14).

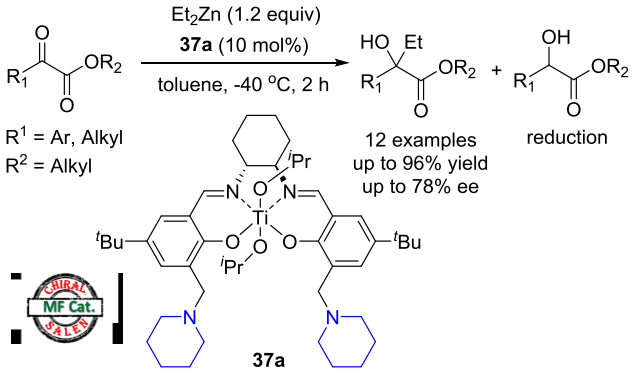
Table 14. Effect of nitrogen bases on the enantioselective catalytic addition of diethylzinc to benzaldehyde

R group	Conv. (%)	ee (%)	pK_a	pK_{BHX}
2-pyridine	99	51	5	2.03
piperidine	90	76	9	2.11
morpholine	72	77	6	1.56
diMePiperidine	33	73	9	?
N(iPr)$_2$	5	52	9	1.05
*t*Bu	2	57	-	-

Conditions: 10 mol% of the corresponding catalyst, 2.1 equiv. of Et_2Zn, 30 °C, 6 h.

This efficiency was explained by a good balance between the good Lewis basicity and moderate steric hindrance within the morpholino group compared to the others. The bifunctionality was demonstrated via a test reaction with a mixture of *N*-methylmorpholine and the non-substituted (salen)Zn complex, showing no conversion at all.

In 2001, Kozlowski *et al.*[91,92] developed an extension of this reaction to ketoesters using the same type of Lewis acid/Lewis base system but with (salen)Ti complexes as catalysts. With α-ketoesters, the development of a selective alkylation is complicated due to a competing reduction pathway (Scheme 43). Within the tested promoters, (salen)Ti complex **37a** with an appended piperidine base group proved the most reactive and selective, while suppressing any unwanted reduction, just above the ligand possessing a 2-pyridyl moiety.



Scheme 43. Addition of diethylzinc to ketoesters using complex 37a containing appended piperidine

The nature of the appended base greatly influences the outcome of the reaction, with various amounts of reduction, and various selectivities (Table 15).

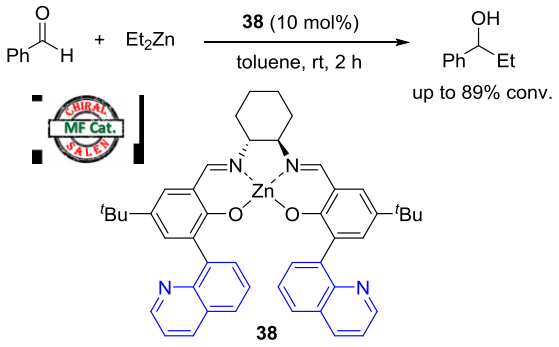
Table 15. Effect of bases as co-catalysts on the diethylzinc addition to $PhCOCO_2Et$ using complex **37a**.

Base	Red. (%)	Add. (%)	ee (%)
No catalyst	45	23	0
Piperidine	0	99	56
Pyrrolidine	3	94	54
Morpholine	9	72	54
Dimethylamino	0	91	44
2-pyridine	0	91	57
diMepiperidine	10	84	20
7-quinoline	5	57	7
*t*Bu salen	20	56	4
*t*Bu salen + NMM	15	56	2
NMM	30	14	0

Conditions: 1.2 equiv of Et_2Zn, cat. **37a** 10 mol % at -40 °C for 2 h.

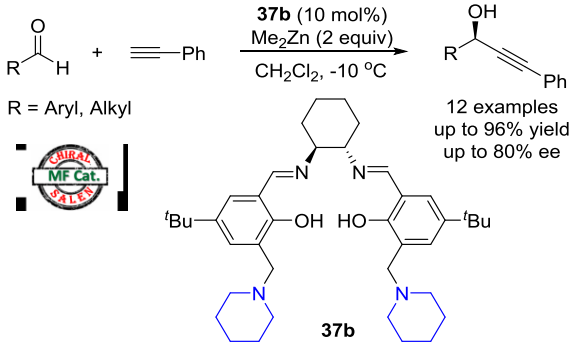
Again, the bifunctionality is crucial since the mixture of a native (salen)Zn with added *N*-methylpiperidine gives a very low conversion, close to the reaction background. It is worthy to note that the authors showed that changing the alkoxide ligands on the titanium center did not dramatically affect the selectivity of this reaction.

Then in 2003, Kozlowski and co-workers[93] designed a novel series of metal-salen complexes containing a 7-quinoline base for use as bifunctional catalysts. The ruthenium, chromium, titanium, and zinc salen complexes were formed and characterized. The zinc complex **38** proved to be a very reactive catalyst in the addition of diethylzinc to benzaldehyde, providing the addition product in 89% conversion in 2 hours at room temperature, however, an eventual enantioselectivity was not discussed (Scheme 44).



Scheme 44. Addition of diethylzinc to aldehydes using (salen)Zn complex 38 containing a quinoline base (chiral induction was not reported)

These bifunctional complexes were later exploited to catalyze the addition of alkynylzinc reagents to aldehydes thus giving access to propargyl alcohols that are versatile building blocks for a wide range of biologically active compounds and pharmaceuticals.[94,95] Hence, Xu and co-workers[96] developed an asymmetric alkynylation procedure of aldehydes using the bifunctional (salen)Zn catalysts developed by Kozlowski (Scheme 46). Similarly, in this system zinc complex generated *in situ* from ligand **37b** acts as a Lewis acid to activate the aldehyde while the tethered base chelates the alkynylzinc nucleophile independently. The best conditions, balancing catalytic reactivity and stereoselectivity, were observed with 10 mol% of the (salen)Zn catalyst bearing two piperidinylmethyl groups at C-3 and C-3' positions, in dichloromethane at -10 °C. This was applicable to a variety of aldehydes, giving the corresponding propargylic alcohols in good yields, with up to 96% yield, and with up to 80% enantioselectivities, (Scheme 45).

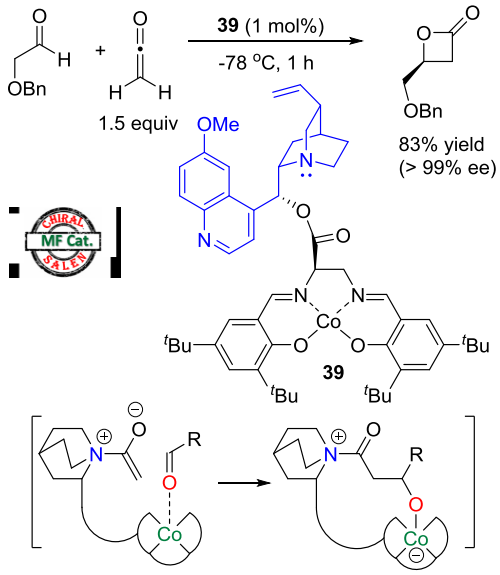


Scheme 45. Asymmetric addition of phenylacetylene to aldehydes catalyzed by *in situ* generated (salen)Zn complex from ligand 37b

3.1.4. Beta-Lactone from Ketenes

Lin and co-workers[97] developed in 2007 a bifunctional catalyst, ensuring a close proximity between the Lewis acid and the Lewis base. The catalyst **39** derived from (salen)Co^{II} and quinine was found to be very efficient for Wynberg cycloaddition between aldehydes and ketenes, giving beta-lactones in up to 83% yield and more than 99% ee (Scheme 46). This bifunctional promoter is very active, loadings as low as 1 mol% of **39** being efficient. Interestingly, the

bifunctionality was demonstrated by the fact that neither of the isolated moieties, quinine derivative or (salen)Co, were able to trigger the reaction, nor the intermolecular combination of them. The transformation thus requires a tight dual activation, of the ketene by the tertiary amine, and at the same time of the aldehyde by the metal complex.

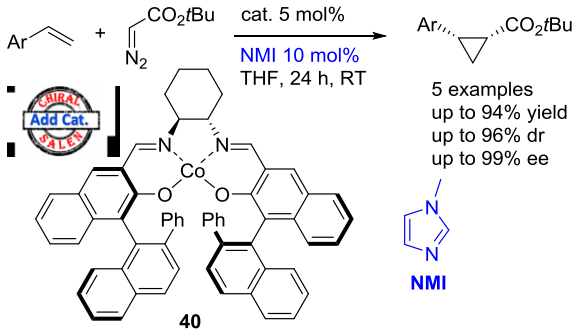


Scheme 46. Cycloaddition of aldehydes and ketene catalyzed by complex 39

The authors noted a very rapid turnover, suggesting a fast aldolisation thanks to the optimal placement of the ammonium enolate *versus* the coordinated aldehyde, and a fast ring-closure of the resulting coordinated alcoholate.

3.1.5. Cyclopropanation

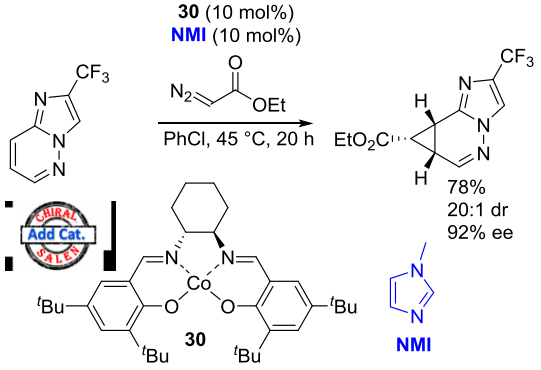
In 2000, Katsuki and colleagues[98,99] were the first to report on the beneficial effect of a basic additive in enantioselective cyclopropanation reactions. Carbene transfer onto styrene derivatives occurred in a *cis* fashion and with excellent conversions and selectivities using (salen)Co^{II} catalyst **40** in presence of NMI as additive, following previous results with different cobalt complexes.[100]



Scheme 47. Enantioselective cyclopropanation of styrenes

It was postulated that apical coordination of the cobalt center induced a more favourable geometry of the complex leading to more selective diazo transfer.

Chen applied this cyclopropanation procedure to imidazo-heterocyclic structures through a cobalt-mediated carbene transfer using simpler (salen)Co^{II} catalyst **30**.[101] Good conversions and enantioselectivities were obtained when *N*-methylimidazole (NMI) was used as an additive (Scheme 48).



Scheme 48. Enantioselective cyclopropanation by (salen)Co complex 30 and NMI as co-catalyst

The authors did not comment on the exact role of the basic additive, but the latter seemed to act as an apical ligand for the cobalt(II) center, providing an octahedral complex with increased activity and a more enantiodifferentiative geometry (Table 16).

Table 16. Effect of additives on the asymmetric cyclopropanation catalyzed by complex **30**.

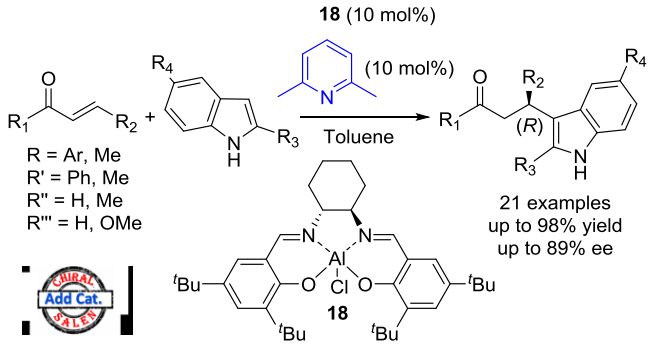
Additive	Conversion (%)	ee
none	30	76
Imidazole	68	78
N-methylimidazole	100	92
N-butylimidazole	100	92
thiazole	95	86
pyridine	92	84
DMAP	100	86

Conditions: 15 mmol% of **30**, 15 mol% of base, chlorobenzene, 45 ℃, 2 h.

Only marginal differences were observed according to the nitrogen base employed, *N*-methylimidazole exhibiting the optimal coordinating properties.

3.1.6. Addition of Indoles to Enones

The development of catalytic asymmetric Friedel-Crafts-type additions has been the subject of intensive studies in order to access enantiomerically enriched aromatic compounds bearing benzylic stereocenters. In this context, Bandini, Umani-Ronchi and co-workers[102,103] reported an effective enantioselective conjugate addition of indoles to (*E*)-enones in the presence of chiral (salen)AlCl complex **18** combined to catalytic amounts of amines. 2,6-Lutidine was initially added as a Brønsted base in order to neutralize the potential traces of HCl liberated during the catalysis, but they found that catalytic amounts of base were also beneficial for the stereochemical outcome of the reaction, leading to an enantiomeric excess increase to 89%. Screening of several other bases additives revealed that 2,6-lutidine was the best (Scheme 49).



Scheme 49. Stereoselective addition of indoles to (*E*)-enones catalysed complex 18 with 2,6-lutidine

The role of the base was examined through spectroscopic and computational analyses, which suggested the *in situ* formation of a stable cationic hexacoordinate complex, formed between (salen)Al^{III} with both substrate and base additive (in a *trans* configuration). Pyridine thus serves as a ligand and not, as anticipated, as a deprotonating/protonating agent, which is reflected in the trend of the ee following the Lewis basicity as expressed by the hydrogen-bond affinity pK_{BHX} and not following the pK_a (Table 17).

Table 17. Effect of additives on the catalytic stereoselective addition of indoles to (*E*)-enones.

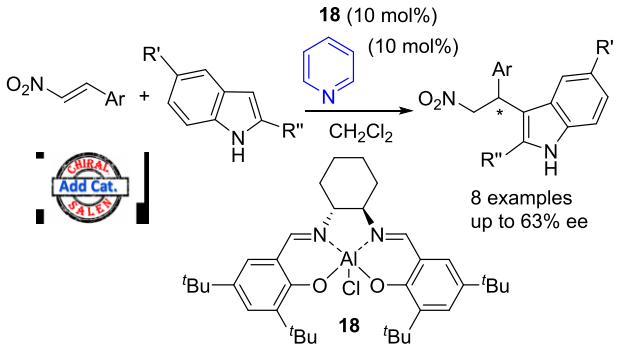
Base	Yield (%)	ee (%)	p$K_{a\,(ACN)}$	pK_{BHX}
none	80	55	-	
aniline	70	71	10.62	-0.26
2-CyanoPyr	87	25	(6.0)	0.48
2,6-ditBuPyr	59	29	(9.8)	(0.9)
pyridine	54	76	12.53	1.86
NEt_3	65	77	18.82	1.98
2,6-lutidine	65	79	14.13	2.14

Conditions: (salen)AlCl 5 mol%, toluene, 48 h, RT, bracketed values extrapolated from very similar compounds.

As previously seen, interactions between the coordinating base and the aluminum complex was proposed to be responsible for the observed improvement in stereocontrol by increasing the twisting angle of the two phenolic moieties within the salen complex. This catalytic system was efficiently applied to the synthesis of a large range of β-indolyl ketones in excellent yields and good enantiomeric excesses.

3.1.7. Addition of Indoles to Nitroalkenes

The same group extended this procedure to more challenging Friedel–Crafts alkylation reactions between indoles and aromatic nitro-olefins.[104] They developed a catalytic protocol for the preparation of useful β-indolyl nitro compounds bearing benzhydryl stereocenters in good yields with up to 63% enantiomeric excess (Scheme 50). As observed for the addition of indoles to (*E*)-enones, the combination of catalytic amounts of chiral (salen)AlCl complex **18** with an organic base was essential for the success of this transformation. In this case, simple pyridine was found to be the most effective additive in CH_2Cl_2 among a variety of bases.



Scheme 50. Stereoselective alkylation of indoles with nitroalkenes catalysed by complex 18 with pyridine

3.2. Metallo-Salen and *N*-Oxides

3.2.1. Alkenes Epoxidation

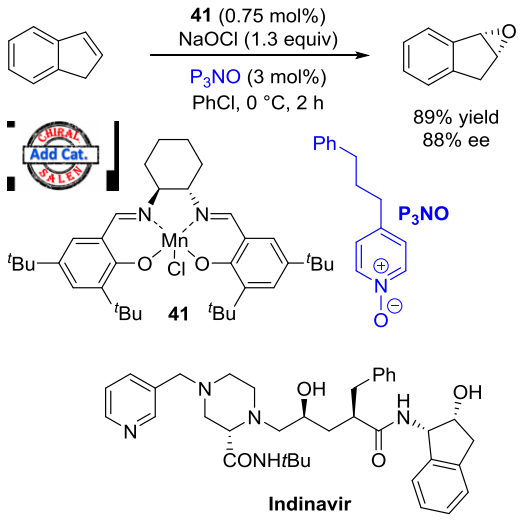
The epoxidation of alkenes is probably one of the catalytic transformations promoted by enantiopure metallic salen complexes which benefited most largely from the positive effect of organic additives for enhancing both reactivity and selectivity. Numerous references in the literature deal with this specific transformation, and to summarize them exhaustively remains outside the scope of this review.[105-110] We have chosen here to mention seminal examples, and a selection of relevant articles, essentially when dealing with mechanistic explanations and presenting the most recent developments.

The enantioselective epoxidation of non-functionalized olefins was discovered independently in 1990 by the groups of Jacobsen[2] and Katsuki.[3]They reported that chiral manganese salen complexes straightforwardly effected epoxidation of alkenes with iodosoarenes as terminal oxidants. Only one year later, Katsuki *et al.* described an important enantioselectivity enhancement when the reaction was performed in the presence of substoichiometric amounts of donor ligands[111,112]such as 2-methylimidazole, pyridine *N*-oxide, and lutidine *N*-oxide.[113] As a first explanation, they mentioned that this positive effect was more important with cationic manganese complexes, in which axial coordination was facilitated. Improvements upon addition of 4-phenyl-pyridine *N*-oxide (4-PPNO) was also shown by the group of Jacobsen. Significant increase in enantioselectivity was observed in the epoxidation of *cis*-ethyl cinnamate, in presence of a (salen)Mn complex, to easily produce a Taxol side chain in a short, practical and highly selective way.[114] By studying the epoxidation of various cinnamate esters, they noticed that the additive did not lead to variations in *cis*/*trans* epoxide ratios, which should occur if the *N*-oxide acted as an axial ligand of the active manganese complex.[115] The active species in asymmetric epoxidation reactions is known to result from the formation of a (salen)Mn^{V}(=O) complex, which may undergo a reversible coupling with (salen)Mn^{III} species to produce an inactive μ-oxo Mn^{IV} dimer. Jacobsen *et al.* thus proposed that the additive serves to increase the concentration into the active species by coordination to the unsaturated Mn^{III} species, hence minimizing formation of the inactive dimer.

Several studies were further devoted to the understanding of the mechanism of this one oxygen atom transfer from the (salen)Mn^{V}(=O) complex to the olefin, involving either radical[116] or metallaoxetane intermediates,[117] what remained much

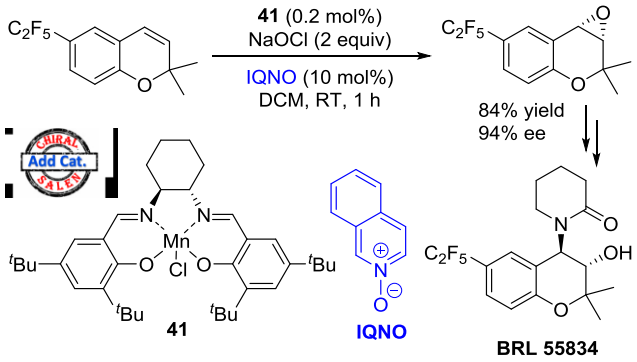
debated.[118,119] Furthermore, in presence of neutral donor ligands, the stereoselectivity of the reaction has been shown to be dependent on the nature of the terminal oxidant.[120]

Interestingly, two independent studies, conducted by industrial groups, explored the contribution of donor ligands addition on the epoxidation catalysis. The Merck group reported the efficiency of 4-(3-phenylpropyl)pyridine *N*-oxide (P_3NO) as a catalytic additive to promote asymmetric epoxidation of indene with sodium hypochlorite and in the presence of the manganese Jacobsen catalyst.[121] The corresponding enantioenriched epoxide was then used as precursor for the preparation of Indinavir, a HIV protease inhibitor (see Scheme 51). Aiming at the discovery of a stable catalytic system to be used in industrial processes, the authors tested a range of pyridine *N*-oxides as additives, with P_3NO allowing both an enhancement of the initial reaction rate and a minimization of catalyst decomposition as demonstrated by HPLC measurements. With the help of IR studies, the authors suggested a fast coordination of the additive to the Mn center, with formation of a (salen)Mn^V-P_3NO oxo species as active catalyst (thus making it an additive). The turnover-limiting step in the catalytic cycle was shown to be the oxidation step of catalyst **41**, occurring in the organic phase, with HOCl as active oxidant. Moreover, it was demonstrated that P_3NO was also a phase-transfer agent, accelerating the oxidation rate by assisting the transport of the oxidant to the organic layer in this biphasic system (which makes it a co-catalyst).[122] Reaction depicted in Scheme 51 could hence be successfully realized on a multi-kilogram scale.



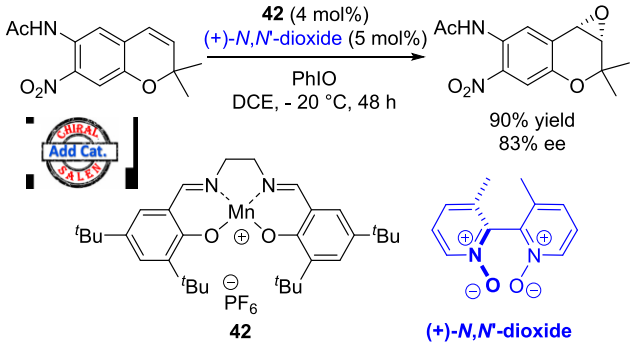
Scheme 51. Asymmetric epoxidation of indene catalyzed by 41 with P_3NO as a catalytic additive

At the same time, researchers from SmithKline Beecham Pharmaceuticals tackled the epoxidation of chromene derivatives towards the preparation of BRL 55834, an airways selective potassium channel activator.[123] They discovered that the use of isoquinoline *N*-oxide (IQNO, see Scheme 52) as a donor ligand allowed to reduce the catalytic charge drastically while maintaining excellent efficiency. In its absence, both reaction rate and enantioselectivity values decreased according to the catalytic loading, reactions could not reach completion as extensive catalyst degradation occurred. The authors argued here again that coordination of the aromatic *N*-oxide to the metallic centre allows extension of the catalyst lifetime. When the reaction was performed in dichloromethane at a 0.2 mol% catalyst loading and in the presence of 10 mol% of IQNO, it led to complete conversion and isolation of the target product in 94% ee. The enantiopure epoxide was isolated in 84% yield after a simple recrystallization from hexane.



Scheme 52. Asymmetric epoxidation of a chromene derivative catalysed by complex 41 with IQNO as an additive

The primordial role of the additive was demonstrated by the group of Katsuki[124,125] which was able to perform enantioselective epoxidations catalyzed with achiral (salen)Mn complex **42** in presence of an enantiopure amine oxide, 3,3'-dimethyl-2,2'-bipyridine *N*,*N*'-dioxide, as a chiral additive. Chirality was hence transferred from the ligand to the manganese complex by inducing a chiral conformation, thus leading to high yield and enantioselectivity for the target epoxide (see Scheme 53).[126]



Scheme 53. Asymmetric epoxidation with achiral (salen)Mn complex 42 catalyzed and an enantiopure additive

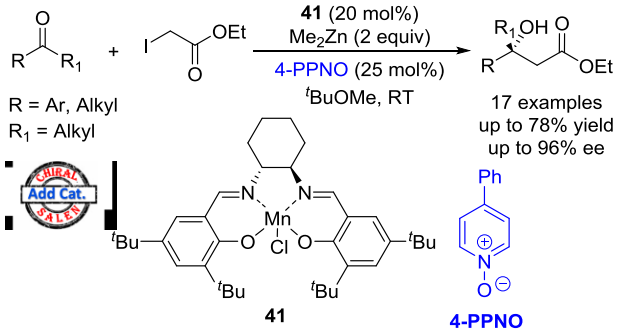
More recent publications, in which a donor ligand is added to the catalyst, can be found in articles dealing with the heterogenization of the whole catalytic system.[127-129] These oxidation systems were supported on various materials after modification of the ligand, both to be easily recovered and reused, and also to increase the catalyst lifetime thanks to the dispersion of the active sites, avoiding their deleterious dimerization. Older examples have dealt with the preparation of organic polystyrene polymers containing an optically active (salen)Mn complex which, showed efficient reactivity when a combination of *m*-chloroperbenzoic acid and *N*-methylmorpholine-*N*-oxide was used.[130] Covalent grafting on inorganic supports was done with, for example, the use of

various mesoporous supports, delivering high enantioselectivity values in epoxidations of non-functionalized olefins in presence of NMO.[131] Other supports such as zirconium phosphates and zirconium phosphonates were successfully used for (salen)Mn complexes immobilization, then used for the epoxidation of α-methylstyrene with aqueous NaOCl and in the presence of pyridine *N*-oxide. In this case, the heterogeneous system exhibited even higher chiral inductions than the homogeneous.[132] Chiral (salen)Mn complexes were not only anchored on pre-existing supports, but were also specifically functionalized towards their polymerization. As salen derivatives are prepared through imine condensation, this procedure was used in polycondensations between various polytopic salicylaldehydes and chiral diamines. For instance, a polymeric (salen)Mn catalyst prepared from a tritopic aldehyde as spacer, with a triazine-piperazine central core, performed well in the epoxidation of non-functionalized olefins, with catalyst loading as low as 1 mol% with NaOCl as oxidant and in the presence of pyridine-*N*-oxide as axial base.[133] Ee values exceeded those achieved by the corresponding homogeneous Jacobsen catalyst.

The last decade has seen the publication of a large number of papers dealing with the immobilization of (salen)Mn complexes into Metal Organic Frameworks (MOFs)[134] or Covalent Organic Frameworks (COFs).[135] Thus crystalline and porous MOFs, possessing enantiopure dicarboxylate struts from (salen)Mn building blocks were prepared, precisely characterized and successfully used to promote asymmetric alkene epoxidation. A rich choice of porous structures was available, allowing to achieve size- and shape-selectivity by exploiting their respective well-defined channels and pores.[136,137] Even more recent developments include the modification of highly stables MOFs, for instance Zr-based UiO-68 MOF, by postsynthetic ligand exchange to introduce chiral salen complexes, bearing the same metallic centers or different ones. Thus, MOFs containing two different salen complexes could be obtained (as Mn/Cr species) with this solvent-assisted linker exchange. This bimetallic Mn/Cr-salen MOF was successfully used to promote a tandem sequential transformation, an epoxidation followed by ring opening of the formed epoxide with anilines, delivering the targeted aminoalcohols in very high yields and in almost enantiopure forms, all that with catalyst loading as low as 0.5 mol %. This heterogeneous catalyst was recovered, after extraction of the products, for 10 runs without any loss in efficacy.[138] In COFs, the salen units are no more connected by coordination bonds but *via* covalent bonds, through multiple imine condensation. When the condensation occurred in the presence of zinc salts, a very stable, crystalline and chiral porous network was obtained. Due to the lability of Zn-O/N bonds, metal exchange occurred readily with various metallic salts, leading to monometallic or bimetallic heterogeneous COFs.[139] Epoxidation of chromene derivatives happened successfully and the mixed species (Cr/Mn-COFs) also led to almost enantiopure aminoalcohols by sequential epoxidation and aminolysis. These very recent, non-exhaustive, examples demonstrate the great efficiency of MOFs and COFS to heterogenize Mn-salen complexes, leading to highly stable and recyclable asymmetric catalysts. Of utmost importance is the use of these materials, without any addition of axial base, which was demonstrated to be necessary to reach high efficiency when the above described homogeneous catalysts were concerned. Thus, the preparation of these crystalline networks, with a perfect control of the location of the active sites, leading to their compartmentalization and preventing bimetallic inhibition, allowed very efficient enantioselective epoxidation reactions, avoiding furthermore the use of supplementary additives since the MOF architecture itself insures the stabilization of the active species.

3.2.2. Reformatsky Reactions

The Reformatsky reaction[140-142] is still widely used in synthesis although it was discovered more than one century ago, it consists of the zinc-induced formation of β-hydroxyalkanoates from α-halocarbonyl compounds and carbonyls, mostly aldehydes. During the last decades, a few reports dealt with the very challenging asymmetric aldol reaction with ketones, forming quaternary stereocenters.[143,144]
For interest in this review is the methodology reported by Cozzi *et al.*[145] where the first effective catalytic enantioselective Reformatsky reaction was developed between ketones and an iodoester, based on the use of inexpensive and readily available (salen)Mn(III) **41** as catalyst, together with 4-phenylpyridine *N*-oxide as an additional ligand (Scheme 54). In this reaction, formation of a reactive zinc enolate occur under mild conditions, which is then able to react with a rather unreactive ketone in a stereoselective manner under activation by the chiral Lewis acid. Screening of the reaction conditions revealed that in presence of 4-phenylpyridine *N*-oxide enantioselectivity of this Reformatsky reaction was substantially improved, probably by coordination the manganese complex (it is thus an additive). This protocol showed a very broad scope, aromatic, aliphatic, heterocyclic, and α,β-unsaturated ketones could all be straightfully converted to give the desired products in up to 78% yields and 96% ee (Scheme 54).



Scheme 54. Catalytic enantioselective Reformatsky reactions promoted by 41 and 4-phenylpyridine *N*-oxide

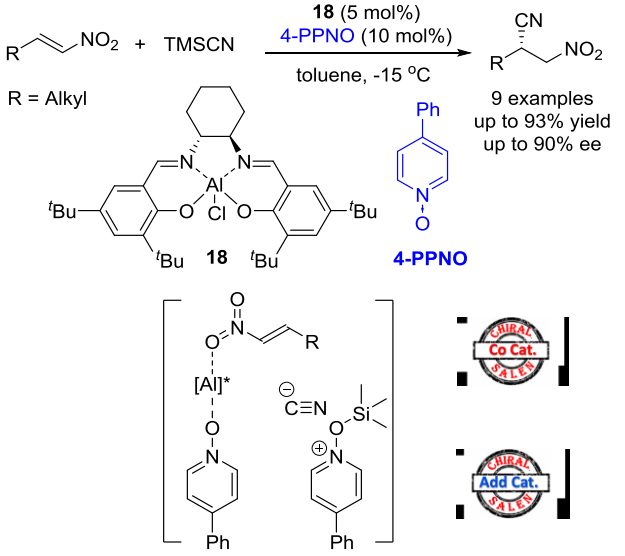
Optimization efforts made by the authors did not include the additive variation; so the role of 4-PPNO can only be speculated, probably as previously seen, as an apical ligand for the manganese, leading to very active Lewis acidic species.

3.2.3. Hydrocyanation of Nitroalkenes

As β-amino acids,[146] 1,3-amino alcohols,[147] and 1,3-diamines play a key role in the synthesis of chiral structures, they are widely used in the pharmaceutical industry, and are among the most versatile synthons.[148] Enantioselective hydrocyanation of nitroalkenes (Michael acceptors) is a facile entry to this class of bifunctional compounds. These nitroalkenes are however

very prone to basic-mediated polymerization, a reactivity pitfall explaining that only four examples of asymmetric cyanide addition to nitroolefins are reported in the literature, be it organocatalyzed[149,150] or catalyzed with a salen complex alone.[151]

In 2014, Khan and co-workers[152] developed an asymmetric hydrocyanation of nitroolefins catalyzed by (salen) aluminum(III) complex **18** in presence of 4-phenylpyridine *N*-oxide (4-PPNO) as an additive, providing enantioenriched β-nitronitriles in good yields and with moderate-to-high enantioselectivity (up to 90% ee and 93% yield) in toluene at -15°C (Scheme 55). In addition, the authors performed spectroscopic experiments to gain insights into the reaction mechanism. Showing a synergistic effect of complex **18** together with 4-PPNO in this asymmetric catalytic system, where the *N*-oxide plays a dual role; as it acts as an axial ligand but also activates the cyanide source (TMSCN) which makes it both an additive and a co-catalyst.



Scheme 55. Asymmetric hydrocyanation of nitroolefins catalyzed by complex 18 and 4-PPNO

Table 18. Effect of additives on the catalytic stereoselective hydrocyanation of nitroolefins by complex **18**.

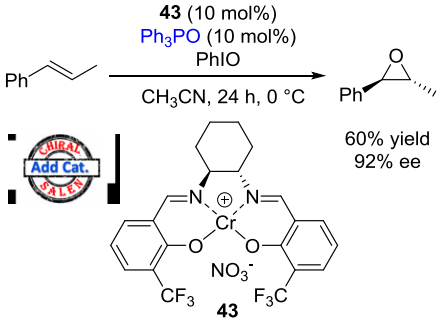
Additive (10 mol%)	Yield (%)	ee %	pK_{BHX}
Ph_3P	0	0	(0.68)
iPrOH	0	0	1.06
PyridineNO	85	71	2.72
4-PPNO	93	76	2.85
Ph_3PO	51	73	3.16
NMO	40	45	(5.05)

Conditions: AlCl(salen) 5 mol%, toluene, RT, values in brackets are estimated from a very similar compound.

Interestingly, increasing the 4-PPNO loading to 15 mol% or decreasing it to 5 mol% induced an erosion of the ee, showing that a 10 mol% is an optimum for the mechanism. This is reflected in the basicity balance observed in the variation of the additive, too weak (TPP) or too basic (NMO) catalysts being detrimental for the transformation, (here compared with the hydrogen-bond ability value pK_{BHX}) (Table 18).

3.3. Metallo-Salen and Phosphine Oxides

The group of Gilheany[153] investigated on the use of chromium complexes **43** instead of the classical manganese ones in epoxidation reactions (Scheme 56). Helped by the stability of chromium species in solution, they conducted a thorough mechanistic study with such salen complexes, which notably perform best with (*E*) alkenes when Katzuki-Jacobsen manganese-based catalysts are superior with (*Z*) alkenes. Firstly, an important additive effect was shown, influencing the ee value, by modulating the twist of the complex. This twisting was already demonstrated to be higher in chromium catalysts than in their manganese counterparts.[154]



Scheme 56. (*E*)-alkene epoxydation with cationic complex 43 and TPPO

Table 19. Effect of additives on the enantioselective epoxidation promoted by salen complex **43**.

Additive	ee (%)	pK_{BHX}
None	90	-
DMF	67	2.10
DMSO	86	2.54
Pyridine NO	85	2.72
Ph_3PO	92	3.16

Conditions: 39 (1 equiv.), PhIO (1-2 equiv.), CH_3CN, additive (1 equiv.), 0 °C, 1.5h.

This twisting effect, improving the enantioselectivity, seems to be directly correlated to the Lewis basicity, as measured by the hydrogen-bond acceptor ability pK_{BHX} (Table 19). Moreover, the ligand effect depends on the metal center acidity as given by the a^{TM} value (coordination ability toward Transition Metals), a parameter linked to counterion nature. Hence, the less coordinating counteranions[155,156] are leading to the most important ee improvements upon TPPO addition (Table 20).

Table 20. Effect of complex **43** counterion on the catalytic enantioselective epoxidation

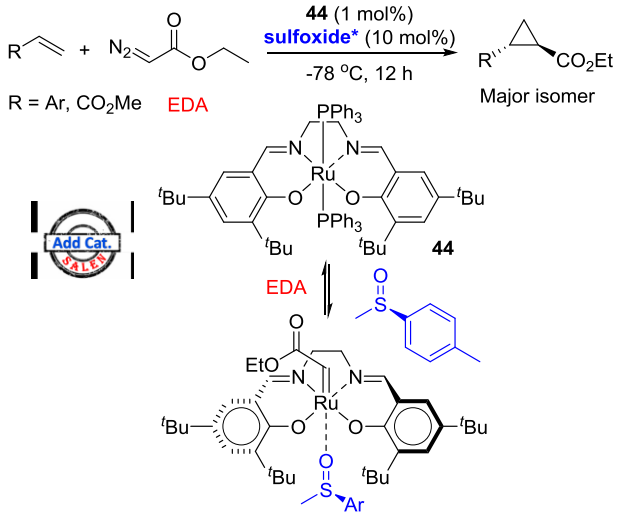
X^-	ee (%) without TPPO	ee (%) TPPO 10 mol%	Δee	a^{TM}
NO_3^-	90	92	+2	0.0
TfO^-	72	88	+16	-0.4
BF_4^-	74	87	+13	-1.1
PF_6^-	86	88	+2	-1.6
$BARF^-$	38	88	+50	-3.4

Conditions: PhIO 2 equiv., (salen)CrX 10 mol%, TPPO 10 mol%, ACN, 0°C.

The discrepancies in the Δee/a^{TM} correlation are probably rising from additive/anion competing equilibriums.

3.4. Metallo-Salen and Sulfoxides

(salen)Ru^{II} was shown to be highly effective for the asymmetric cyclopropanation of olefins with ethyl diazoacetate (EDA) as carbene precursor, though only on specific alkenes.[157] In 2002, Nguyen and co-workers[158] described the first example of an asymmetric cyclopropanation mediated by the combination of achiral (salen)Ru^{II} catalyst **44** and a catalytic amount of enantiopure sulfoxide additives which were chosen as chiral ligands for the metal center. In this system, the sulfoxide Lewis base controls the chirality of the active species by forcing the achiral salen complex into an asymmetric conformation. Transfer of the chiral information to the carbene occurs at the opposite face of the catalyst, which was called 'chiral environment amplification' by Balsells and Walsh.[159] Screening of the reaction conditions including different achiral (salen)Ru^{II} catalysts and chiral sulfoxides revealed that the best *ee* values for the *cis* and *trans* products were obtained with 10 mol% of (*R*)-methyl *p*-tolyl sulfoxide as the chiral Lewis base, at -87 °C and without solvent, leading to 93% ee and 87% ee respectively (Scheme 57).

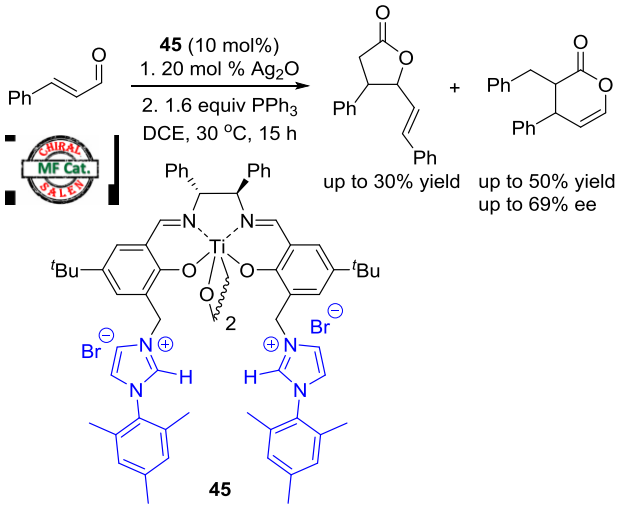


Scheme 57. Olefins cyclopropanation with achiral Ru^{II} complex 44 using chiral sulfoxides

The authors observed a fast reaction between the precatalyst and EDA with departure of the two phosphine ligands. They could prove that the resulting complex is rather slow to realize the cyclopropanation, while, upon complexation of the latter with the sulfoxide ligand (with an equilibrium constant K_{eq} = 129 ±6 M^{-1}) the resulting octahedral complex is highly effective in transferring the carbene to the alkene.

3.5. Metallo-Salen with Carbenes

By turning away from NHCs used as ligands for transition metals, Peters and co-workers[160] developed a bifunctional catalytic system to promote cooperative asymmetric catalysis, taking advantage within the same structure of the Lewis acidic character of a salen complex and the nucleophilicity of a NHC in a Stetter-like reaction (Scheme 58). They prepared salen derivatives with attached, and diversely functionalized azolium moieties. They then isolated the corresponding Ti-salen complexes, as μ-oxo-bridged dimeric species; then Ag-NHC complexes prepared for instance from **45** and silver oxide were formed as masked nucleophilic carbenes, which could be unmasked upon treatment with PPh_3. These precatalysts **45** catalyzed the Setter-type formation of enol-δ-lactone as main product rather than the expectable ɤ-lactone. This actually constitutes a new reactivity in the dimerization of enals, it goes in up to 42% GC yield and up to 69% ee for the *cis* isomer (Scheme 58); nevertheless, the product instability to hydrolysis prevented its isolation. Control experiments highlighted the important role of PPh_3 to trigger the reactive system by liberating the NHC moieties. The best yield and enantioselectivity values were obtained with precatalyst **45** bearing *N*-mesityl-substituted imidazolium moieties.

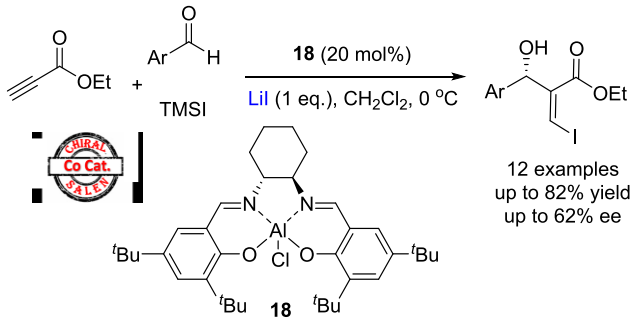


Scheme 58. Synthesis of enol-δ-lactones by cooperative NHC/(salen)Ti/Ag catalysis with precatalyst 45

NHC formed without silver did not give the same outcome, indicating that Ag^{I} ion plays another role besides that of masking the carbene. Therefore, the authors suggest a mechanistic scenario where the liberated NHC reacts with a first equivalent of aldehyde to form the corresponding Breslow intermediate, which then engages in a Michael addition onto the second unsaturated aldehyde rendered highly electrophilic by a double activation, both by the titanium center at the oxygen of the carbonyl, and the by the silver ion at the alkene pi-system.

3.6. Metallo-Salen with Halides

We are here touching at the border for this review, since mineral halides are not strictly belonging to the field of organocatalysis, the interest of the work justify this addition here. Li and co-workers[161] reported the enantioselective synthesis of β-halo Morita-Baylis-Hillman ester adducts, using (*R*,*R*)-salen with diethylaluminum iodide as the halogen source in 2004, however, a stoichiometric amount (1.3 equiv) of (*R*,*R*)-salen was necessary. A year later, 2005, the same group[162] then reported the first truly catalytic aldol reaction of *in situ* generated β-iodoallenoates with aldehydes by using (Salen)AlCl **18** as chiral catalyst, trimethylsilyl iodide being the final iodide source (Scheme 59).

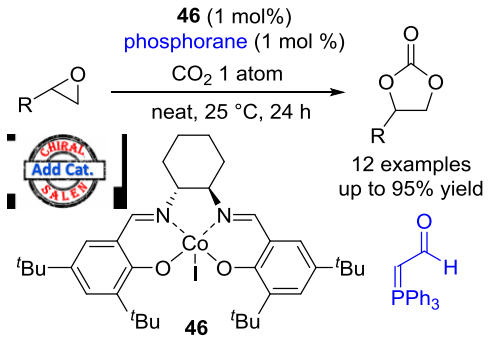


Scheme 59. Asymmetric catalytic synthesis of β-halo MBH ester adducts catalysed by complex 18

Addition of lithium iodide was found to be beneficial for both the reaction rate and for the chemical yield. Screening of the reaction conditions revealed that 20 mol% of chiral (*R*,*R*)-(salen)AlCl and 1 equivalent of LiI were the best combination for this enantioselective catalytic reaction in dichloromethane at 0°C. Free iodide anion is best suited to attack the triple bond and form a transient iodo-allenoate, which subsequently attacks the aldehyde under electrophilic activation by the aluminum catalyst; final silylating quench of the aldolate anion by TMSI liberates an iodine ion, which is thus regenerated. This new catalytic system showed a good substrate scope in which both aromatic and aliphatic aldehydes could be employed, providing the desired products in moderate enantioselectivities but in useful yields (See Scheme 59).

3.7 Metallo-Salen with Phosphoranes

In 2017, the group of Zhou[163] made an unconventional use of Wittig reagents in the preparation of cyclic carbonates from epoxides with incorporation of carbon dioxide. The most efficient system relies on (salen)Co-I **46** and (triphenylphosphoranylidene)acetaldehyde (Scheme 60).



Scheme 60. Carbonate formation from CO_2 and epoxides with catalyst 46 and a phosphorane additive

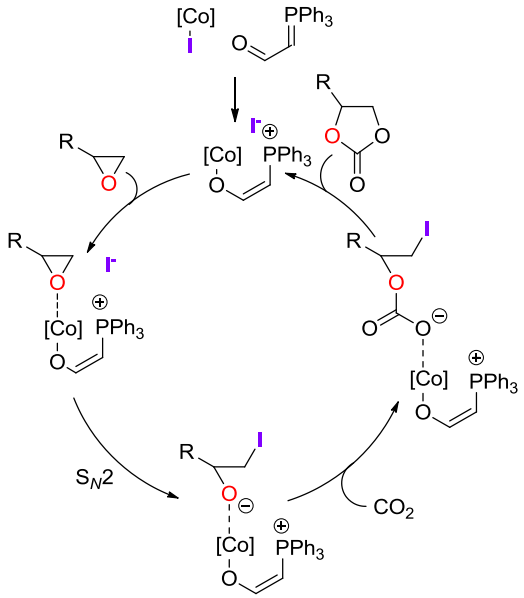
In this reaction, the phosphorane serves as a very strong coordinating ligand of the transition metal, while the displaced halide anion also enters the catalytic cycle to ring-open the epoxide starting material. Hence, in optimization studies, it was observed that the overall efficiency depended on the nucleophilic strength of the phosphorane oxygen atom (Table 21).

Table 21. Effect of the phosphorane additives in the synthesis of carbonates from epoxides and CO_2.

Ph3P, O, R Phosphorane	Conv. (%)	σ_p[164]
none	0	-
R = CO_2Et	trace	0.45
R = Ph	trace	0.43
R = Me	9	0.50
R = H	27	0.42

Conditions: (salen)AlCl 2.5 mol%, phosphorane 2.5 mol%.

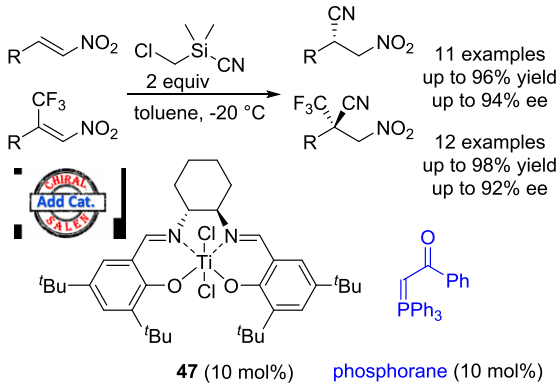
The crucial role of the halide counter ion was also unveiled while comparing (salen)CoX differential efficiencies in the process, the conversion increasing from 50% to 80% and then to 100% in the Cl, Br, I series. Under optimized conditions, the scope was examined with respect to the epoxide substrate, and all targeted carbonates were obtained in high to excellent yields. Noteworthy, the synthesis of optically active carbonates from enantiopure epoxides was achieved with excellent retention of enantiopurity. Further spectroscopic and MS experiments allowed drawing a plausible mechanism picture, Scheme 61.



Scheme 61. Proposed mechanism for the catalytic synthesis of carbonates with 46 and a phosphorane additive

The zwitterion, mesomeric form of the phosphorane, can displace the iodide at the cobalt center; the resulting complex can activate an epoxide molecule, which is then attacked by the liberated iodide anion to form a liganded alcoholate. Carbon dioxide can insert into the cobalt-oxygen bond to proceed to a liganded carboxylate which finally cyclizes to give the carbonate while releasing the halide anion.

The same synergistic combination of a salen complex with a phosphorane was then exploited by the same group[165] to perform highly enantioselective hydrocyanations of nitroalkenes.



Scheme 62. hydrocyanation of nitroalkenes with 47 and phosphorane additive

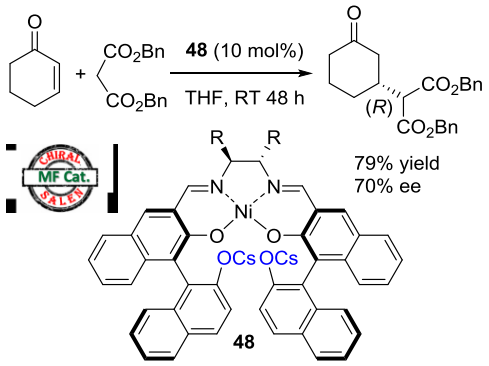
For this transformation, optimizations led to identify the (salen)$TiCl_2$ **47** as best catalyst, in combination with the phenyl-substituted phosphorane additive as ligand, conducting to highly effective conversions and selectivities (Scheme 62).

4. Metallo-Salen and Brønsted Bases

In certain instances, basic organocatalysts does not act as a coordinating ligands or nucleophiles (Lewis basicity) but as deprotonating agents, which action then depends on their Brønsted basicity.

4.1. Addition of Malonates to Enones

The enantioselective addition of benzyl malonate to enones was investigated by Kozlowski and co-workers.[166] To realize this, well-defined bifunctional catalysts of type **48** were synthesized, incorporating a salen metal complex appended with two phenolates from chiral BINOL moieties (Scheme 63). Among the various metal combinations applied in Michael additions, the (salen)Ni-BINOL-Cs_2 catalyst **48** (R = Ph) gave the best results.



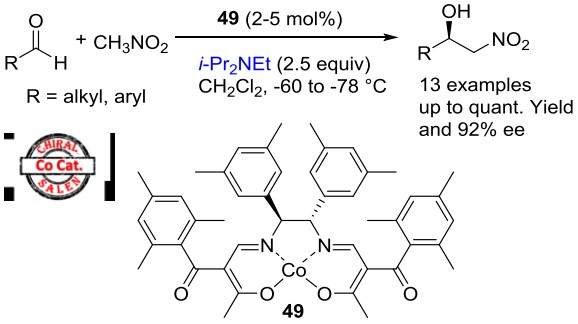
Scheme 63. Bifunctional Ni salen naphthoxide catalyst in the enantioselective Michael addition reaction

The optimal "matched" combination of chiralities on the two active sites (salen and BINOL) was identified, allowing to reach 90% ee at -40 °C. BINOL phenolate alone was able to promote the reaction, although without any selectivity, while the (salen)Ni^{II} alone was totally inactive. Hence, it was postulated that the phenolate is deprotonating the malonate substrate, while the nickel center coordinates the enone and organizes the transition-state in which the enolate attack the former in a 1,4-fashion. With this result, they demonstrated that it is possible to construct a bifunctional chiral framework in which the Lewis acid can accommodate a basic moiety to access high enantioselectivity level with this formal frustrated Lewis/Brønsted pair.

Kozlowski and co-workers[167] then reported a second paper in which they extended their initial study. Other well-characterized salen metal complexes incorporating two chiral BINOL moieties were synthesized and used as Lewis acid/Brønsted base catalysts for the Michael addition of several malonates to different enones with selectivity up to 90% ee. Kinetic data and mechanistic experiments indicated that both moieties were indeed essential to achieve asymmetric catalysis and support a bifunctional activation in which the apical nickel site activates the enone and the naphthoxide base activates the malonate.

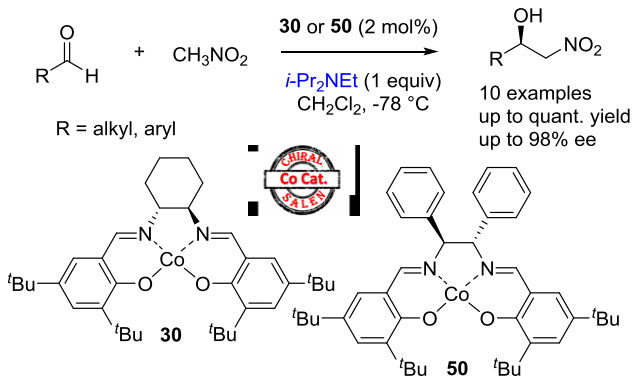
4.2. Henry Reactions

Yamada and co-workers reported for the first time an asymmetric Henry reaction which was feasible by using ketoiminatocobalt complexes **49** in the presence of tertiary amines (Scheme 64). Chiral nitro-alcohols were obtained in good-to-high yields with high enantioselectivity (up to 92% ee).[168] Various amine bases were screened (e.g. DBU, primary, secondary amines and tertiary amine). Among them, it was found that diisopropylethylamine was the most suitable one to generate the nitronate anion, which serves as nucleophile in the reaction; the alcoholate produced after the asymmetric aldolisation is then protonated by the ammonium salt of DIPEA. This bicatalytic could be applied to a large variety of aldehydes.



Scheme 64. Henry reaction catalysed by complex 49

Yamada and co-worker rapidly extended this catalytic approach combining cobalt salen complexes with tertiary amine to efficiently produce β-hydroxynitroalkanes with high enantioselections (Scheme 65).[169]



Scheme 65. Catalytic enantioselective Henry reaction with complexes 30 or 50 and DIPEA

Examination of several salen-cobalt complexes revealed that the commercially available Jacobsen (salen)Co^{II} complex **30** and its derivative **50**, bridged by 1,2-diphenylethane-1,2-diamine worked best in this reaction. The role of the base was not discussed, neither the choice of this tertiary amine.

Three years later, the group of Skarzewski[170] conducted a similar investigation. Among all tested metals (e.g. Al, Cu, Ni, Fe, V, Mn, Zn, and Ti) they found that only Co and Cr salen complexes showed relevant enantioselectivities, (salen)CrCl complex being the optimal catalyst in combination with DIPEA (13 examples, up to 98% yield, up to 76% ee). An array of different bases was investigated, showing that less chelating amines were most efficient in the transformation (Table 22).

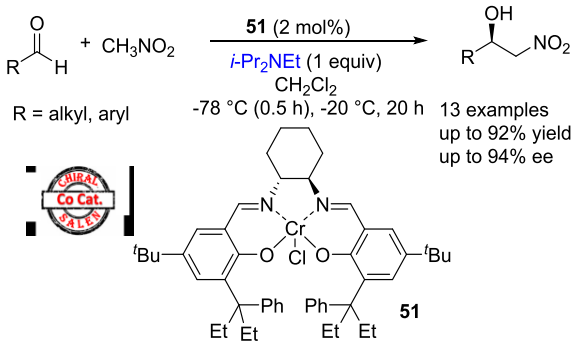
Table 22. Influence of bases as additives on the catalytic enantioselective Henry reaction.

Base	Yield (%)	ee (%)	p*K*a	pK_{BHX}
DBU	29	0	24.34	3.85
NEt_3	49	40	18.82	1.98
DMAP	58	0	17.95	2.80
DABCO	83	30	(9.07)	2.33
Quinine	97	52	(9.67)	(2.7)
DIPEA	98	46	(10)	1.05

Conditions: 2 mol % of SalenCrCl, 1 equiv. of base, CH_2Cl_2, -78 °C. pK_a given in ACN, except for DABCO and quinine in DMSO, and in THF for DIPEA.

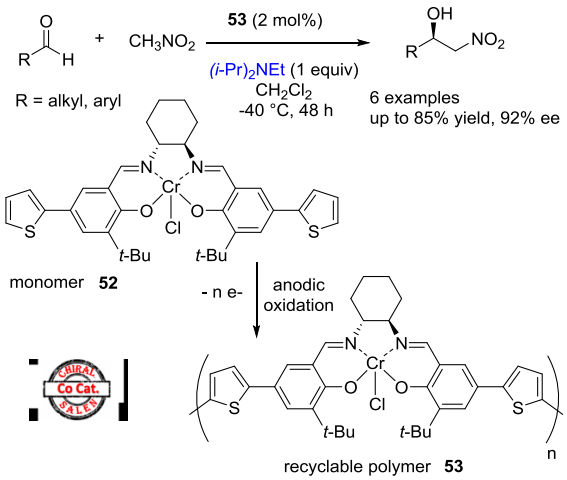
It was concluded that strongly chelating additives (as reflected in high pK_{BHX} values) were inactivating the metal center, while encumbered amines were limiting this detrimental interaction while being able to deprotonate nitromethane and reprotonate the Henry alcoholate adduct.

In collaboration with Jurczak, the same group[171] later extended their studies on asymmetric Henry reactions, then with broader optimizations, leading to the use of chromium salen complexes, modified by varying the steric congestion around the active center, namely by replacing *t*Bu moieties with more bulky substituents. This strategy was fruitful, gaining 20-30% in yields and 20-30% in enantioselectivity values when the catalyst possesses 2,2' positions bearing C(Et_2)Ph substituents (see **51** in Scheme 66), again with 1 equiv. of DIPEA as ancillary base. In this case, the base effect was not discussed and following the previous reports, a stoichiometric amount of DIPEA was used combined with only 2 mol% of chromium complex to produce the nitro alcohols in up to 92% yield and 94% ee.



Scheme 66. Henry reaction with catalyst 51 with very congested 2,2' positions.

About the same time, chiral thiophene-salen chromium complexes were investigated in the enantioselective Henry reaction, both in their monomeric and polymeric forms by Schulz and coworkers.[172] They described the synthesis of new chiral chromium Schiff base complexes of type **52**, substituted by thiophene units at the 5,5′-positions of the phenolic rings and their efficient use as catalysts for the enantioselective Henry reaction between nitromethane and various aldehydes (Scheme 67).

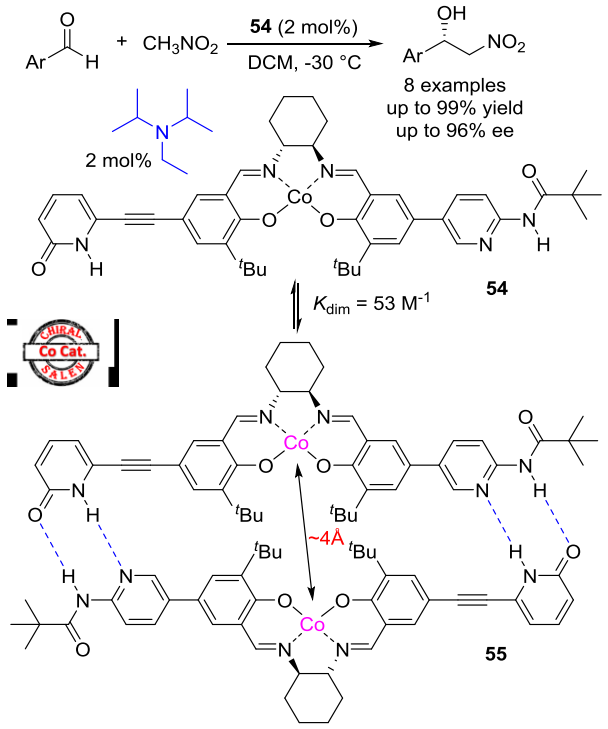


Scheme 67. Chiral thiophene (salen)Cr catalysts 52 and 53 developed by Schulz and co-workers

The desired nitroaldols were obtained with enantiomeric excesses up to 92% ee. The polymerization by electrochemical oxidation of the modified salen complex led to an insoluble material **53** that was also successfully used as heterogeneous catalyst for the transformation of 2-methoxybenzaldehyde with enantiomeric excesses up to 77%. The polymerized catalyst **53** could be recovered and reused in an original multisubstrate procedure. Effect of the base was also evaluated and the presence of 1 equiv of DIPEA is indeed required. A similar result was obtained when triethylamine was used as the base, whereas K_3PO_4 led to a much less efficient catalytic system (19% yield and 9% ee). Notably, the authors observed a substantial improvement in ee's (34% to 69%) when the

amine loading was decreased from 1 equiv. to 5 mol%, although at the expense of an important conversion dropping.

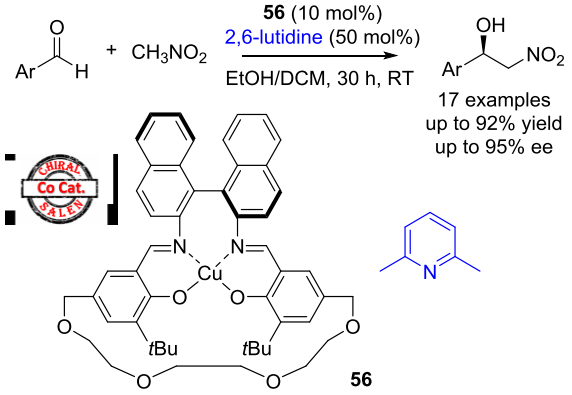
Then in 2008, Hong and coll.[173] exploited the catalytic system used by Yamada in a supramolecular setting. The initial (salen)Co^{II} promoter was modified to give catalyst **54**, which allows a head-to-tail dimerisation through a quadruple hydrogen-bond interaction (see **55** in Scheme 68). Hence, the catalyst design features two 2-pyridone/aminopyridine hydrogen bonding pairs to create self-assembled dimers of type **55** in solution. Dimerisation was confirmed in the solid state by the X-ray structure and ^1H NMR experiments in solution.



Scheme 68. Self-assembled (Salen)Co 55, catalyzing asymmetric Henry reaction in presence of DIPEA as co-catalyst

The dimeric species **55** proved 48 faster than the monomeric catalyst **54** in Henry reactions, again in presence of DIPEA as base, which loading could be decreased from 1 equiv to 2 mol%; moreover, the dimer exhibited improved yields and enantioselectivities. This remarkable result can originate in the ability of the dimer to accommodate both partners, and thus simultaneously activate the aldehyde electrophile and coordinate the nitronate anion in its inner space. The authors could obtain X-ray diffraction analysis of the parent (salen)nickel^{II} complex, which shows a metal-metal distance of about 4Å. The reaction scope was evaluated by using the bimetallic (salen)Co^{II} complex **55** and varying aromatic aldehydes. The resulting nitroaldols were obtained in good to excellent yields and with high enantiomeric excesses (81-96% ee).

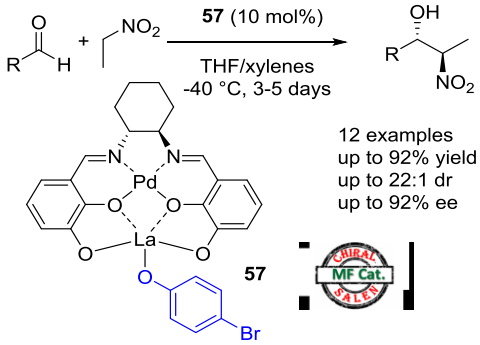
The group of Kureshy explored in 2012 the capabilities of copper-based salen complexes **56** to perform the Henry condensation (Scheme 69).[174]



Scheme 69. Asymmetric Henry reaction catalysed by 56 and 2,6-lutidine

To that end, they employed a tethered ligand with a trisPEG link, and generated *in situ* the parent copper complex **56**. Thorough catalyst optimizations identified Cu^{II} chloride as the best metal source, and the BINAM scaffold as the most selective. Conditions were screened and an unusual DCM/ethanol mixture proved optimal, using 2,6-lutidine as the most effective ancillary base. The authors hypothesized a transition-state with an octahedral copper-center accommodating both the aldehyde substrate and the nitronate anion in a vicinal disposition, helped in that by the bending effect of the PEG linker. Interestingly, this macrocyclic catalyst **56** could be recycled 8 times without significant loss in performance.

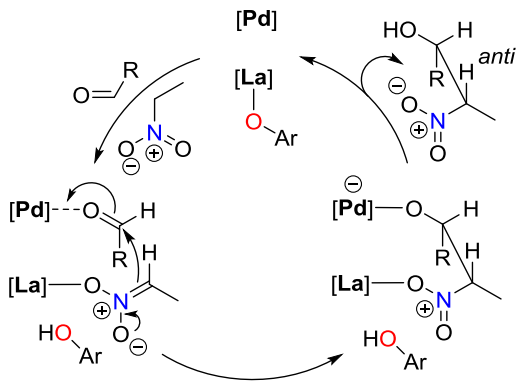
We can finish this part with an elegant protocol involving a trisfunctional catalyst **57** developed by the group of Shibasaki en 2008.[175] A series of metallic catalysts was investigated in Henry reactions with aldehydes and nitroethane, the complexes were made by *in situ* mixing of a catechol-salen ligand with various transition metals and rare earth cations, as well as different additional phenols (Scheme 70).



Scheme 70. Asymmetric Henry reaction catalyzed catechol-salen Pd/La complex and 4-bromophenol

The combination of palladium^{II} and lanthanum^{III} proved the most active. The role of the phenolate, employed as apical ligand of the rare earth, was crucial, identifying 4-bromophenol as the most suitable. The resulting complex **57** proved efficient in term of yield, enantioselectivity as well as diastereoselectivity for the *anti* Henry product (12 examples, up to 92%, 92% ee and 22:1 d.r.).
The speculated mechanism involves the double and selective chelation of both reagents, the aldehyde by the palladium center and nitroethane by the lanthanum center (Scheme 71).

The phenolate ligand is then able to deprotonate the nitro substrate to conduct to a liganded nitronate after liberation of bromophenol. Intramolecular nucleophilic attack creates the C-C bond and final reprotonation of the resulting complexed alcoholate by the free phenol leads to the *anti* Henry adduct and regenerates the trisfunctional catalyst.

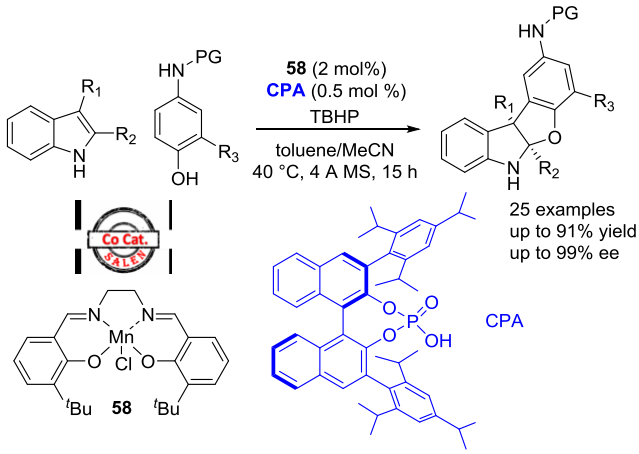


Scheme 71. Mechanism of Henry reaction with trisfunctional catalyst 57

Hence, in this intricate catalyst, both metals are selective Lewis acids, while the phenolate acts as a Brønsted base.

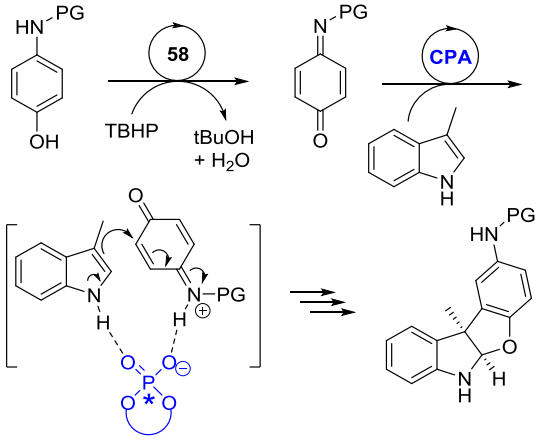
5. Metallo-salen and Brønsted Acids

This particular catalytic setting is interesting because it displays a rare example of relay catalysis engaging a salen-based Lewis acid and then a chiral Brønsted acid in a truly sequential manner. Hence, in 2019, the group of Wu and Zhong[176] reported an asymmetric coupling of aminophenols and indoles through relay catalysis combining an oxidative step promoted by an achiral (salen)$Mn^{III}Cl$ complex **58**, and a [3+2] formal cycloaddition triggered by a chiral phosphoric acid (CPA) (Scheme 72).



Scheme 72. Enantioselective indole/aminophenol oxidative [3+2] cycloaddition catalysed by achiral 58 and CPA

In a one-pot protocol, the protected aminophenol is oxidized into an aminoquinone by TBHP under the auspices of the (salen)$Mn^{III}Cl$ catalyst. This aminoquinone is then protonated by the CPA catalyst to form a quinone-iminium that is attacked by the indole in an enantioselective manner thanks to the chiral environment. Final aminoquinone-indolinium ring closure leads to the product in excellent yield and enantiomeric excess (25 examples, see Scheme 72).



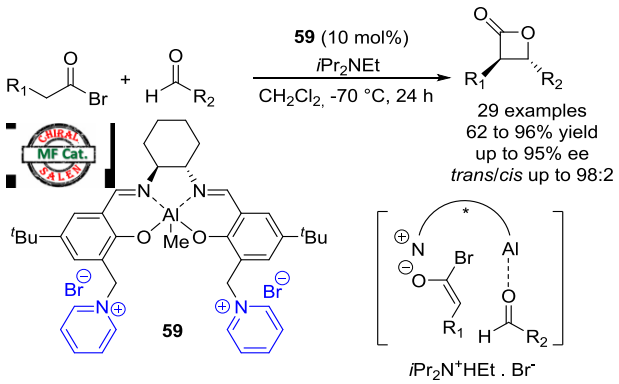
Scheme 73. Mechanism proposal for the indole/aminophenol oxidative [3+2] cycloaddition with 58 and CPA

Both catalytic cycles are independent, and no deleterious interaction seems to occur between the active intermediates. Enantioselection is solely dictated by the CPA, optimizations having determined the most encumbered BINOL-TRIPS derivative as the most suitable to properly organize the chiral transition state.

6. Metallo-Salen and Onium Salts

As already described in part II.2., the dual activation exerted by (salen)Al^{III} complexes containing an attached ammonium moiety has been successfully applied to the enantioselective construction of cyanohydrin carbonate derivatives. Thanks to the ion pairing ability of these onium salts, the quaternarized heteroatom serves as an anchor for various nucleophilic anions that are kept in close proximity by coulombian interactions.

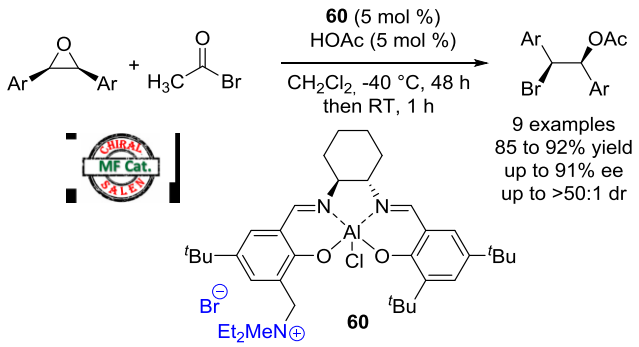
This strategy was also employed for asymmetric synthesis of *trans*-configured β-lactones by the group of Peters.[177,178] A bifunctional catalyst **59** was devised to combine a Lewis acid with an ion-pairing moiety in order to trigger the [2+2] cyclocondensation between acyl halides and aliphatic or aromatic aldehydes.



Scheme 74. Formation of *trans*-β-lactones promoted by a cooperative ion pair/Lewis acid catalyst 59 (intermediate simplified for clarity)

After deprotonation of the acyl halide with DIPEA, the resulting bromo-enolate, in equilibrium with the ketene, forms a contact ion pair with the appended pyridinium on the ligand. It is thus perfectly placed to react with an aldehyde coordinated by the aluminum Lewis acid, and then evolves to the *trans*-configured β-lactone product after ring-closure (see Scheme 74). The authors screened a variety of catalysts possessing various positively charged substituents at the phenolic 6-position and showed that the pyridinium system was the most selective, compared to ammonium or imidazolium groups (probably because of its planarity combined with a larger positive charge delocalization). With this system in hands, they evaluated the cyclocondensation of various aliphatic and aromatic aldehydes, the corresponding β-lactones were isolated in high yield (up to 96%) and excellent selectivity (up to 95% ee and *trans*/*cis* ratio of 98:2), provided the reaction was performed at -70 °C, in the presence of 10 mol% of the dual catalyst (Scheme 74).

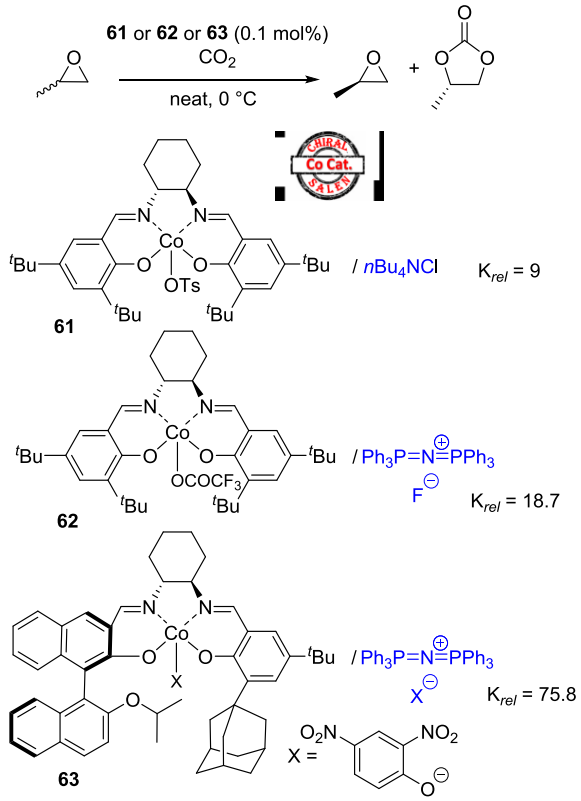
Having proven the key role of the anchored pyridinium groups to control the high *trans*- and enantioselectivity values, Peters' group further screened cationic heterocycles to understand how it influences the selectivity of this reaction.[179] They discovered that picolinium groups slightly enhanced both dr and ee values; NBO calculations nevertheless ruled out a significant impact of the effective charges within the heterocycle to explain this result.
The same authors[180] were also able to exploit this dual activation mode to carry out the desymmetrization of *meso* epoxides, by promoting their opening with bromide ions in presence of acetyl bromide, a reactivity rarely described in prior literature. In this case again, the aluminum Lewis acidic center allows a strong activation of the *meso*-epoxide, while the enantioselective nucleophilic attack of the bromide anion is guided by the onium moiety attached to the salen ligand (see **60** in Scheme 75). The generated aluminum alkoxide is then protonated by the catalytic acetic acid, and the decoordinated alcohol is finally esterified by acetyl bromide, regenerating both acetic acid and bromide anion.



Scheme 75. Desymmetrization of *meso*-epoxides with a bifunctional (salen)Al / ammonium salt catalyst

In this case, although active, the pyridinium substituted complexes **59** proved less selective than the quaternary alkyl ammonium ones, and the unsymmetrical catalyst **60** being the most efficient, without a clear rational behind that result. The reaction proceeded optimally with aromatic epoxides, particularly for those bearing electron withdrawing groups, whereas lower enantioselectivity values were recorded during the transformation of aliphatic ones. The benefit of a bifunctional catalyst was proven by a reactivity test of the conventional Jacobsen catalyst supplemented with nBu$_4$NBr. Even if this additive improved the yield and diastereoselectivity values delivered by the salen alone, confirming a cooperative catalysis, results remained far lower than those delivered by the bifunctional catalyst **60** carrying the ammonium function in close proximity with the metal center.

Preparation of chiral carbonates following this procedure remains challenging, because exploitable conversions are generally obtained only at high temperatures and under high CO_2 pressures, which remains experimentally unfavorable; furthermore competitive polycarbonate formation still as to be minimized, leaving room for improvement is this particular field. For instance, Lu *et al.*[181] in 2004, have successfully performed the catalytic kinetic resolution of racemic epoxides through their coupling with CO_2, to form optically active propylene carbonate, by using enantiopure (salen)Co^{III} complexes **61**, **62** and **63** in the presence of a quaternary ammonium salts.



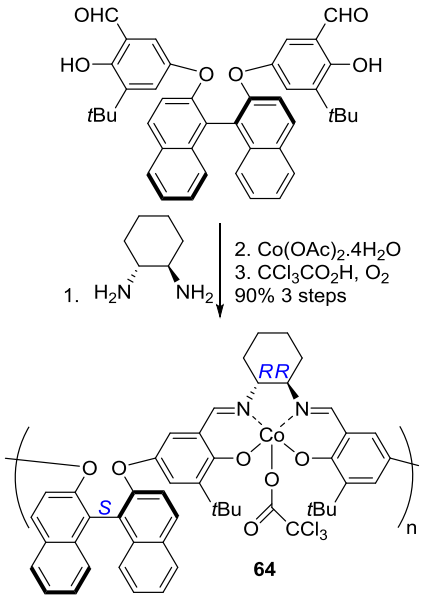
Scheme 76. Synthesis of chiral carbonates with (salen)Co complexes and ammonium additives

They proved that both axial ligand carried by the cobalt center, and counterion of the ammonium salt influenced the enantioselectivity of the reaction; the temperature and complex/ammonium ratio altered the activity of the catalytic system (Scheme 76). The best results were observed in presence of tetrabutylammonium chloride, the (salen)Co^{III} complex bearing a tosylate group as axial ligand **61**, but even under

these optimized conditions, the selectivity constant never exceeded the value of 9.

Berkessel *et al.*[182] discovered in 2006 that the use of catalysts **62** with bis-(triphenylphosphoranylidene) ammonium halides (PPNX) as co-catalyst delivered better selectivities (70% ee with the chloride, and 75% ee with the fluoride) optimizations with PPNF led to 83% ee at -40 °C thus reaching a selectivity factor of 18.7 for the same transformation. Importantly, the authors noted the initial formation of large quantities of poly-carbonate, which slowly converts into the desired monocyclic carbonate.

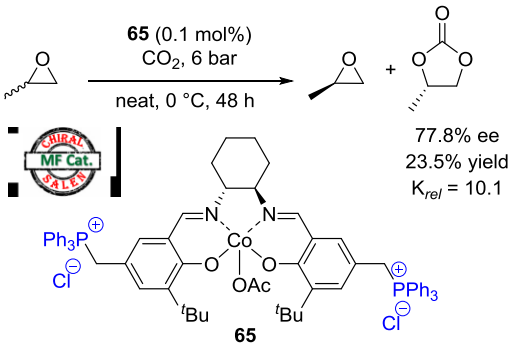
Jing *et al.*[183] developed in 2009 a polymeric catalyst **64** prepared through polycondensation of BINOL-bis-salicylaldehyde with cyclohexyldiamine, delivering (salen)Co^{III} species after complexation, and which was active in the aforementioned reaction in presence of tetrabutylammonium fluoride (see Scheme 77).



Scheme 77. Synthesis of chiral polymeric (BINOL-salen)Co catalyst 64

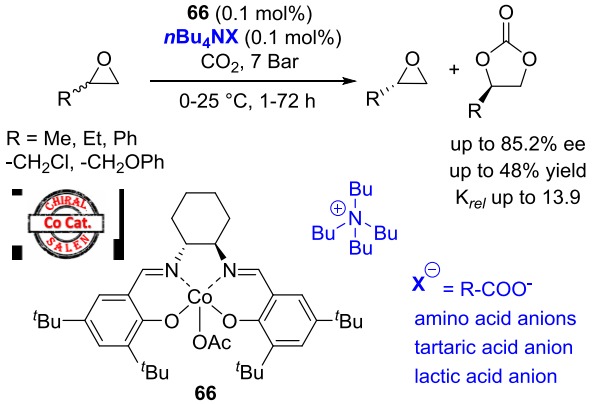
From the two possible combinations of chiralities (axial for BINOL and centred for the diamine) the match pair conducted to 73% ee in propylene oxide kinetic resolution, corresponding to a selectivity factor of 10.2; the polymeric catalyst being very easily recycled up to ten times with only marginal erosion of activity and selectivity.

About the same time, the same group[184] obtained similar level of selectivity by using (salen)Co^{III} bifunctional catalyst **65** incorporating quaternary phosphonium salts in its structure (see Scheme 78). The catalyst could be easily recovered and reused, showing interestingly almost no loss of activity and even slight increase in selectivity along the next four runs.



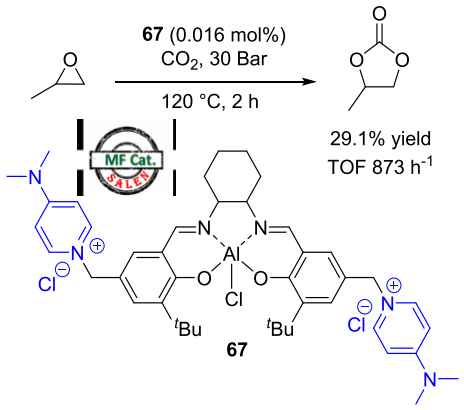
Scheme 78. Synthesis of chiral carbonates with complex 65 bearing an appended phosphonium salt

Another concept explored by Jing's group,[185] relied on the simultaneous use of a classical Jacobsen (salen)CoOAc catalyst **66** as chiral Lewis acid together with chiral ionic liquids prepared from tetrabutylammonium bromide (TBAB) and various amino-acid carboxylates. The reactions were notably conducted under mild conditions (0-25 °C, CO_2 7 bar) and enantioselectivity values were improved in the presence of the amino acid anions, compared to those obtained with TBAB alone, tetrabutylammonium L-alaninate being the best with 85.2% ee, and a selectivity factor of 13.9. Cooperative effect of both chiralities was checked, and improvement in asymmetric induction was observed when natural (*S*)-amino acid anions were employed with the (*R*,*R*)-salen catalyst, a negative effect being observed with the diastereomeric combination: (*S*)+(*S*,*S*) (Scheme 79).



Scheme 79. Asymmetric cycloaddition reaction of CO_2 and epoxides with 66 and chiral ionic liquids

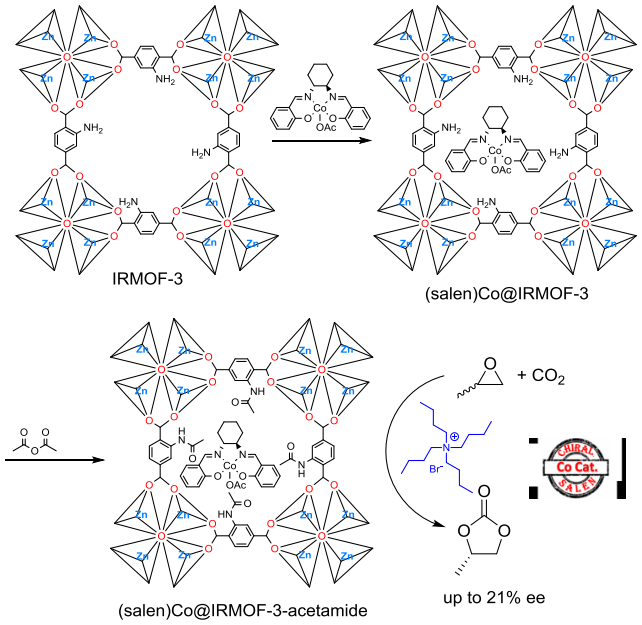
Liu and Darensbourg[186] investigated in 2012 the use of modified (salen)Al catalyst **67**, substituted at the 5,5' positions with various pyridinium and imidazolium moieties (Scheme 80). Without consideration of chirality, the authors identified the bifunctional catalyst (salen)AlCl flanked with two 4-dimethylaminopyridinium chloride to be the most active, reaching turnover frequency of $873h^{-1}$.



Scheme 80. Cycloaddition reaction of CO_2 and epoxides with 67 bearing appended pyridinium salts

A huge step further in selectivity was achieved in 2012 by the group of Lu,[187] using a (salen)Co^{III} complex possessing an additional BINOL-type backbone associated to PPN salt and an anion with poor leaving-group ability (see Scheme 77, preceding page). Hence, best results were observed with (triphenylphosphoranylidene)ammonium-2,4-dinitrophenoxide (PPN-DNP) reaching 97.1% ee corresponding to the impressive selectivity factor of 75.8. It is important to mention that using a large excess of this ammonium relative to the Lewis acid (typically 200 equiv.) was compulsory to avoid the formation of the corresponding polycarbonates. The authors rationalized the positive effect of a nucleophilic anion with a bulky counter-cation by postulating that the cobalt centre was strongly coordinating both epoxide and phenoxide anion, itself tightly interacting with the PPN^+ cation. Therefore, this compact transition state favors the phenoxide attack on only one enantiomere of the epoxide. The resulting alcoholate then adds to carbon dioxide to form an open carboxylate anion, which slowly ring closes into a cyclic carbonate thanks to the remaining leaving-group ability of the phenoxide.

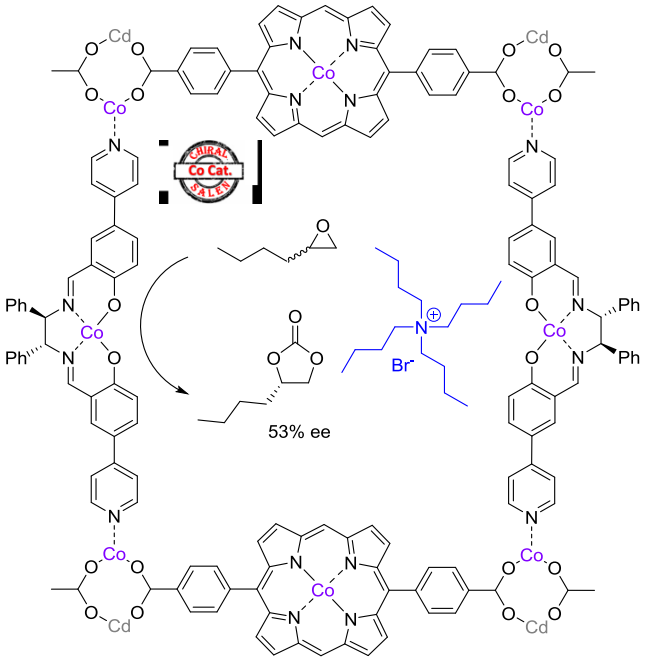
Zhang *et al.*[188] used the catalytic duet within the cage of metal organic frameworks (MOFs) to test the carbonate formation from epoxides, thus employing both Jacobsen cobalt catalyst (salen)Co^{II} and TBAB confined in the material pores (Scheme 81). The two catalysts were adsorbed and subsequently trapped by synthetic post-modification of the MOFs walls upon acylation. Condensation of CO_2 with epoxides to obtain optically active cyclic carbonates occurred successfully at room temperature with these heterogeneous catalysts (up to 41 % ee).



Scheme 81. Schematic description of imprisoning of homogeneous chiral (salen)Co^{III} catalyst within the cage of IRMOF-3 in two steps

Control experiments confirmed that the reaction occurred inside the pores, and bulky substrates were poorly converted due to their low diffusion rate. The catalytic system was reused three times with constant values in terms of activity and selectivity.

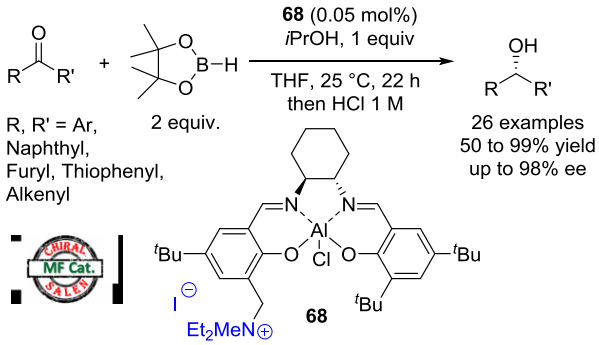
Ren and Jiang[189] also used MOF species to promote this reaction but the active enantiopure Co-salen complexes were used as struts for the construction of an isostructural porphyrin-salen chiral MOF, obtained through postsynthetic metallation based on single-crystal to single-crystal transformation (Scheme 82). After impregnation with TBAB, the material could catalyse the formation of various enantioenriched cyclic carbonates from racemic epoxides (up to 53% ee for the transformation of 2-butyloxirane, with an s factor of 4.8) under mild conditions. The material could be recycled five times maintaining both activity and selectivity.



Scheme 82. Porphyrin-salen based chiral MOF

In 2015, North and collaborators[190] reinvestigated the field using a catalyst of type **66**, but where the cobalt is replaced by aluminum with the idea of limiting polymerisation side reactions, as well as the hydrolysis of the starting epoxide, and therefore increase the overall yield of carbonate formation (Scheme 79). The best results of kinetic resolution were obtained with an acetate group as axial ligand for the classical Jacobsen catalyst and tetrabutylammonium bromide as co-catalyst, and a selectivity constant of 15.4 was attained; the authors have revealed a strong dependence of this value on the structure of the substrates to be transformed.
As seen in chapter 3.1.2. with the work of Pasquale's group[84], tetrabutylammonium bromide is crucial to perform the CO_2 incorporation into epoxides to produce cyclic carbonates. We have previously seen that a very complex triple-activation setting is at play in which the quaternary ammonium serves as bromide anion carrier into the organic phase where the reaction takes place.

This efficient cooperativity between a salen complex and quaternary ammonium salts has furthermore been illustrated in 2021 by the groups of Kästner and Peters,[191] in the promotion of enantioselective hydroboration of ketones. The authors indeed tackled this challenging transformation in the presence of pinacolborane, and discovered the highly efficient cooperativity within the bifunctional (salen)AlCl complex appended with an ammonium iodide **68** (Scheme 83).



Scheme 83. Asymmetric hydroboration of ketones with complex 68 bearing an appended ammonium salt

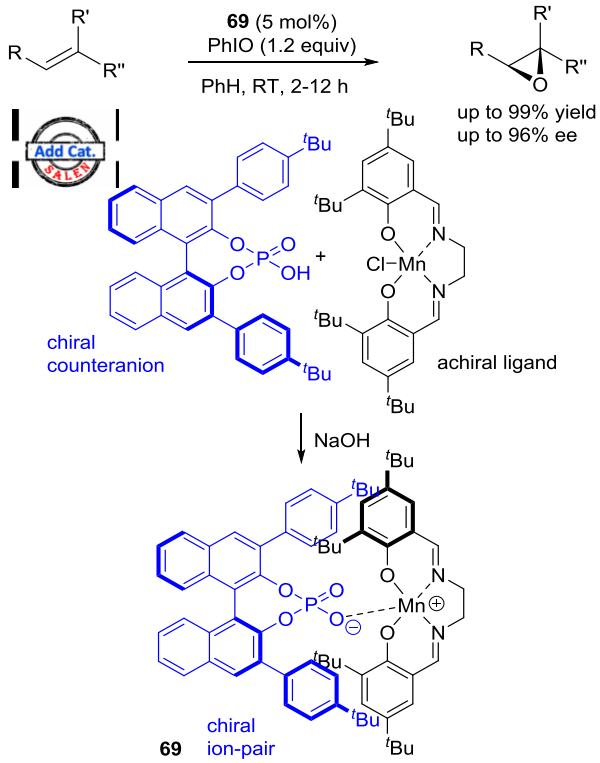
NMR studies, kinetic investigations and DFT calculations, demonstrated that the aluminum Lewis acid, oxophilic center of the catalyst could activate the ketone substrate, while the borane reagent was rendered nucleophilic via a boron/iodide interaction. The reaction occurs through a concerted mechanism, with the reagents accurately positioned between the aluminum and ammonium centers, the latter keeping the iodide ion in good place through ion pairing. The efficiency of the bifunctional catalyst **68** was further highlighted by its use at very low catalytic loadings (50 ppm), yet delivering highly enantioenriched secondary alcohols in excellent yields. TONs up to 15400 were attained, by far the highest activity in asymmetric hydroboration reactions. Moreover, the catalyst was easily recovered by precipitation in pentane, thanks to the presence of the attached ammonium salt, and it was efficiently reused in 10 successive runs, maintaining its high selectivity, and showing only a slight decrease in activity for the last two runs.

7. Metallo-Salen and Chiral Anions

7.1. Epoxidation Reactions

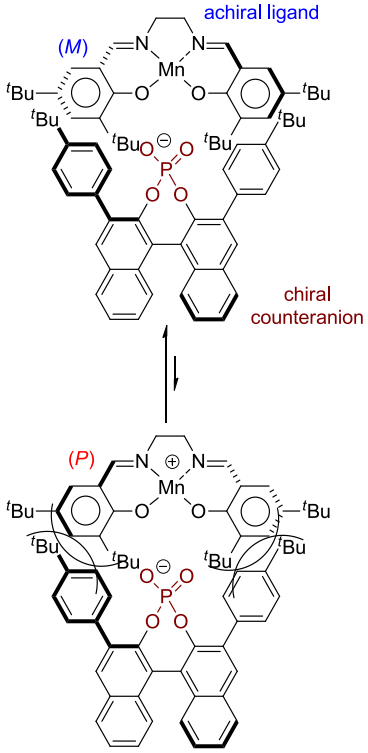
In 2010, List and coworkers[192] successfully used ion-pair catalyst **69** combining an achiral (salen)Mn^{III} cation with a chiral phosphate anion derived from BINOL in enantioselective epoxidations of alkenes. They found that the catalyst performance strongly depended on the anion structure. Among all chiral phosphate anions screened, the chiral binaphthol-based phosphate with bulky 4-*tert*-butyl-phenyl substituents in the 3,3′-positions (Scheme 84) was the best, and promoted the epoxidation in 99% yield, with an enantioselectivity of 96% ee.

With this ion-pair catalyst **69**, various olefins, chromenes and other non-cyclic akenes were epoxidized with good function tolerance. In general, (*Z*)-alkenes were preferable substrates. In this way, they demonstrated that an enantiopure anion could imposed a chiral conformation to a catalytically relevant achiral (salen)Mn cation. This approach represents a powerful application of the concept of asymmetric counteranion-directed catalysis using a chiral additive.



Scheme 84. (Salen)Mn^{III}/chiral phosphate ion pair for catalytic asymmetric epoxidations of unfunctionalized olefins

In order to understand the mechanistic and structural aspects of this catalytic transformation, the same group, in collaboration with Merten,[193,194] used vibrational circular dichroism (VCD) spectroscopy to monitor the stereochemical communication from the chiral phosphate anion to the (salen)Mn^{III} cation. They we able to demonstrate how a chiral anion forces the achiral cation of the ion-pair catalysts, to adopt an enantiomeric conformation responsible for the observed asymmetric induction (Scheme 85).

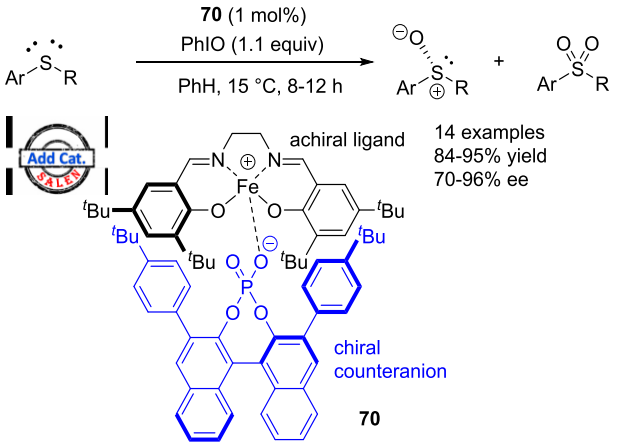


Scheme 85. (Salen)Mn^{III} / chiral phosphate ion pair equilibrium confirmed by VCD spectroscopy

The authors showed that depending of the solvent, intensity of the VCD signature correlates with the enantiomeric induction observed in the same solvent, tight ion-pairs leading to more distorted conformations, corresponding to higher enantioselection.

7.2. Sulfide Oxidations

In parallel, still in 2012, the same group[195] got interested in enantioselective oxidations of sulfides using this type of ion-pair catalysts. In this investigations, the best system **70** was constituted of an achiral (salen)Fe^{III} cation and a chiral phosphate counteranion (Scheme 86). Based on the reaction conditions previously established, application of the concept of asymmetric counteranion-directed catalysis to iron catalysis again proved very effective. Indeed, for the chosen transformation, oxidization of prochiral sulfides, the produced chiral sulfoxides were obtained in high yields and enantioselectivities.

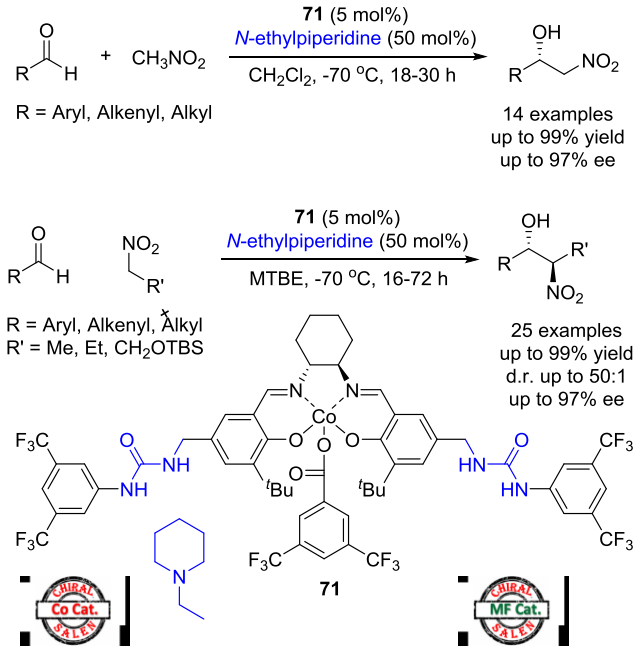


Scheme 86. (Salen)Fe^{III}/chiral phosphate ion pair for catalytic asymmetric oxidation of sulfides

Various ion-pair catalysts based on achiral salen complexes of Mn, Fe, Cr and Co were evaluated in asymmetric oxidation of methyl phenyl sulfide. It was found that the (salen)iron^{III} complex combined with chiral binaphthol-based phosphate bearing bulky 4-tert-butyl phenyl substituents in the 3,3'-positions provided better enantioselectivity and significantly improved sulfoxide chemoselectivity, limiting overoxidation to the corresponding sulfone. The ion-pairing concept was furthermore validated by the fact that enantioselectivities were generally much higher than those obtained with classical chiral (salen)Mn or (salen)Fe complexes under analogous conditions.[196] The reaction scope was then performed under the optimized reaction conditions demonstrating that all sulfides tested gave the desired sulfoxides in high chemoselectivity and enantioselectivity (Scheme 86).

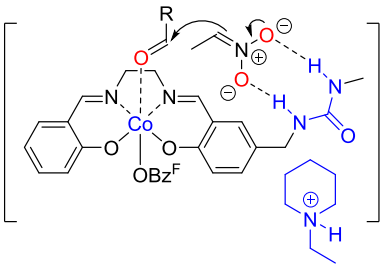
8. Metallo-salen and Hydrogen Bonding

Hong and co-workers[197] have developed a new type of cooperative catalyst that features both H-bonding and Lewis acid activation by a cobalt center for *anti*-selective asymmetric nitroaldol reactions (Henry reactions). Contrary to the previous work of this group on asymmetric Henry reactions promoted by a dimeric salen catalyst (assembled via quadruple H-bonding), this procedure uses a monometallic catalyst **71**. It is bifunctional as the (salen)Co^{III} core is flanked with two urea groups, a versatile activating moiety through H-bonding[198-201] (Scheme 87).



Scheme 87. Henry reactions with (salen)Co-OBz^{F}bisurea catalyst 71

The bis-urea (salen)Co^{III}-based catalyst **71** with bis(trifluoromethyl)benzoate as counter anion, gave excellent yields when used with *N*-ethylpiperidine as ancillary base in MTBE at -70 °C. The optimal catalyst was first applied to enantioselective Henry reactions with nitromethane, showing excellent enantioselectivities (up to 99% ee) and yields (up to 99%) with variously substituted aldehydes. Most importantly, the authors next applied the optimal conditions to the Henry reactions with nitroethane, retaining excellent enantioselectivities and yields, moreover with excellent *anti* diastereoselectivities (d.r. up to 48:1). Furthermore, high *anti* selectivities and enantioselectivities were still observed with highly substituted benzaldehydes as well as other functionalized nitroalkanes (Scheme 87). It is worth mentioning that, examples of highly *anti*-selective asymmetric nitroaldol reactions with encumbered aryl-aldehydes are very rare.[202]



Scheme 88. Proposed activation pattern for the Henry reactions with (salen)Co-OBz^{F}bisurea catalyst 71

After control experiments, proving the cooperativity of both functions, Lewis base at cobalt center and hydrogen bonding at urea, and the beneficial proximity effect compared to separate catalysts, the authors proposed an activation pattern as depicted in Scheme 88. The tertiary base deprotonates the nitroalkane to form a nitronate, which is chelated by the urea moiety, while coordination of the aldehyde reactant at the

cobalt center increases its electrophilicity ensuring high activity, and organizes the mutual approach in a well organized manner, controlling both diastereo- and enantioslectivities. Final decomplexation of the resulting alcoholate through protonation by the piperidinium salt delivers the Henry adduct.

9. Outlook and perspectives

Beyond the immense recognition gained by the metallic salen complexes as ubiquitous species in asymmetric catalysis, this review aimed at demonstrating that their efficiency was not limited to the classical mechanisms of organometallic chemistry. The number of examples is huge for which organic additives have been intimately linked in intricate reactivity modes to provide the targeted functionalized molecules in high yields and with relevant enantioselectivity values. To cite just one example, this is especially true for the couple amine/salen complex for which the nucleophilicity of the amine exerted a direct influence on the reaction rate; despite the hindsight on this discovery, which is not recent, the study of the mechanisms remains relevant because of the many parameters involved which interfere with the kinetics and thermodynamics of the reaction. Most data have been found on the cyanation reaction; it is less marked for other transformations which are at earlier stage of their development. The necessity for a good balance between Lewis basicity and steric hindrance of the additive has been clearly demonstrated for an efficient acceleration and enhancement of the selectivity in these catalytic transformations.

The nature of the additive is of course fundamental; while the addition of nitrogenous base has proved crucial to promote acylcyanation reactions, oxygenated nucleophiles are the main promoters of cyanide displacement in silylcyanations, due to the intrinsic oxophilicity of the silicon atom. In most cases, the chemistry of salen complexes is intimately linked to the nature of its counterion; in this context, it has been shown that the effect of the organic additive depends on the acidity of the metal center involved. But, the role of the additive is multiple; it has also been shown to stabilize the metal center in the oxidation state in which it is active to prevent its decomposition. This has been proved in the case of olefins epoxidation with salen manganese complexes, for which the addition of *N*-oxides made it possible to avoid the formation of inactive Mn(IV) dimers. Its involvement can also allow chemoselectivity improvements in targeted reaction, such as avoiding overoxidation in asymmetric sulfoxidation reactions. An additive can also be beneficial to induce a twisting effect on the complex geometry, creating a more favorable geometrical arrangement for high enantioselectivity values.

Perhaps the most impressive use of these organic additives is the induction of a chiral conformation of an achiral salen cationic complex when paired with a chiral anion. Additionally, when both complex and organocatalyst are chiral, exploitation of matched/mismatched effects can lead to interesting outcomes. Although usually active as independent catalytic species, sometimes, the necessity to have a bifunctional catalyst was demonstrated to fully benefit from the synergistic action of both metallic/organocatalytic moieties in an intramolecular fashion, to the detriment of the more arduous catalyst synthesis. For instance, in the case of enantioselective C-C bond formation via diethylzinc addition to carbonyls, the use of a bifunctional catalyst was compulsory, when neither of each moiety alone was able to trigger the reaction, nor their intermolecular combination.

The choice of an organic additive remains a difficult task, but we assume that the examples reported in this review, together with the few physicochemical clues presented to rationalize their effect, are a solid basis for moving towards a further improvement of asymmetric transformations catalyzed by salen chiral complexes.

Our last words go to the latest developments of such dual catalytic systems, Beyond the assembly of two salen complexes by hydrogen bonds, their efficient gathering has also been recently reported through donor-acceptor interactions to promote hydrolytic kinetic resolution benefiting from the cooperativity exerted by (salen)Co complexes hence maintained in close proximity.[203,204] Although a field in rapid blooming, halogen-bonding offers complementary opportunities to H-bonding, but was however not exploited so far in the field of dual catalysis with salen derivatives. Finally, control of the catalytic system was realized by means of an external stimulus with the incorporation of azobenzene units in between two (salen)Ti complexes. It was hence possible to control their relative distance, and therefore their catalytic effectiveness, by photoisomerization under light stimuli.[205] We are confident that investigations in the chemistry of chiral salen complexes together with organocatalysts still has a bright future ahead.

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ACKNOWLEDGMENT

We acknowledge Université Paris Saclay, CNRS, and Charm3At LabEx (ANR-11-LABEX-0039) for financial support. Dr. Karen Wright is warmly thanked for careful correction of the manuscript.

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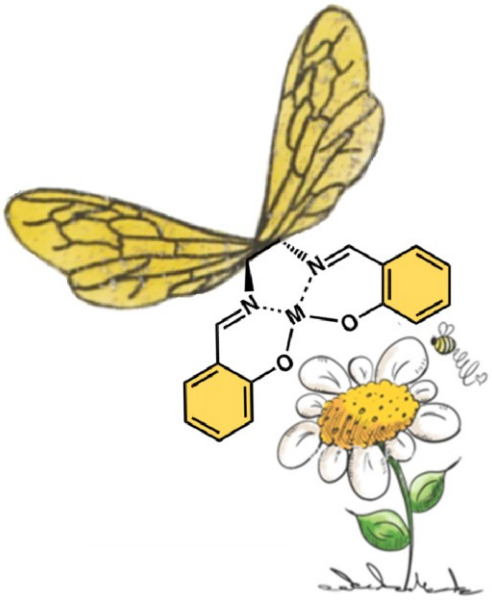
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