

Making Chiral Salen Complexes Work with Organocatalysts

Yu-Chao Yuan, Mohamed Mellah, Emmanuelle Schulz,* and Olivier R. P. David*

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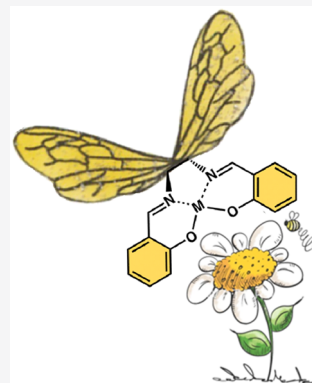


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ABSTRACT: Bisimine derivatives of salicylaldehyde with chiral diamines (salens) are privileged ligands in asymmetric organometallic catalysis, which can be used in cooperation with organocatalysts as additives. The latter can be a modifier of the metal 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

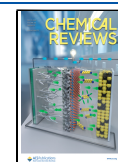
1. Introduction	8841	3.7. Metallo-salen with Phosphoranes	8867
2. Cyanation of Carbonyl Compounds and Imines	8845	4. Metallo-salen and Brønsted Bases	8868
2.1. Acylcyanation with Amines	8845	4.1. Addition of Malonates to Enones	8868
2.2. Acylcyanation with Cyanide Ion Catalysis	8847	4.2. Henry Reactions	8868
2.3. Acylcyanation with Quaternary Ammoniums	8847	5. Metallo-salen and Brønsted Acids	8871
2.4. Acylcyanation with Heterogenous Bases	8848	6. Metallo-salen and Onium Salts	8871
2.5. Cyanosilylation of Carbonyl Compounds	8849	7. Metallo-salen and Chiral Anions	8875
2.5.1. Cyanosilylation with <i>N</i> -Oxides	8849	7.1. Epoxidation Reactions	8875
2.5.2. Cyanosilylation with Phosphine Oxides	8852	7.2. Sulfide Oxidations	8876
2.5.3. Cyanosilylation with Amines	8855	8. Metallo-salen and Hydrogen Bonding	8876
2.6. Strecker Reactions: Cyanation of Imines	8855	9. Outlook and Perspectives	8876
3. Catalysis with a Metallo-salen and a Lewis Base	8857	Author Information	8877
3.1. Metallo-Salen and Amines	8857	Corresponding Authors	8877
3.1.1. Epoxide Ring-Opening	8857	Authors	8877
3.1.2. Reaction of CO ₂ with Epoxides	8857	Author Contributions	8877
3.1.3. Organozinc Addition onto Carbonyl Compounds	8859	Notes	8877
3.1.4. β -Lactone from Ketenes	8861	Biographies	8877
3.1.5. Cyclopropanation	8861	Acknowledgments	8877
3.1.6. Addition of Indoles to Enones	8862	References	8878
3.1.7. Addition of Indoles to Nitroalkenes	8862		
3.2. Metallo-salen and <i>N</i> -Oxides	8862		
3.2.1. Alkene Epoxidation	8862		
3.2.2. Reformatsky Reactions	8864		
3.2.3. Hydrocyanation of Nitroalkenes	8865		
3.3. Metallo-salen and Phosphine Oxides	8865		
3.4. Metallo-salen and Sulfoxides	8865		
3.5. Metallo-salen with Carbenes	8866		
3.6. Metallo-salen with Halides	8866		

1. INTRODUCTION

The chemistry of salen-type complexes can be traced back to 1889 when Alphonse Combes¹ prepared the first bis-imine of

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ethylenediamine with acetylacetone and made the corresponding copper complex (Figure 1).

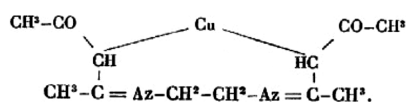


Figure 1. Bis-imine complex synthesized by Combes¹ in 1889, as drawn in the original article (open source).

The field reached 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.

This 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 revealing the potential synergistic effect brought by the use of two promoters to reach enantioselectivities above 95%. The manifold advantages of multistep catalysis in enantioselective tandem reactions was reviewed by Pelissier⁶ in 2020 from a general perspective and challenges associated with the merging of organocatalysis and transition metal catalysis were reviewed by Shao and Zhang.^{7,8}

Here we want to concentrate on double 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

complex 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 2). Larger tables of affinities were built using SbCl₅ or BF₃ as reference Lewis acids, allowing for the quantitative ranking of classical functions in organic chemistry (Figures 3 and 4).¹⁰

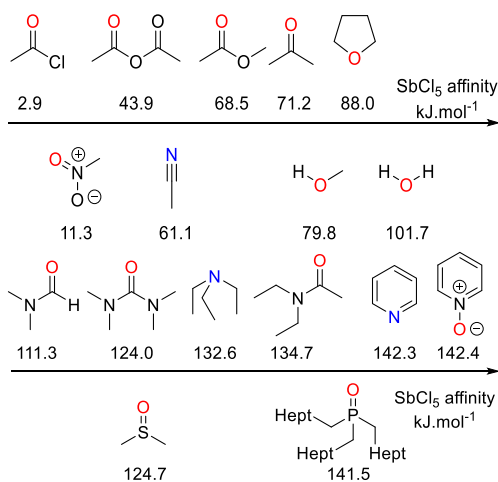


Figure 3. SbCl₅ affinities, (in kJ mol^{−1}), of Lewis bases in 1,2-dichloroethane at 298 K.

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).

Although not quantitative, this table allows one to perceive the general preferences of these cations in the presence of

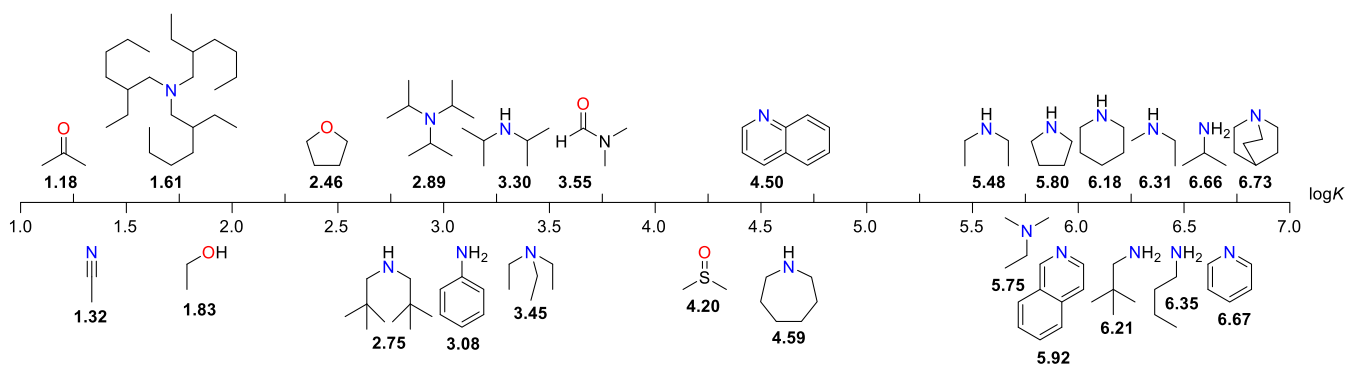


Figure 2. Equilibrium constants for various Lewis bases toward (salen)Zn in DCM (log *K*).

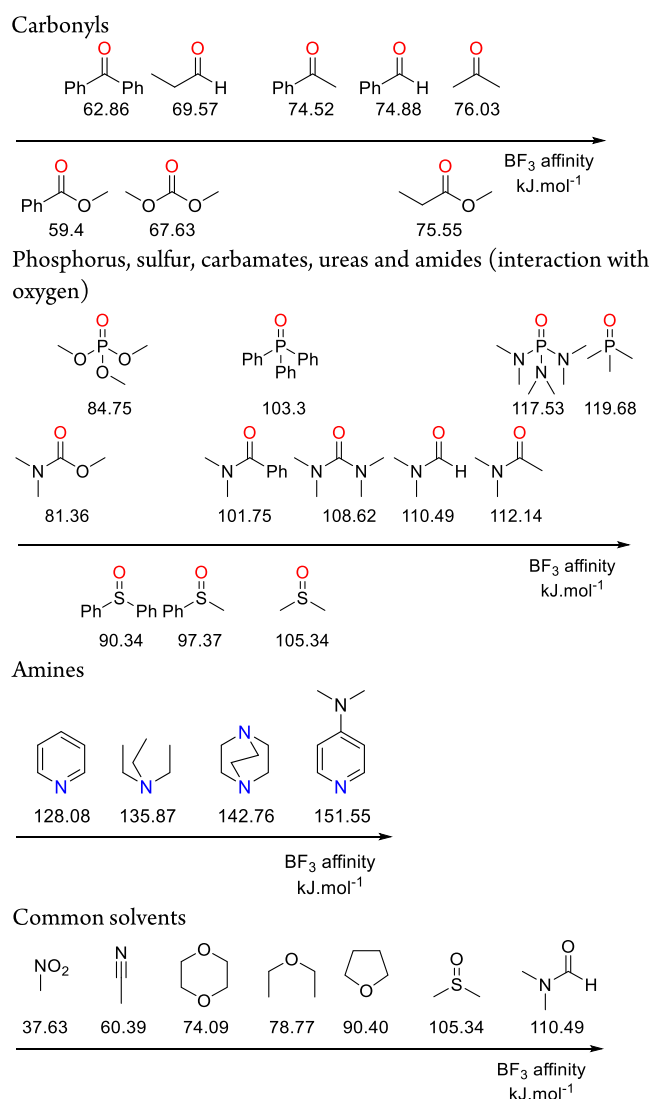


Figure 4. BF_3 affinities (kJ mol^{-1}) of Lewis bases in dichloromethane at 298 K.

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 catalysts.

As only a limited array of Lewis bases were investigated in these affinity scales, it is interesting to consider a closely related thermodynamic property, the hydrogen-bond affinity, as measured by $\text{p}K_{\text{BHX}}$ on a far larger range of compounds, which allows an approximate ranking of Lewis basic catalysts.¹⁰

What are the different co-catalysis modalities? When mixed with a salen–metal complex, 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 the 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 stepped geometry is also strongly modulated by the nature of axial ligands, as shown by the group of Fujii¹³ with (salen) Mn^{IV} complexes in the solid state (Figure 5C). 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 pronucleophile substrate, while the salen–metal complex 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

Table 1. Benchmark Reaction to Classify Oxo- and 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 ^a		
BCl_3, TiCl_4, GaCl_3, ZrCl_4, AlCl_3, NbCl_5, SnCl_2, SbCl_5, HfCl_4, ReCl_3		
Imine Selective ^a		
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	
Nonselective		
MoCl_5, MoCl_3, SnCl_3, TaCl_5, WCl_6, WCl_5, ReCl_3, TiCl_3	ZnCl_2, RuCl_3	PCl_5, VCl_3, CrCl_3, MnCl_2, NiCl_2, RhCl_3, PdCl_2, AgCl, CdCl_2, IrCl_3, AuCl, HgCl_2, PbCl_2

^aIn bold, selectivity > 9/1.

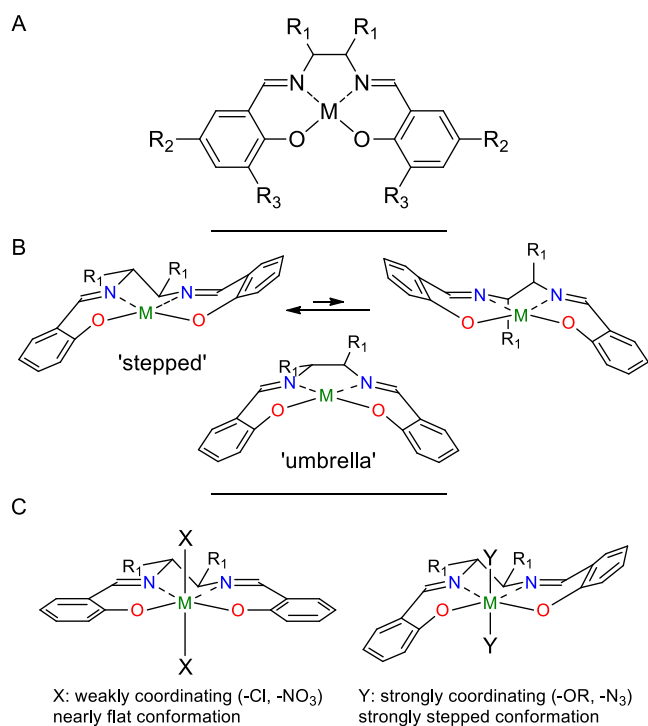


Figure 5. (A) General formula of salen complexes; (B) possible conformations; (C) influence of axial ligands on the conformation of (salen)MX₂.

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 a 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 pK_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, and 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) giving a semiquantitative kinetic ranking of the considered catalysts.^{20,21} 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 being 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). 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, contrarily, tributylphosphine, sensibly more basic than nucleophilic.

4. The additive is a Brønsted acid, increasing the electrophilicity of the substrate by protonation, and 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

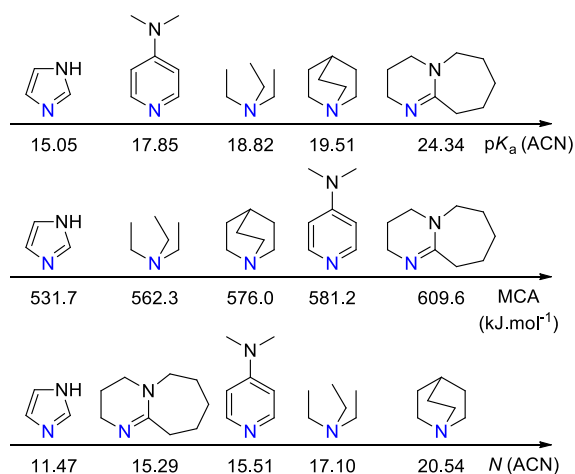


Figure 6. Relative rankings of five amines, according to their Brønsted basicity, Lewis basicity (methyl cation affinity) and nucleophilicity (*N*).

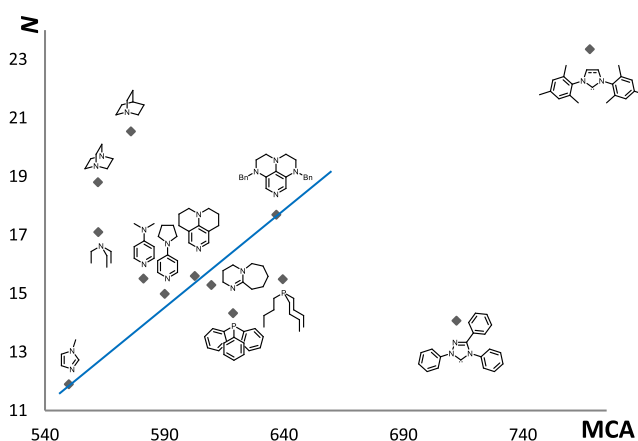


Figure 7. Nucleophilicity (*N*) against Lewis basicity MCA, for a selection of organocatalysts.

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 controlling its position in the transition-state.

The various scenarios of multicatalysis²² led to introduction of 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.

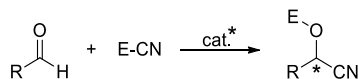
Co-catalysis [Co Cat.], when several catalytic species are acting in synergy. This is similar to *dual catalysis* for some authors.

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 section to make specific comparisons within this homogeneous subfield and show the relative advantages brought by the different double and even triple catalytic systems used to cyanate carbonyl compounds.

Scheme 1. Enantioselective Cyanation of Aldehydes



2. CYANATION OF CARBONYL COMPOUNDS AND IMINES

The topic of asymmetric cyanation reactions was reviewed in 2020 by Zhou, Wu, and Yu,²³ focusing on the most recent strategies (Scheme 1). We aim here to give 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.

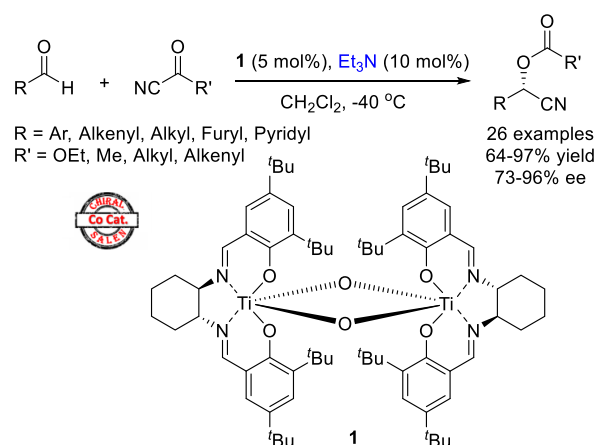
2.1. Acylcyanation with Amines

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

The base-catalyzed 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. For instance, the groups of North²⁷ 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 leads to important erosion in enantioselectivity of the cyanohydrin.

A typical procedure with acylcyanides relying solely on 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 is necessary to achieve complete conversion within 18 h, 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 trimethylsilyl cyanide (TMSCN) is employed. Furthermore, 2 equiv of EtOCOCN is needed, undermining the atom economy of the process. In this context, Moberg and her group reported in 2005 an upgrade of this catalytic system,

Scheme 2. Enantioselective Cyanation of Aldehydes Using Ethyl Cyanoformate or α -Ketonitriles with **1** and Et₃N



while studying the use of acetyl cyanide in this cyanation reaction (Scheme 2).^{30,31}

As the use of catalyst **1** alone proved unsuccessful to promote the reaction between benzaldehyde and acetyl cyanide, the group explored a dual activation, including **1** as active Lewis acid together with an additional Lewis base. Initially, addition of 4-dimethylaminopyridine (DMAP) allowed the formation of the desired product; screening of

Table 2. Effect of Amines As Additives to Catalyst **1 for the Cyanation of Benzaldehyde^a**

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)

^aConditions: [(salen)TiO]₂ (5 mol %), base (10 mol %), −40 °C for 6–9 h. N is nucleophilicity parameter according to Mayr,^{20,21} in ACN. MCA is methyl cation affinity in kJ mol^{−1} as calculated by Zipse,¹⁹ see Introduction, section 1. Values in parentheses are estimated from very similar compounds.

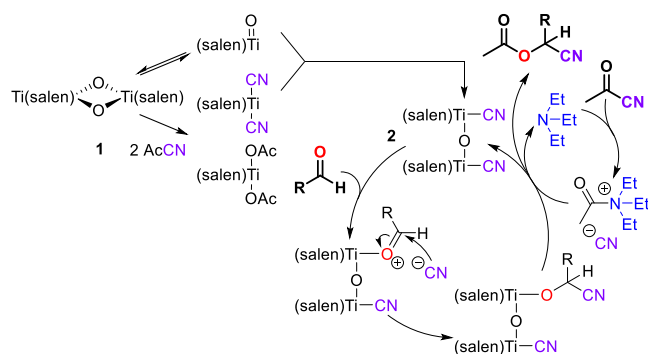
different amine bases showed the superiority of triethylamine. Hence, complete conversion was obtained in 8 h with 5 mol % **1** and 10 mol % NEt₃ delivering the O-acetylated cyanohydrin from benzaldehyde in 94% ee with 96% conversion (Table 2). Use of chiral bases such as quinine derivatives did not lead to usefully improved results and led to marginally matched or mismatched effects between the two chiral promoters.

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 equiv and the reaction duration was reduced 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. ¹³C-labeling tests ruled out 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 was 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

Scheme 3. Proposed Mechanism for the Enantioselective Cyanation of Aldehydes with 1 and Et₃N^a



^aAll intermediates are Ti^{IV} species.

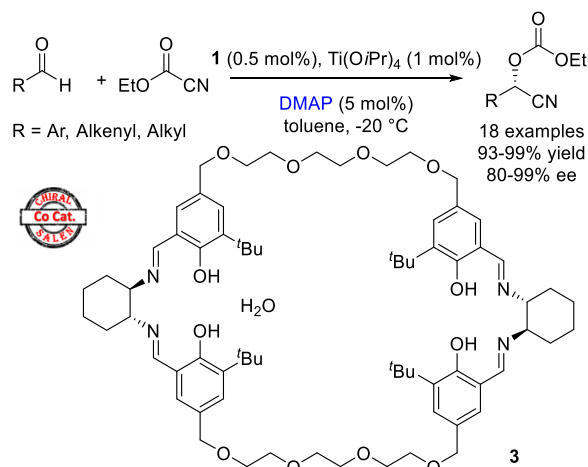
nucleophilic attack as the rate-determining step for aldehyde substrates bearing electron-donating or halogen substituents, whereas the acylation step was limiting for those with highly electron-withdrawing groups. A detailed mechanism was suggested, which is simplified in Scheme 3 below, with omission 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 cyanohydrin moiety gives the final product, while alcoholate substitution by the cyanide anion regenerates the dicyano-dimetallic species 2, closing the primary catalytic cycle.

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 $-20\text{ }^{\circ}\text{C}$, 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

Scheme 4. Asymmetric Cyanoethoxycarbonylation of Aldehydes with an *In Situ* Generated Macrocyclic Ti-Catalyst and DMAP



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

Table 3. Effect of Amines as Additives in the Cyanoethoxycarbonylation of Benzaldehyde Catalyzed by Ti–Salen Macrocyclic Catalyst 3^a

base	<i>t</i> (h)	yield (%)	ee (%)	p <i>K</i> _{BHX}	<i>N</i>
NEt ₃	1	99	69	1.98	17.10
iPr ₂ NH	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)

^aConditions: Ti catalyst (0.5 mol %), base (5 mol %), toluene, RT.

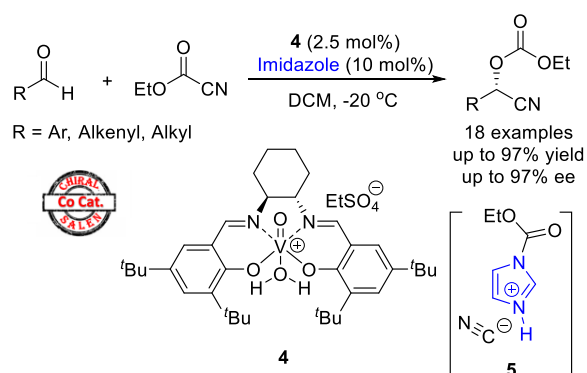
pharmaceutically important chiral drugs, (*R*)-proethanol and (*R*)-phenylephedrine.

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.

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, p*K*_{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 Khan³⁷ using the (salen)V^V complex 4 to promote the same transformation.

Scheme 5. Asymmetric Cyanoethoxycarbonylation of Aldehydes with a (Salen)^V Complex and Imidazole



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).

In this case, imidazole was the best Lewis base and led to the efficient asymmetric addition of ethyl cyanoformate to benzaldehyde at $-20\text{ }^{\circ}\text{C}$, with a (salen)^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 (76–97%).

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.

Table 4. Effect of Amines as Additives with (Salen)^V Catalyst **4**^a

base	<i>t</i> (h)	yield (%)	ee (%)	<i>pK</i> _{BHX}	<i>N</i>
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)

^aConditions: Catalyst **4** (2.5 mol %), base (10 mol %), DCM, $-20\text{ }^{\circ}\text{C}$.

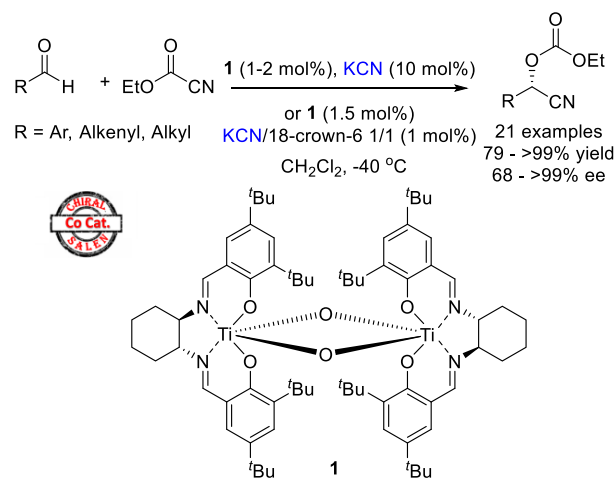
The fact that the virtually non-nucleophilic lutidine is however able to promote this transformation efficiently and, in contrast, the fairly nucleophilic pyridine is incompetent in doing so (see Table 4) suggests a more complex reaction mechanism with amine–metal interactions tuning its activity, in concurrence with amine/cyanoformate addition.

2.2. Acylcyanation with Cyanide Ion Catalysis

As previously seen, amine derivatives are not the only efficient catalysts for accelerating and enhancing selectivity in asymmetric cyanohydrin carbonate synthesis. North and co-workers indeed reported the valuable use of the cyanide ion as a co-catalyst. Although the cyanide ion is not strictly speaking an organic entity, 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.³⁸ The reaction between benzaldehyde and ethylcyanoformate could

Scheme 6. Asymmetric Cyanoethoxycarbonylation of Aldehydes with a Dimeric (Salen)Ti Complex and Cyanide Ion as Co-catalyst



occur at $-40\text{ }^{\circ}\text{C}$ 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).

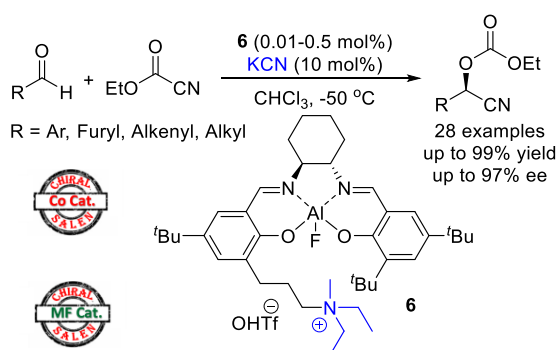
Since the catalytic reactions were performed in dichloromethane using solid, insoluble KCN as catalyst, the mixture remained heterogeneous. The authors could further improve their procedure by employing a 1:1 complex made from KCN and 18-crown-6, freely soluble in DCM. With only 1 mol % of this complex 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 anion³⁹ 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

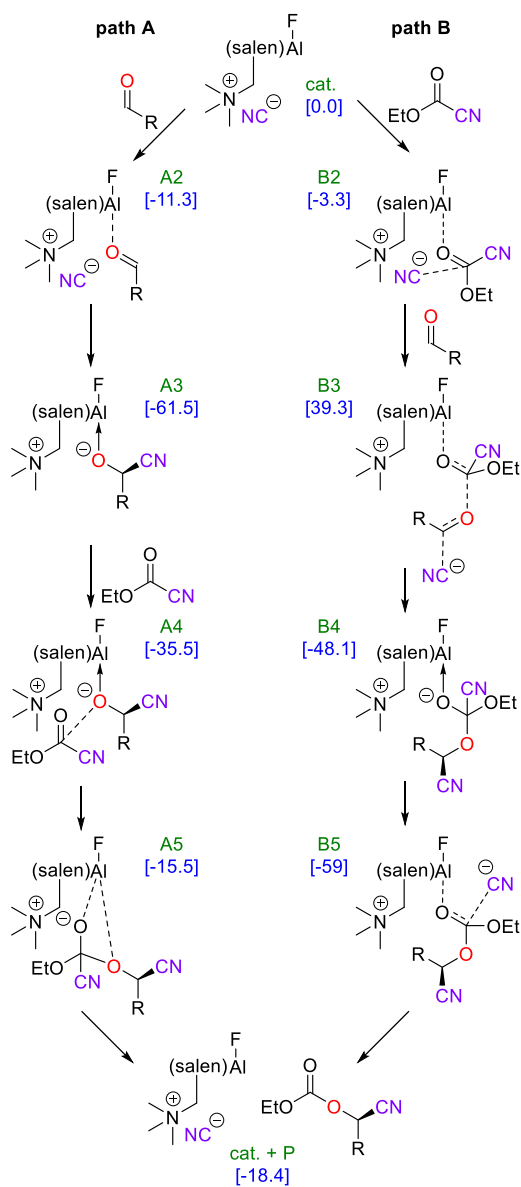
The group of Peters⁴⁰ in 2017 employed bifunctional catalysts, combining a (salen)Al^{III} complex with an ammonium salt **6** as ion-pairing already proved highly effective in other asymmetric transformations.⁴¹ Here, the authors reasoned that a salen complex bearing a linked ammonium unit could both activate 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).

Control experiments proved that the covalent link between both active moieties was necessary to access high reactivity and enantioselectivity. The use of an aluminum fluoride associated with the ammonium bearing a noncoordinating 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

Scheme 7. Asymmetric Carboxycyanation of Aldehydes with a (Salen)Al Fluoride Complex with an Appended Ammonium Salt



Scheme 8. DFT Calculations for the Carboxycyanation in the Presence of KCN and Complex 6



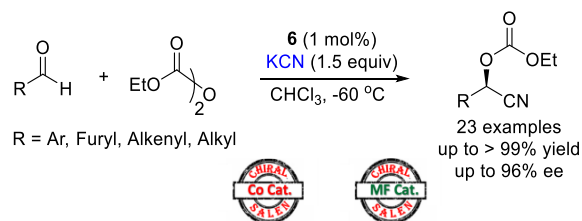
activity to the robustness of the Al–F bond leading to a stable catalyst with an increased Lewis acidity.

DFT studies were conducted by the same group⁴² in 2019, on the basis of which the classical mechanism (path A in Scheme 8) implying 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 $-61.5 \text{ kJ mol}^{-1}$) and the A4 \rightarrow A5 transition state is located at 16.7 kJ mol^{-1} , corresponding to an activation barrier of 78.2 kJ mol^{-1} . Thus, the alternative path B was proposed, calculations showing a less energy-demanding profile, the largest gap being 42.7 kJ mol^{-1} in the B4 \rightarrow 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 cyanoalcoholate 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.

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.

Scheme 9. Carboxycyanation Catalyzed by 6 with Stoichiometric KCN and Pyrocarbonate



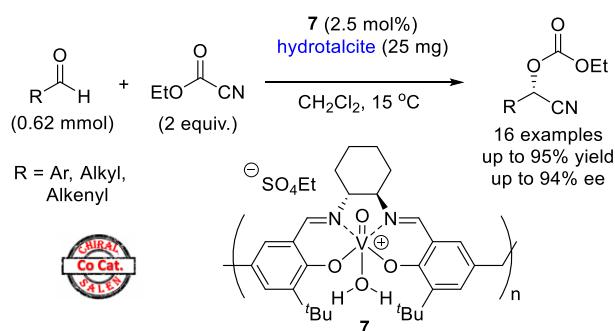
In this mechanistic article, the authors also explored an elegant procedure, using potassium cyanide as the source of the cyano group, to replace the cyanoformate reagent, carbonation of the cyanohydrin being assured by diethyl pyrocarbonate, with the cyanide anion additionally assuming an ancillary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

This new procedure led to results similar to 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 Khan⁴³ tackled the challenge of working out a procedure leading to 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 as recoverable co-catalysts was further explored. The authors optimized the reaction parameters and particularly

Scheme 10. Enantioselective Addition of Ethyl Cyanoformate to Various Aldehydes Using a Polymeric (Salen)V^V Complex Together with Hydrotalcite



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 (25 mg/mmol of aldehyde substrate), delivered the target product from benzaldehyde in 94% yield and 88% ee at 15 °C.

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 substrate 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, which activates the carbonyl substrates, with a Lewis base additive, which liberates cyanide anions by nucleophilic displacement, ensures 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, which is hence protected from any reversion to the starting materials (Scheme 11).

Scheme 11. General Mechanism of Cyanosilylation under Co-catalysis

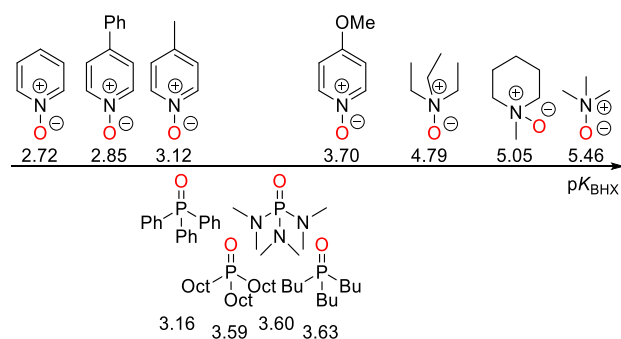
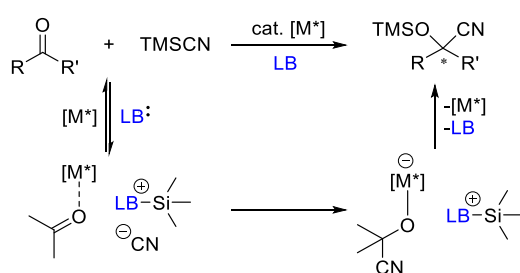


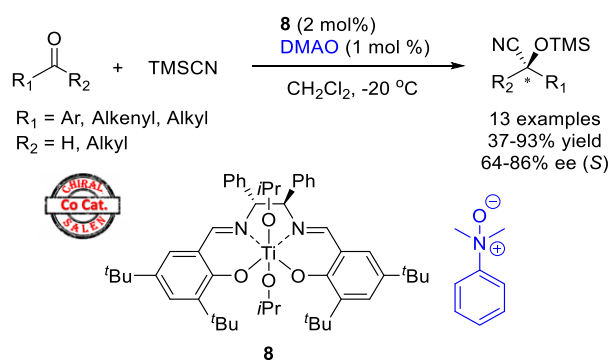
Figure 8. Hydrogen-bond affinity (pK_{BHX}) of various *N*-oxides and phosphine oxides.

From the very first studies, oxygen nucleophiles demonstrated their efficacy, with numerous examples using *N*-oxides and phosphine oxides (Figure 8) and an example relying on acylphosphoranes. This predominance probably stems from the high oxophilicity of the TMS group making these classes of Lewis base prime promoters for cyanide displacement. The authors in this field seem to have favored the association of *N*-oxides with (salen)Ti^{IV} catalysts and of phosphine oxides with (salen)Al^{III} ones, although exceptions are present.

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 nucleophilicity 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 using both metals, which will be discussed at the end of the section, was reported.

Scheme 12. Catalytic Enantioselective Cyanosilylation of Ketones Developed by Feng et al.⁴⁵



Beginning with 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).

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

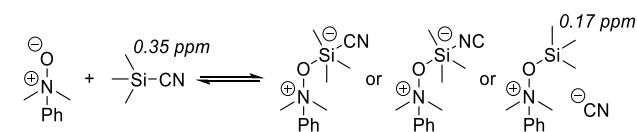
To explain this optimal combination metal complex/*N*-oxide, the authors suggested that strongly nucleophilic *N*-oxides (like Me₂NO) quickly activate the silyl derivative but

Table 5. Effect of Amines as Additives with (Salen)Ti^{IV} Catalyst **8^a**

Lewis base	yield (%)	ee (%)	pK _{BHX}	SbCl ₅ affinity (kJ mol ⁻¹)
PyrNO	0	0	2.72	142.4
Me ₃ NO	26	65	5.46	
HMPA	30	34	3.60	(140)
NMNO	32	60	(4.9)	
Et ₃ NO	53	66	4.79	(218)
CyMe ₂ NO	63	51		
PhNMe ₂ O	95	67		

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

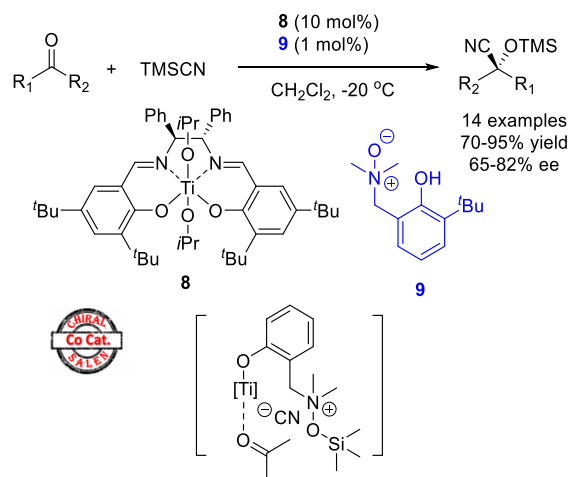
also strongly coordinate the metal center with formation of a nonactive Lewis pair that cannot serve to activate the ketone substrate. DMAO thus represents the optimum balance in

Scheme 13. Potential Structures Resulting from Nucleophilic Attack of TMSCN with DMAO

nucleophilicity and coordination behaviors. It was noted that upon mixing of TMSCN with the *N*-oxide additive in CDCl₃, 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).

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 siliconate⁴⁸ being around –0.18 pm).

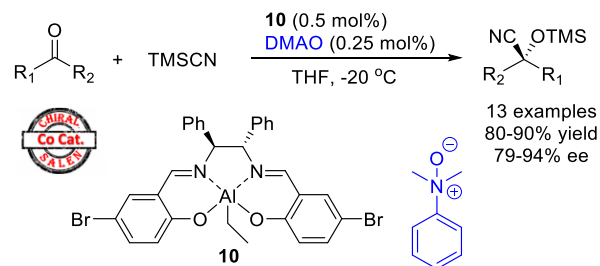
Around the same time, Feng and collaborators^{49,50} explored the potential offered by the use of a bifunctional additive, **9**,

Scheme 14. Enantioselective Cyanosilylation of Ketones in the Presence of a Bifunctional Phenol/*N*-Oxide Additive

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).

The synergistic activation was effective, and the authors proposed *in situ* generation of a bifunctional catalyst as 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 reasonably identical activities and selectivities.

Then, when examining the aluminum-based systems, the group of Feng⁵¹ conducted in 2004 an in-depth investigation

Scheme 15. Enantioselective Cyanosilylation of Ketones Catalyzed by **10/DMAO**

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 complex **10** at a very low catalyst loading with half the quantity of DMAO (Scheme 15).

Table 6. Lewis Acid Effect on the Enantioselective Cyanosilylation of Ketones with DMAO as Co-catalyst^a

Lewis acid	yield (%)	ee (%)
(salen)AlCl	<i>b</i>	87
(salen)Zn	<i>b</i>	72
(salen)Ni	<i>b</i>	0
(salen)Ti(OiPr) ₂	11	74
(salen)Al(OiPr)	17	14
(salen)AlCN	36	56
(salen)AlEt	45	83
(salen)Cu	80	0

^aConditions: 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. *b*Trace.

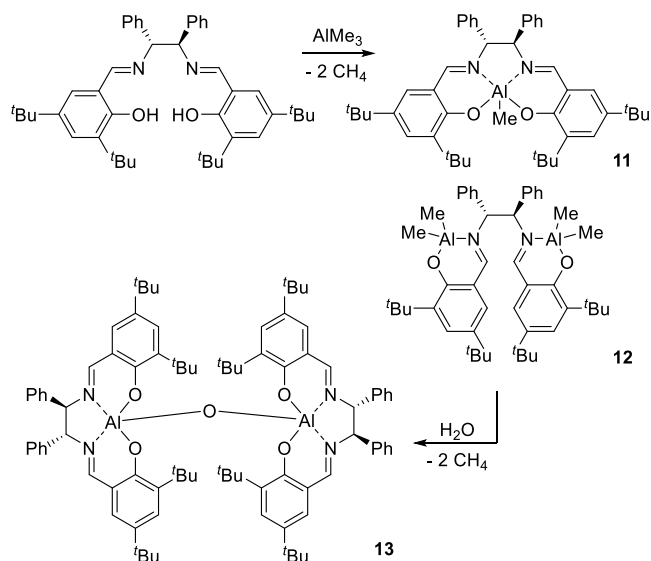
This study is notably interesting because it highlights the drastic effect of each parameter of the catalytic conditions on the reaction efficacy, conversely showing that the previously employed titanium complex was far from being optimal in terms of activity, while DMAO, as previously selected, was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

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 Carpentier⁵² 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

Scheme 16. Monometallic and Bimetallic Complexes Developed by Carpentier et al.⁵² for Enantioselective Cyanosilylation of Ketones



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 monometallic “closed” complex 11 and bimetallic “open” complex 12 (Scheme 16).

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 toward the expected monometallic 11, could favorable mixtures be obtained, though 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, a compound first characterized by Barron et al. in 1991,⁵³ was

Table 7. Lewis Base Effect on the Enantioselective Cyanosilylation of Acetophenone with DMAO Co-catalyst^a

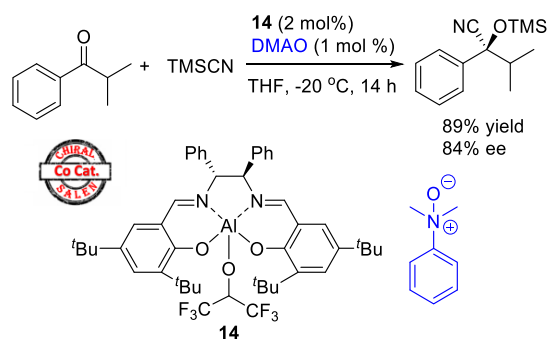
Lewis acid	yield (%)	ee (%)
(salen)H ₂ + AlMe ₃	52	80
(salen)AlMe	81	84
(salen)(AlMe) ₂	8	81
[(salen)Al] ₂ O	98	80
(salen)H ₂ + Al(OiPr) ₃	17	14
(salen)AlOiPr	71	81

^aConditions: acetophenone + TMSCN (2 equiv), THF, Lewis base (2 mol %; 1,2-diamino-1,2-diphenylethane salen), DMAO (1 mol %), -20 °C, 48 h.

easily generated. 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).

Hence, well-defined species behave with various activities and stereocontrol, the monometallic 11 being the most active, while the bimetallic 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

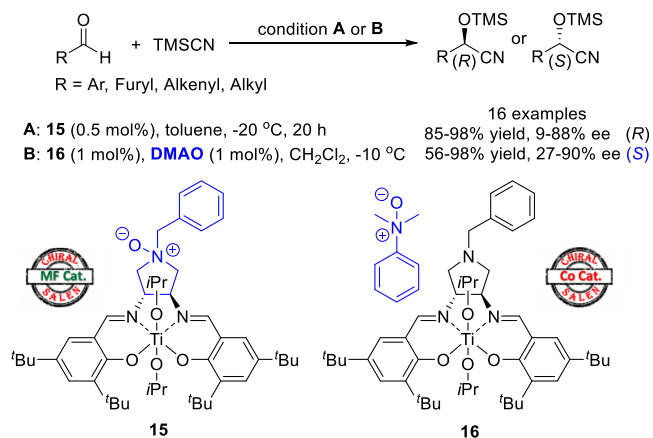
Scheme 17. Enantioselective Cyanosilylation of Ketones with Hexafluoroisopropoxide Catalyst 14



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).

Bifunctional catalysts were also examined 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

Scheme 18. Catalytic Enantioselective Cyanosilylation with the “Two-Center Catalyst” Developed by Sun’s Group⁵⁴

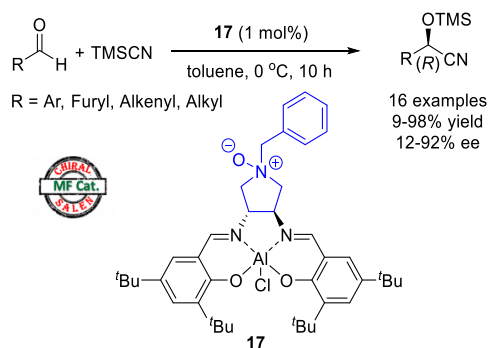


complexes, notably for the cyanation of aldehydes and not ketones, as was the case in previous studies. Here, the diamino core of the Jacobsen catalyst was replaced by a chiral, C₂-symmetrical diaminopyrrolidine, whose nitrogen atom was then oxidized to give the corresponding *N*-oxide. Both ligands

were converted into their respective titanium isopropylate complexes **15** and **16** (see Scheme 18).⁵⁴

Methodological optimization 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

Scheme 19. Enantioselective Cyanosilylation of Aldehydes Catalyzed by Al Salen Bifunctional Catalyst 17

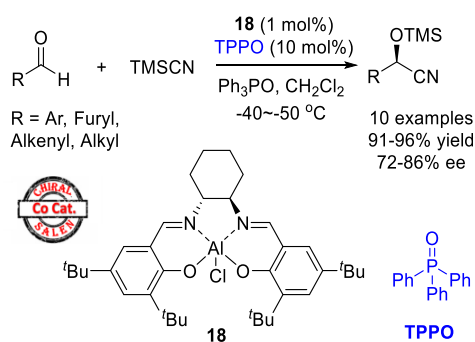


generally more active; but most interestingly, the system delivered opposite enantiomers of the cyanohydrins, with good selectivities in either case. This switching phenomenon was not explained but arises from the differential transition states when dual intramolecular or separate parallel activations take place.

The same methodology was applied with the corresponding aluminum complexes by the same group⁵⁵ in 2012 (Scheme 19).

This metal switch from titanium to aluminum brought a notable boost in selectivity, allowing the bifunctional catalytic

Scheme 20. First Example of (Salen)AlCl Catalyzed Enantioselective Cyanosilylation of Aldehydes with TPPO as Co-catalyst



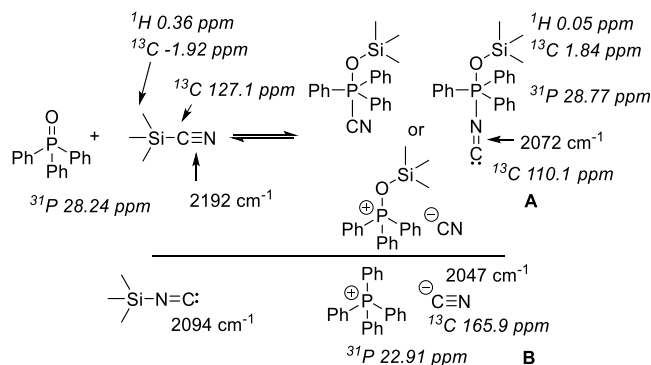
system to perform with better selectivities even at 0 °C, while titanium catalyst **15** was at its optimum at −20 °C.

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

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 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 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.

Scheme 21. Potential Structures Resulting from Nucleophilic Attack of TMSCN by TPPO^a



^aIR in cm^{−1} and ¹H NMR in ppm.

At this stage, it is useful to examine in more detail the exact role of TPPO. From experiments of the different contributors in this section 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.

In a different context, Ryu and Corey⁵⁷ 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 while TPPO loading was increased to 30 mol % and the temperature increased to 25 °C in order to maintain good conversion. Under these conditions,

Scheme 22. (Salen)AlCl Catalyst 19 Based on an Anthracene-Derived Diamine

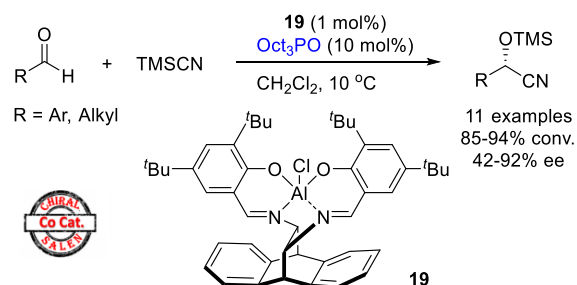
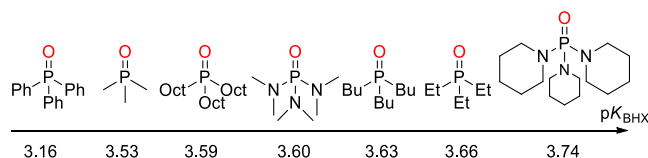


Table 8. Effect of Various Phosphine Oxides as Co-catalysts on the (Anthrax-Salen)AlCl (19) Catalyzed Cyanosilylation of Aldehydes^a

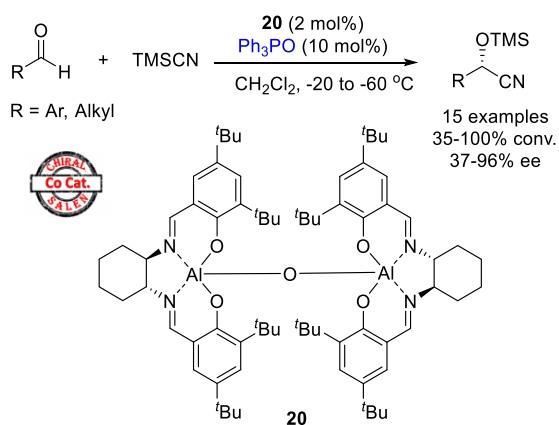
phosphine oxide	yield (%)	ee (%)	pK _{BHX}
Ph ₃ PO	89	81	3.16
<i>n</i> Bu ₃ PO	93	64	3.59
<i>n</i> Oct ₃ PO	93	86	3.63

^aConditions: (anthrax-salen)AlCl, 19 (1 mol %), DCM, 10 °C, 16 h.**Figure 9.** Hydrogen-bond affinity (pK_{BHX}) for a range of phosphine oxides.

yields ranged between 75 and 98%, while ee values were between 60 and 91%. Both works on aldehydes and ketones were reviewed by Kim in 2006.⁶⁰

In 2008, the group of Zhou⁶¹ explored the use of a chiral diaminoethanoanthracene-based salen ligand, again with an Al^{III} Lewis acidic center, 19, Scheme 22.

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 trioctylphosphine oxide (Oct₃PO) as the best co-catalyst, performing better in terms of activity and selectivity. Optimization led to the use of

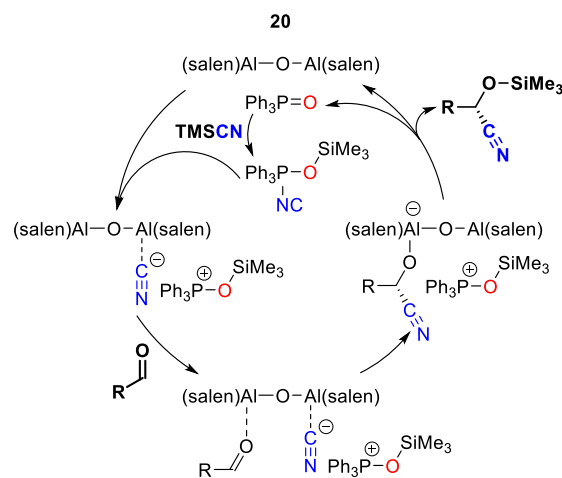
Scheme 23. Cyanosilylation of Aldehydes with Bimetallic Catalyst 20 and TPPO as Co-catalyst

DCM at 10 °C with 1 mol % (anthra-salen)AlCl and 10 mol % Oct₃PO. Preparation of 11 cyanohydrins derived from aldehydes exemplified the procedure, 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

North and Williamson⁶² in 2009 studied the bimetallic aluminum catalyst 20, always in conjunction with TPPO as co-catalyst, to carry out the cyanation of aldehydes (Scheme 23).

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 the TPPO co-catalyst. This suggests a trimolecular process in the rate-determining step of the reaction.

This was further substantiated by the same group⁶³ 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

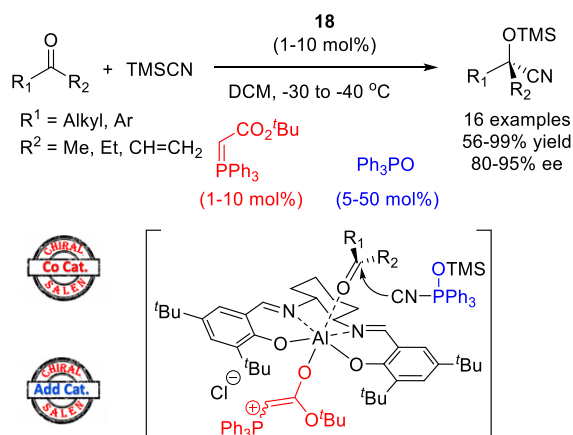
Scheme 24. Proposed Mechanism for the Cyanosilylation of Aldehydes Catalyzed by Bimetallic Catalyst 20 and TPPO

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 section, the dual system aluminum and TPPO is most significantly 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 ensures 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.

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 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 nucleophilic attack then takes place in the chiral environment exerted by the two salen ligands, favoring the formation of one cyanoalcoholate enantiomer. The counteranion, silyloxyphosphonium, finally serves as silylating agent to deliver the TMS cyanohydrin with regeneration of both catalysts.

The group of Zhou⁶⁴ in 2016 developed a cyanation protocol relying on a ternary system, (salen)AlCl 18 (see

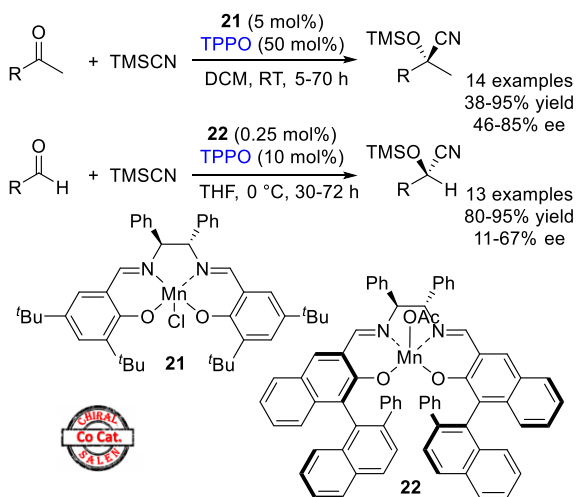
Scheme 25. Cyanosilylation Catalyzed by (salen)AlCl (18), TPPO, and Phosphorane as Co-catalysts



Scheme 20) with TPPO and a phosphorane. After the serendipitous discovery of 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-function-alized Wittig reagent (thus considered as an additive) plus five times this catalyst loading of TPPO (a true cocatalyst), see Scheme 25.

With this very active catalytic triad, a large selection of ketones could be cyanated at low temperature with good

Scheme 26. Enantioselective Cyanosilylation of Ketones and Aldehydes with (Salen)Mn^{III} Catalysts



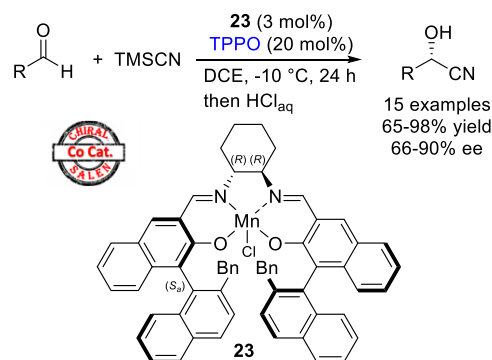
conversions and excellent selectivities. Mechanistic studies were then conducted, and an elegant conductometric approach showed the dramatic effect of the phosphorane, which strongly coordinates the (salen)AlCl complex and led to a cationic species by release of a chloride anion. The resulting aluminum complex is highly electrophilic and can thus strongly activate the ketone moiety by tight coordination.

If we return focus to 2006, the group of Kim also explored the use of manganese complexes **21** and **22** in the

cyanosilylation of carbonyls, first of ketones⁶⁵ and then of aldehydes (Scheme 26).⁶⁶

The 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, being intrinsically more reactive, required far lower catalyst loadings but afforded cyanohydrins with only modest selectivities (11–67% ee),

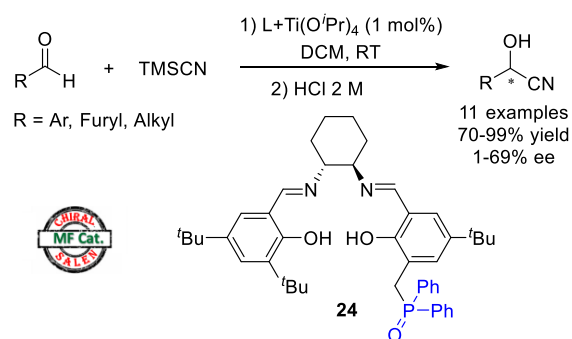
Scheme 27. Cyanosilylation of Aldehydes Catalyzed by Salen Complex 23 and TPPO



probably through the occurrence of unselective background reaction. The authors 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 and mismatched pairs of centered and axial chiralities revealed that the most efficient catalyst possessed benzyl groups at the BINOL tip (see **23** in

Scheme 28. Cyanosilylation of Aldehydes with Bifunctional (Salen)Ti/TPPO Catalyst 24^a



^aAbsolute configuration unspecified.

Scheme 27), bringing chiral information around the metal center, and combined (*R,R*) and (*S_a*) configurations.

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 Lu⁶⁸ demonstrated in 2011 the potential of (salen)Ti^{IV} in cyanations with a bifunctional catalyst (Scheme 28). Catalyst **24** proved nicely active, far more than the classical (salen)Ti(OiPr)₂ with added TPPO, capitalizing on the improvement brought by the synergistic effect of having both promoters on the same catalyst.

If the great acceleration of cyanation in the presence of the bifunctional catalyst by internal Lewis base assistance is undeniable, this system does not compare well with the

Scheme 29. Cyanation with Amine-Functionalized Catalysts 25

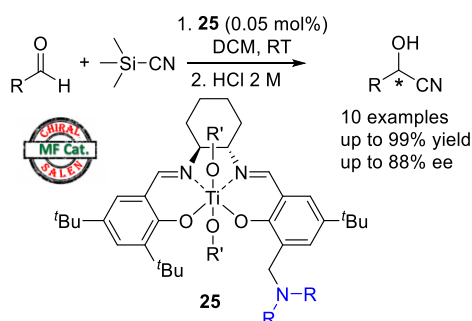


Table 9. Effect of Amines as Co-catalysts on the Cyanosilylation of Benzaldehyde with 25^a

-NR ₂	[amine] (mol %)	time (min)	yield (%)	p <i>K</i> _{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 ^b	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		

^aConditions: ligand + Ti(OiPr)₄, PhCHO, DCM, RT. ^bTBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

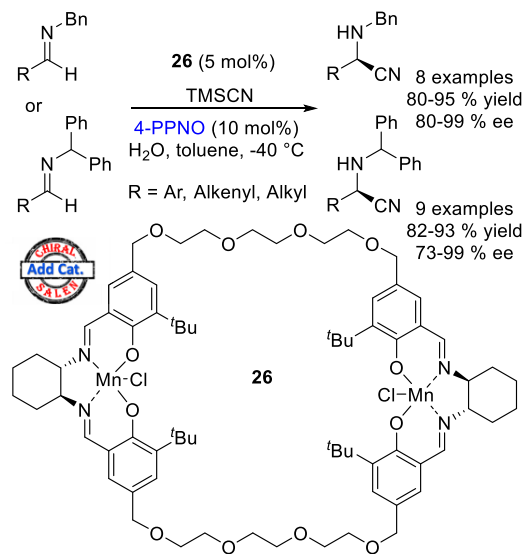
aluminum and manganese complexes, reaching only modest enantioselectivities.

2.5.3. Cyanosilylation with Amines. In a 2011 study, the group of Lu⁶⁹ studied the cooperative catalytic performance 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 exceptional activity at 1 mol % compared to the other tested complexes in the cyanation of benzaldehyde with TMSCN. Optimization allowed the use of 0.05 mol % of this bifunctional promoter with a small array of aldehydes, showing a strong substrate dependence in terms of activity and enantioselectivity (Scheme 29 and Table 9).

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 does not correlate with either nucleophilicity (*N*, kinetic parameter) or Lewis basicity

(p*K*_{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 and deleterious interactions being best balanced in the case of the diethylamino group.

Scheme 30. Asymmetric Strecker Reaction of Benzyl- and Benzhydrylimines with TMSCN Catalyzed by 26 and 4-PPNO as Co-catalyst



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 and selectivity results in cyanoformylation reactions with a bimetallic macrocyclic catalyst with titanium, the group of Khan⁷⁰ exploited the same ligand in the cyanosilylation of *N*-benzylimines and *N*-benzhydrylimines using the bimetallic macrocyclic manganese^{III} complex **26**.

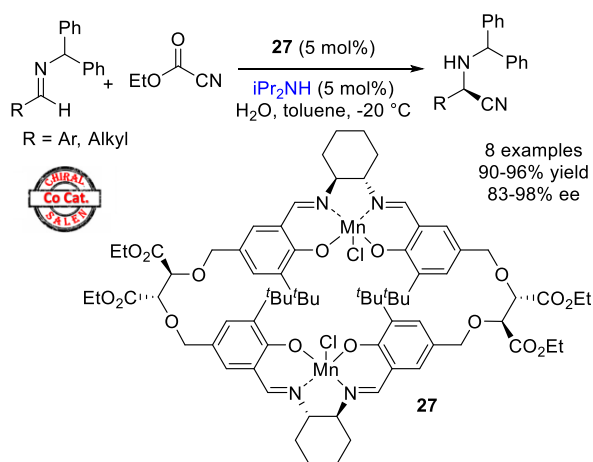
Optimization studies identified catalyst **26** with PEG-3 linkers as the most selective in combination with 4-phenylpyridine *N*-oxide (4-PPNO) as co-catalyst. A small array of benzyl- and benzhydryl-imines were reacted, preparing aminonitriles in enantioenriched forms with excellent yields and selectivities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

Kinetic measurements showed first-order dependence on both substrates (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

Table 10. Effect of *N*-Oxide Co-catalysts on the Asymmetric Strecker Reaction with Complex **26**^a

Lewis base	yield (%)	ee (%)	p <i>K</i> _{BHX}
none	73	70	
PyrNO	70	74	2.72
4-PPNO	80	79	2.85
Ph ₃ PO	62	61	3.16
4-Pr-PyrNO	59	62	(3.12)

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

Scheme 31. Asymmetric Strecker Reaction with Benzhydrylimines and Ethyl Cyanoformate Catalyzed by Complex **27**

by the larger quantity of cyanide ion then released in the solution.

It can be noted that among the co-catalysts tested, the most Lewis basic one (according to its p*K*_{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.

Table 11. Effect of Brønsted Bases as Co-catalysts in the Asymmetric Strecker Reaction with Bimetallic Complex **27**^a

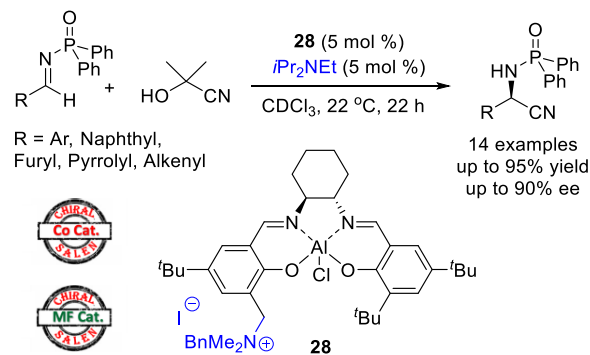
base	yield (%)	ee (%)	p <i>K</i> _{BHX}	p <i>K</i> _a
none	57	79		
ImH	83	73	2.42	15.05
2,6-lutidine	95	62	2.14	13.92
iPr ₂ NH	95	87	2.00	18.81
NEt ₃	98	65	1.98	18.82

^aConditions: (salen)Mn catalyst **27** (10 mol %), toluene, −20 °C, 8 h.

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).

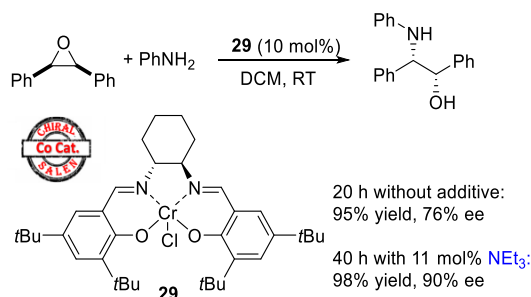
Excellent conversions and enantioselectivities could be obtained with various *N*-benzhydrylimines, efficiently deliver-

ing 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 sections 2.1–2.4. The water slowly hydrolyzes the cyanoform-

Scheme 32. Catalytic Asymmetric Hydrocyanation of *N*-Phosphinoyl Aldimines with Complex **28** Bearing an Appended Ammonium Salt

mate reactant to liberate cyanide anions, probably with Brønsted-base assistance from the amine (Table 11).

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 byproduct) to phosphinoyl aldimines (as storable and easily deprotected imine precursors). After optimization of the catalytic system, that is, 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 cyanohydrin, 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 33. Anilinolysis of Epoxides Catalyzed by Complex **29**

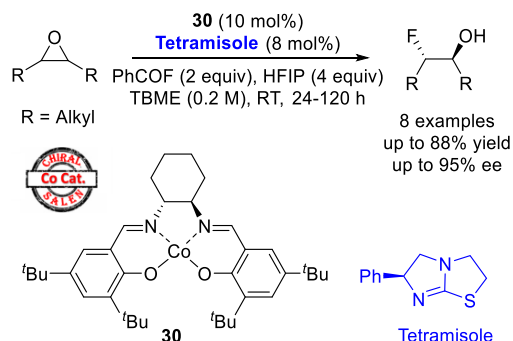
The authors proposed here again that the imine electrophile was activated by the Lewis acidic aluminum center and the cyanide anion by the ammonium moiety, allowing for efficient control of its attack on the imine thus leading to enantiofacial differentiation. They also proved that the generated conjugated 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

Scheme 34. Enantioselective Fluoride Ring Opening of *meso*-Epoxides Using a Cooperative Dual-Catalyst System



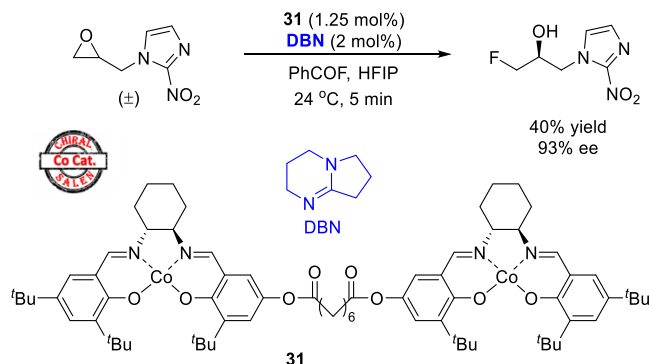
(salen)Cr^{III} complex **29**, Bartoli, Melchiorre, and co-workers⁷² noted that in the case of *meso*-stilbene, catalytic amounts of triethylamine dramatically increased the selectivity, at the expense of a prolonged reaction time (Scheme 33).

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

In 2010, Kalow and Doyle⁷³ then developed a highly enantioselective fluoride ring opening of *meso*-epoxides using a 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). With application of this effective method to the ring opening of various *meso*-epoxides, a series of products can be obtained in excellent yields and ee values.

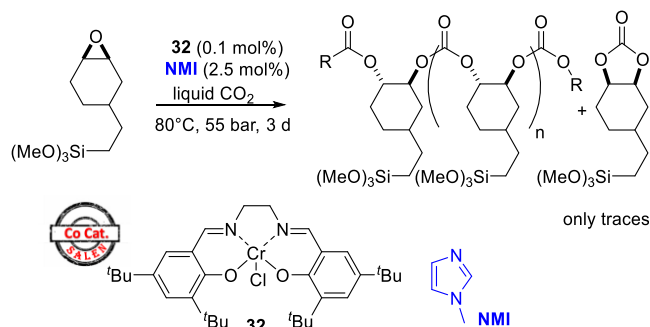
In 2011, the same group⁷⁴ reported mechanistic studies of this transformation. The authors investigated the kinetics, substituent effects, nonlinear effects, and reactivity of this system. Interestingly, they observed a strong match/mismatch effect; as the combination of (salen)Co^{II} **30** with (–)-tetramisole gives very high conversion and ee on a model cyclic *meso*-epoxide (88% conv, 95% ee) while the use of the (*S,S*)-

Scheme 35. Synthesis of Fluoromisonidazole Using Dimeric Catalyst (*R,R,R,R*)-31** and DBN**



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 1,5-diazabicyclo(4.3.0)non-5-ene (DBN) for the production of

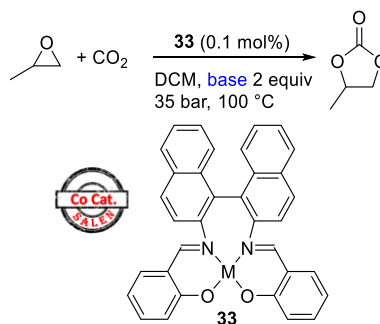
Scheme 36. (Salen)Cr^{III}/N-Methylimidazole Catalyzed Copolymerization of Epoxide with CO₂



a known PET tracer, fluoromisonidazole (F-MISO) with a high ee value of 93% in only 5 min (Scheme 35).

3.1.2. Reaction of CO₂ with Epoxides. In recent years, carbon dioxide (CO₂) has attracted widespread attention as a nontoxic, nonflammable, 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 a 100% atom-economic cycloaddition reaction between epoxides and CO₂ is one of the most promising reactions for the simple and economical

Scheme 37. Carbonate Formation from Propylene Oxide Catalyzed by *rac*-Binam Salen Complex **33 and Nitrogen Bases**



fixation of CO₂. In this context, the development of efficient enantiopure catalytic systems for their enantioselective preparation is currently very timely.

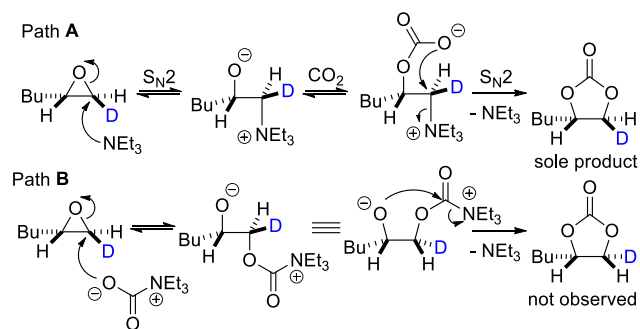
The first use of a combined catalytic system was reported by Darensbourg et al.⁸⁰ with the copolymerization of an epoxide

Table 12. Effect of Base Co-catalyst on Carbonate Formation from Propylene Oxide and CO₂^a

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

^aConditions: 0.1 mol % catalyst, 0.2–1.0 mol % organic base, CH₂Cl₂, RT.

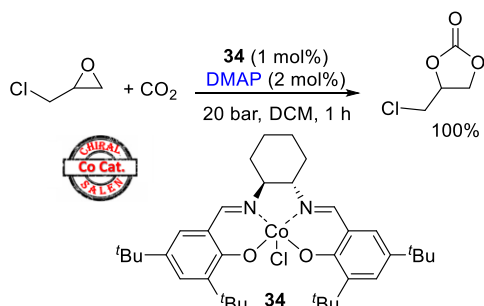
with carbon dioxide in the presence of an achiral (salen)Cr^{III} complex **32** and *N*-methylimidazole (Scheme 36).

Scheme 38. Carbonate Formation from a Deuterated Epoxide

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 Shi⁸¹ 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).

First, it was shown that the Lewis acid or the base alone could not promote the transformation. In all the tested combinations, triethylamine appeared as the most potent base,

Scheme 39. Carbonate Formation from Epichlorohydrin with CO₂ Promoted by Complex **34 and DMAP**

together with the zinc or the cobalt complex, DMAP being just below (see Table 12).

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

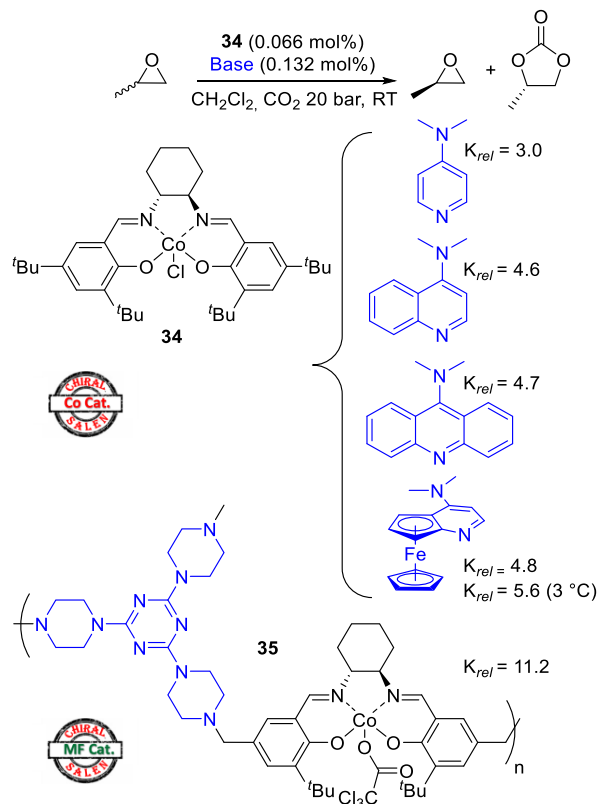
Hence, between the two possible reaction scenarios, only path A matches the experimental result, that is, global retention of configuration. The reaction would thus occur with initial

Table 13. Effect of Bases as Co-catalysts on Carbonate Formation from Propylene Oxide and CO₂^a

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

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

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 attack takes 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.

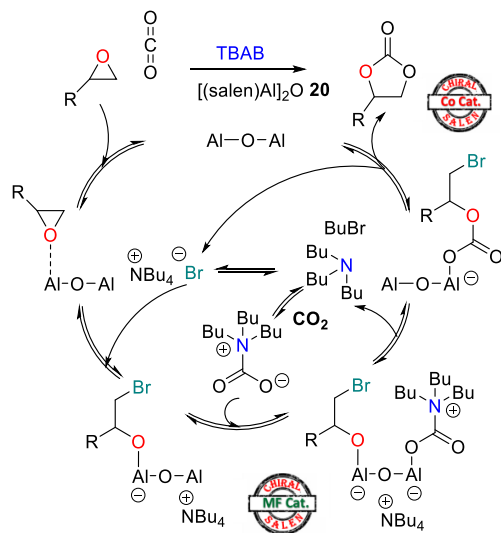
Scheme 40. Kinetic Resolution of Propylene Oxide with CO₂ Promoted by Complexes **34 and **35** with Various Bases**

In 2004, Paddock and Nguyen⁸² extended this study using a chiral (salen)Co^{III} complex, **34**, and a small series of nitrogen bases (Scheme 39).

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.

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 CO₂ by running the reaction at low

Scheme 41. Kinetic Resolution of Propylene Oxide with CO₂ Promoted by a Bimetallic (Salen)Al Complex **20** in the Presence of TBAB



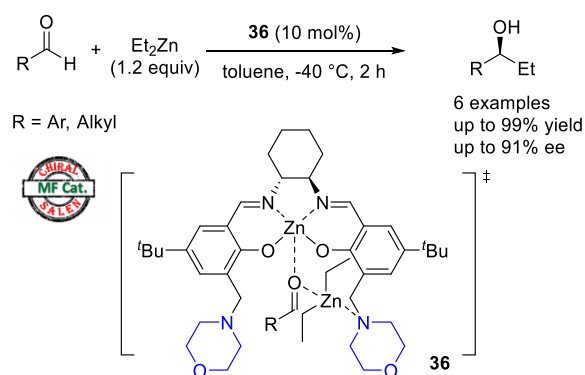
temperature with chiral DMAP, with selectivity factors of up to *s* = 5.6 obtained, but at the cost of a dramatically reduced TOF.

As shown by the authors, 2 equiv 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 to act as a nucleophile to ring open the epoxide.

Almost ten years later, Kureshy's group⁸³ employed a polymeric (salen)Co^{II} complex **35** linked by triazine-piperidine moieties for the same reaction, hence constituting a bifunctional and chiral catalyst containing the Lewis acid and Lewis basic centers (see Scheme 40). The best selectivity value was obtained with CCl₃COO[−] as a bulky axial ligand when the reaction was run at low temperatures and atmospheric pressure of CO₂. 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 colleagues⁸⁴ to promote the same kinetic resolution at room temperature under atmospheric pressure of CO₂ in the presence of tetrabutylammonium bromide (TBAB) as co-catalyst (Scheme 41). Although TBAB is not a Lewis base *per se*, 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

Scheme 42. Enantioselective Catalytic Addition of Diethylzinc to Aldehydes Using Catalyst **36** Containing Morpholine Groups and Proposed Transition State



in the absence of tributylamine in the system, almost no conversion was observed.

Table 14. Effect of Nitrogen Bases on the Enantioselective Catalytic Addition of Diethylzinc to Benzaldehyde^a

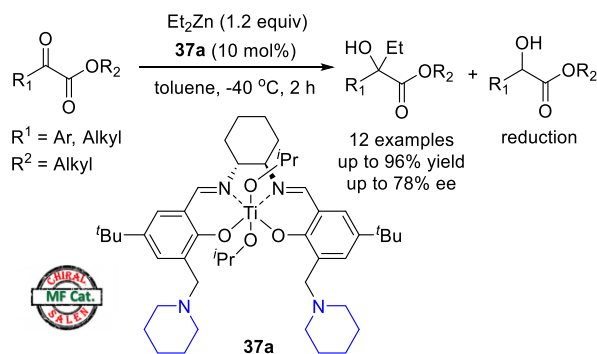
R group	conv (%)	ee (%)	p <i>K</i> _a	p <i>K</i> _{BHX}
2-pyridine	99	51	5	2.03
piperidine	90	76	9	2.11
morpholine	72	77	6	1.56
diMe-piperidine	33	73	9	?
N(<i>i</i> Pr) ₂	5	52	9	1.05
<i>t</i> Bu	2	57		

^aConditions: 10 mol % corresponding catalyst, 2.1 equiv of Et₂Zn, 30 °C, 6 h.

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 that contain both a Lewis acid center and Lewis basic moieties that showed a powerful effect, especially for organozinc addition onto carbonyl compounds.

Scheme 43. Addition of Diethylzinc to Ketoesters Using Complex 37a Containing Appended Piperidine



In 2001, Kozłowski et al.^{89,90} developed a new class of catalysts that demonstrate excellent reactivity and good enantioselectivity for the addition of diethylzinc to aldehydes. With application of the modular bifunctional (salen)Zn catalyst **36** to this reaction, an apical coordination site on

Table 15. Effect of Bases as Co-catalysts on the Diethylzinc Addition to PhCOCO_2Et Using Complex **37a**^a

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
diMe-piperidine	10	84	20
7-quinoline	5	57	7
<i>t</i> Bu salen	20	56	4
<i>t</i> Bu salen + NMM	15	56	2
NMM	30	14	0

^aConditions: 1.2 equiv of Et_2Zn , cat. **37a** (10 mol %), -40°C , 2 h.

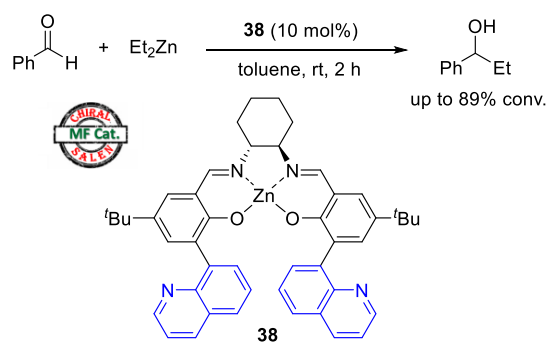
the salen metal center could act as a Lewis acid site to activate the aldehyde while the tethered base could independently activate the Et_2Zn nucleophile (Scheme 42).

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

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. Bifunctionality was demonstrated via a test reaction with a mixture of *N*-methylmorpholine and the unsubstituted (salen)Zn complex, showing no conversion at all.

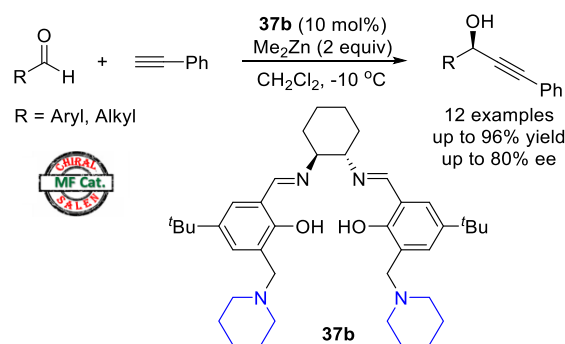
In 2002, DiMauro and Kozłowski^{91,92} developed an extension of this reaction to ketoesters using the same type of Lewis acid/Lewis base system but with (salen)Ti complexes as catalysts. With α -ketoesters, the development of selective alkylation is complicated due to a competing reduction pathway (Scheme 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 44. Addition of Diethylzinc to Aldehydes Using (Salen)Zn Complex 38 Containing a Quinoline Base^a



^aChiral induction was not reported.

Scheme 45. Asymmetric Addition of Phenylacetylene to Aldehydes Catalyzed by *in Situ* Generated (Salen)Zn Complex from Ligand 37b



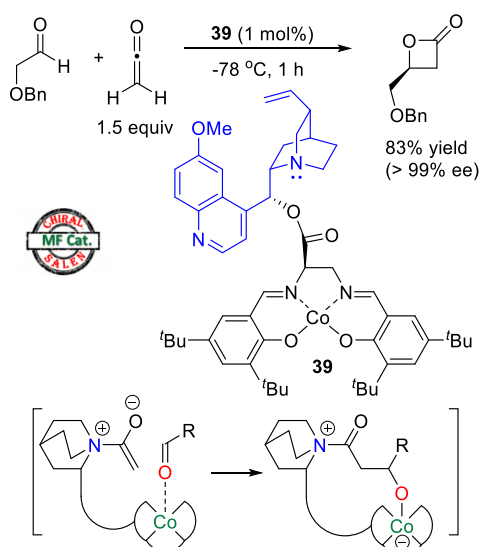
The nature of the appended base greatly influences the outcome of the reaction, with various amounts of reduction and various selectivities (Table 15).

Again, the bifunctionality is crucial since the mixture of a native (salen)Zn with added *N*-methylpiperidine gives very low conversion, close to the reaction background. It is worth noting 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, Kozłowski and co-workers⁹³ 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 h at room temperature; however, eventual enantioselectivity was not discussed (Scheme 44).

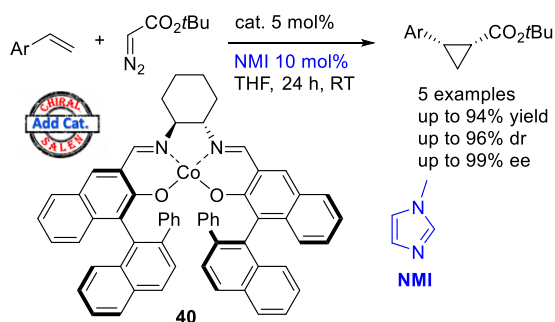
These bifunctional complexes were later exploited to catalyze the addition of alkynylzinc reagents to aldehydes thus giving access to propargyl alcohols, which are versatile building blocks for a wide range of biologically active compounds and pharmaceuticals.^{94,95} Hence, Xu and co-workers⁹⁶ developed an asymmetric alkynylation procedure of aldehydes using the bifunctional (salen)Zn catalysts developed by Kozłowski (Scheme 45). Similarly, in this system, the 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

Scheme 46. Cycloaddition of Aldehydes and Ketene Catalyzed by Complex 39



observed with 10 mol % of the (salen)Zn catalyst bearing two piperidinylmethyl groups at C-3 and C-3' positions in dichloromethane at $-10\text{ }^{\circ}\text{C}$. 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 47. Enantioselective Cyclopropanation of Styrenes



3.1.4. β -Lactone from Ketenes. Lin and co-workers⁹⁷ in 2007 developed a bifunctional catalyst, ensuring 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 β -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 was 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.

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

Scheme 48. Enantioselective Cyclopropanation by (Salen) Co Complex 30 and NMI as Co-catalyst

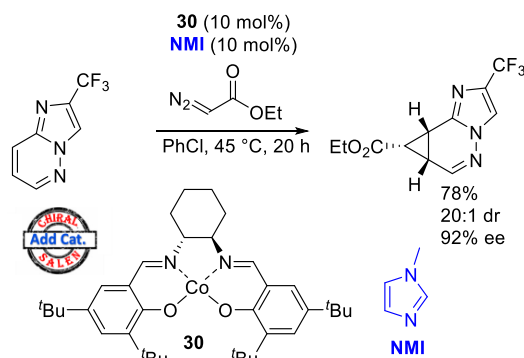


Table 16. Effect of Additives on the Asymmetric Cyclopropanation Catalyzed by Complex 30^a

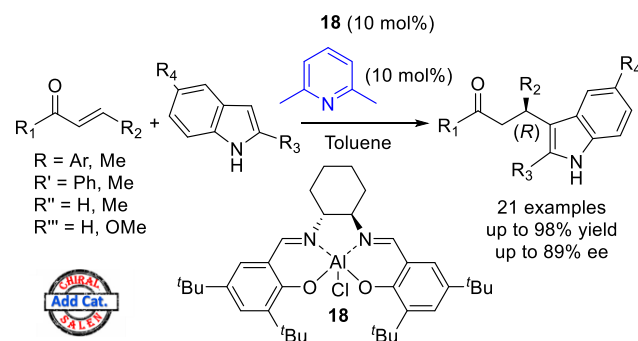
additive	conversion (%)	ee
none	30	76
imidazole	68	78
<i>N</i> -methylimidazole	100	92
<i>N</i> -butylimidazole	100	92
thiazole	95	86
pyridine	92	84
DMAP	100	86

^aConditions: 15 mmol % 30, 15 mol % base, chlorobenzene, 45 $^{\circ}\text{C}$, 2 h.

3.1.5. Cyclopropanation. In 2000, Katsuki and colleagues^{98,99} were the first to report 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 the presence of *N*-methylimidazole (NMI) as additive (Scheme 47), following previous results with different cobalt complexes.¹⁰⁰

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

Scheme 49. Stereoselective Addition of Indoles to (*E*)-Enones Catalyzed by Complex 18 with 2,6-Lutidine



Chen et al. 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 NMI was used as an additive (Scheme 48).

The authors did not comment on the exact role of the basic additive, but it seemed to act as an apical ligand for the cobalt(II) center, providing an octahedral complex with

Table 17. Effect of Additives on the Catalytic Stereoselective Addition of Indoles to (*E*)-Enones^a

base	yield (%)	ee (%)	pK _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

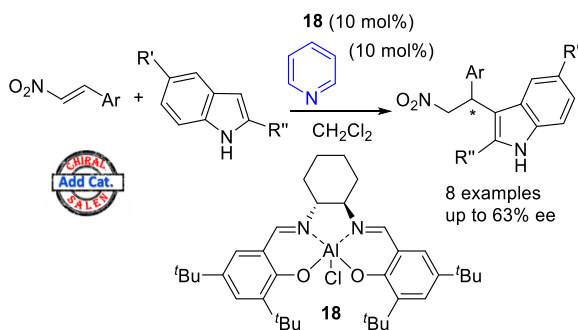
^aConditions: (salen)AlCl (5 mol %), toluene, 48 h, RT. Values in parentheses were extrapolated from very similar compounds.

increased activity and a more enantiodifferentiative geometry (Table 16).

Only marginal differences were observed based on 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 with catalytic amounts of amines. 2,6-Lutidine was initially added as a Brønsted base in

Scheme 50. Stereoselective Alkylation of Indoles with Nitroalkenes Catalyzed by Complex **18 with Pyridine**



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 base additives revealed that 2,6-lutidine was the best (Scheme 49).

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} and 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).

As previously seen, interactions between the coordinating base and the aluminum complex were 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 nitroolefins.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 CH₂Cl₂ among a variety of bases.

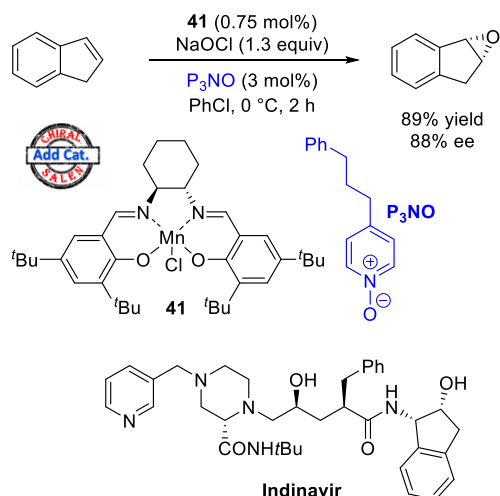
3.2. Metallo-salen and *N*-Oxides

3.2.1. Alkene Epoxidation. The epoxidation of alkenes is probably one of the catalytic transformations promoted by enantiopure metallic salen complexes that benefited most significantly 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 nonfunctionalized olefins was discovered independently in 1990 by the groups of Jacobsen² 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) were also shown by the group of Jacobsen. Significant increase in enantioselectivity was observed in the epoxidation of *cis*-ethyl cinnamate, in the 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 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 in the active species by coordination to the unsaturated Mn^{III} species, hence minimizing formation of the inactive dimer.

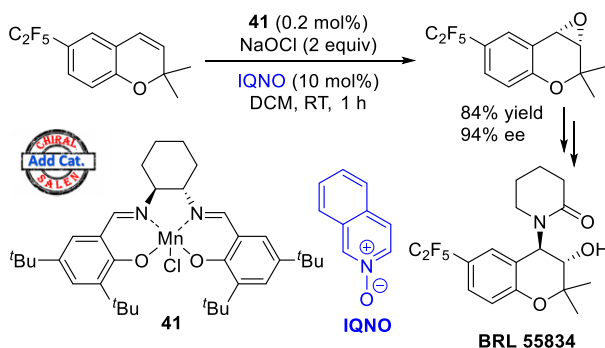
Several studies were further devoted to the understanding of the mechanism of this one oxygen atom transfer from the

Scheme 51. Asymmetric Epoxidation of Indene Catalyzed by **41** with P_3NO as a Catalytic Additive



(salen) $Mn^V(=O)$ complex to the olefin, involving either radical¹¹⁶ or metallaoxetane intermediates,¹¹⁷ which remained much debated.^{118,119} Furthermore, in the presence of neutral donor ligands, the stereoselectivity of the reaction has been shown to be dependent on the nature of the terminal oxidant.¹²⁰

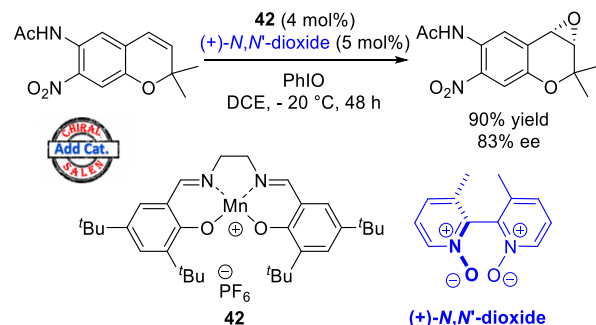
Scheme 52. Asymmetric Epoxidation of a Chromene Derivative Catalyzed by Complex **41** with IQNO as an Additive



Interestingly, two independent studies, conducted by industrial groups, explored the contribution of donor ligand 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 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 enhancement of the initial reaction rate and minimization of catalyst decomposition as demonstrated by HPLC measurements. With the help of IR studies, the authors suggested 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 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

Scheme 53. Asymmetric Epoxidation with Achiral (Salen) Mn Complex **42** Catalyst and an Enantiopure Additive



assisting the transport of the oxidant to the organic layer in this biphasic system (which makes it a co-catalyst).¹²² The reaction depicted in Scheme 51 could hence be successfully realized on a multi-kilogram scale.

At the same time, researchers from SmithKline Beecham Pharmaceuticals tackled the epoxidation of chromene derivatives toward the preparation of BRL 55834, an airway-selective potassium channel activator.¹²³ They discovered that the use of isoquinoline N -oxide (IQNO, see Scheme 52) as a donor ligand allowed reduction of the catalytic charge drastically while maintaining excellent efficiency. In its absence, both reaction rate and enantioselectivity values decreased according to the catalytic loading, and 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 center 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.

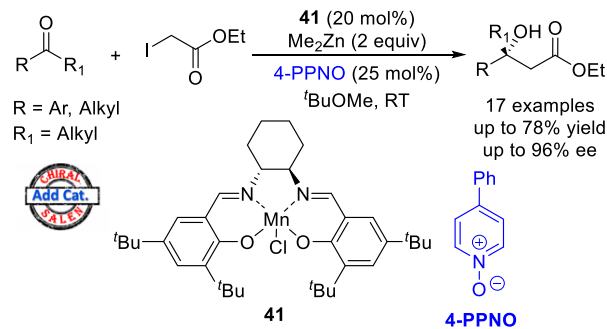
The fundamental role of the additive was demonstrated by the group of Katsuki,^{124,125} who were able to perform enantioselective epoxidations catalyzed with achiral (salen) Mn complex **42** in the presence of an enantiopure amine oxide, 3,3'-dimethyl-2,2'-bipyridine N,N' -dioxide, as a chiral additive. 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

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 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 (NMO) 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 nonfunctionalized olefins in the presence of NMO.¹³¹ Other supports such as zirconium phosphates and zirconium phosphonates were successfully used for (salen)Mn complex immobilization, which was 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 one.¹³² Chiral (salen)Mn complexes not only were anchored on pre-existing supports but also were specifically functionalized toward 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 nonfunctionalized 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 Enantiomeric excess 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 achievement of size- and shape-selectivity by exploiting their respective well-defined channels and pores.^{136,137} Even more recent developments include the modification of highly stable 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 amino alcohols 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 longer 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 occurred successfully, and the mixed species (Cr/Mn-COFs) also led to almost enantiopure amino alcohols by sequential epoxidation and aminolysis. These very recent, nonexhaustive 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 used. Thus, the preparation of

Scheme 54. Catalytic Enantioselective Reformatsky Reactions Promoted by **41** and 4-Phenylpyridine *N*-Oxide

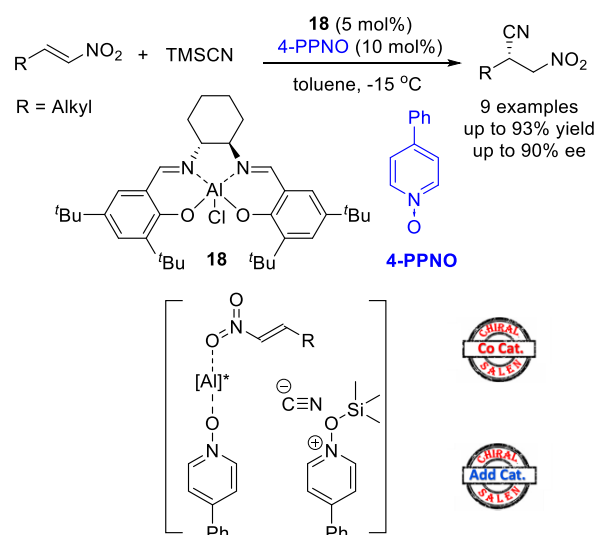


these crystalline networks, with perfect control of the location of the active sites, leading to their compartmentalization and preventing bimetallic inhibition, allowed very efficient enantioselective epoxidation reactions, avoiding furthermore the use of supplementary additives since the MOF architecture itself ensures 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}

Of interest in this review is the methodology reported by Cozzi¹⁴⁵ 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 occurred under mild conditions, which was 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 the presence of 4-phenylpyridine *N*-oxide enantioselectivity of this Reformatsky reaction was substan-

Scheme 55. Asymmetric Hydrocyanation of Nitroolefins Catalyzed by Complex **18** and 4-PPNO



tially 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 directly converted to give the desired products in up to 78% yields and 96% ee (Scheme 54).

Optimization efforts made by the authors did not include 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.

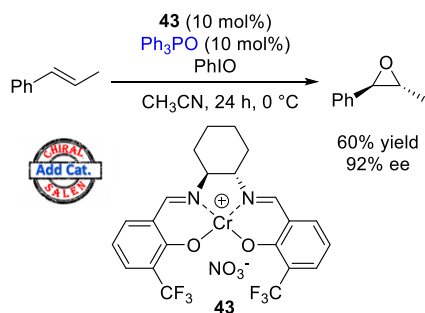
Table 18. Effect of Additives on the Catalytic Stereoselective Hydrocyanation of Nitroolefins by Complex 18^a

additive (10 mol %)	yield (%)	ee (%)	pK _{BHX}
Ph ₃ P	0	0	(0.68)
iPrOH	0	0	1.06
pyridine-NO	85	71	2.72
4-PPNO	93	76	2.85
Ph ₃ PO	51	73	3.16
NMO	40	45	(5.05)

^aConditions: AlCl(salen) (5 mol %), toluene, RT. Values in parentheses are estimated from a very similar compound.

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

Scheme 56. (*E*)-Alkene Epoxydation with Cationic Complex 43 and TPPO



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 base-mediated polymerization, a reactivity pitfall explaining why only four examples of asymmetric cyanide addition to nitroolefins are reported in the literature, be it organo-catalyzed^{149,150} or catalyzed with a salen complex alone.¹⁵¹

In 2014, Khan and co-workers¹⁵² developed an asymmetric hydrocyanation of nitroolefins catalyzed by (salen)aluminum(III) complex 18 in the 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 insight into the reaction mechanism. A synergistic effect of complex 18 together with 4-PPNO was shown in this asymmetric catalytic system, where the *N*-oxide plays a dual role, as it acts as an axial ligand but

Table 19. Effect of Additives on the Enantioselective Epoxidation Promoted by Salen Complex 43^a

additive	ee (%)	pK _{BHX}
none	90	
DMF	67	2.10
DMSO	86	2.54
pyridine-NO	85	2.72
Ph ₃ PO	92	3.16

^aConditions: 39 (1 equiv), PhIO (1–2 equiv), CH₃CN, additive (1 equiv), 0 °C, 1.5 h.

Table 20. Effect of Complex 43 Counterion on the Catalytic Enantioselective Epoxidation^a

X [−]	ee (%) without TPPO	ee (%), TPPO 10 mol %	Δ ee	a^{TM}
NO ₃ [−]	90	92	+2	0.0
TrfO [−]	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

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

also activates the cyanide source (TMSCN), which makes it both an additive and a co-catalyst.

Interestingly, increasing the 4-PPNO loading to 15 mol % or decreasing it to 5 mol % induced an erosion of the ee, showing that 10 mol % is optimal 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 Gilheany¹⁵³ investigated 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, whereas Katzuki–Jacobsen manganese-based catalysts are superior with (*Z*)-alkenes. First, 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

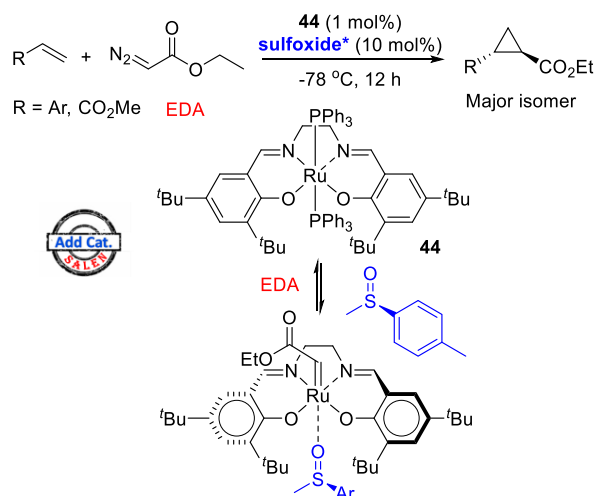
This twisting effect, improving the enantioselectivity, seems to be directly correlated to the Lewis basicity, as measured by the hydrogen-bond acceptor ability, pK_{BHX} (Table 19). Moreover, the ligand effect depends on the metal center acidity as given by the a^{TM} value (coordination ability toward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

The discrepancies in the Δ ee/ a^{TM} correlation probably arise from additive/anion competing equilibria.

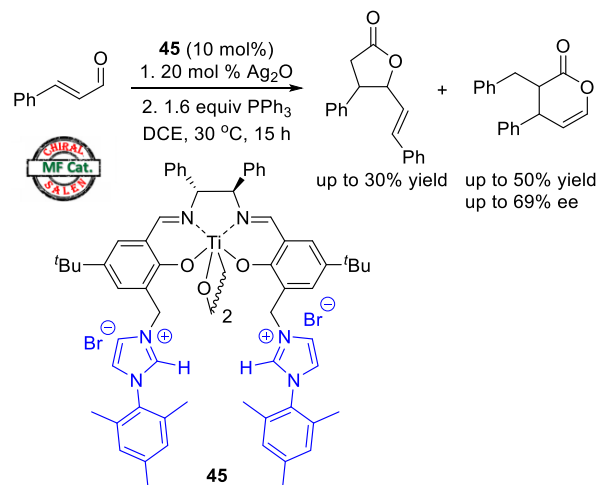
3.4. Metallo-salen and Sulfoxides

(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-workers¹⁵⁸ described the first example of asymmetric cyclopropanation mediated by the

Scheme 57. Olefin Cyclopropanation with Achiral Ru^{II} Complex 44 Using Chiral Sulfoxides



Scheme 58. Synthesis of Enol- δ -lactones by Cooperative NHC/(Salen)Ti/Ag Catalysis with Precatalyst 45



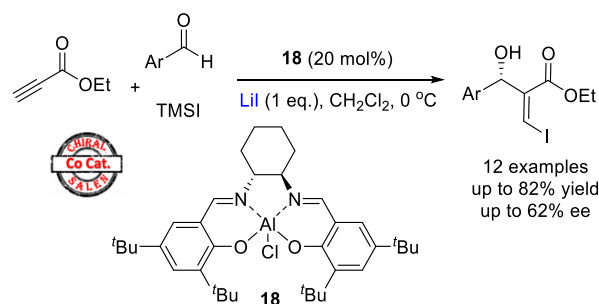
combination of achiral (salen)Ru^{II} catalyst **44** and a catalytic amount of enantiopure sulfoxide additives, which were chosen as chiral ligands for the metal center. In this system, the sulfoxide Lewis base controls the chirality of the active species by forcing the achiral salen complex into an 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 % (*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).

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 $K_{eq} = 129 \pm 6 \text{ M}^{-1}$) 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-workers¹⁶⁰ 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 an 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 PPh₃. These precatalysts **45** catalyzed the Stetter-type formation of enol- δ -lactone as the main product rather than the expectable γ -

Scheme 59. Asymmetric Catalytic Synthesis of β -Halo-MBH Ester Adducts Catalyzed by Complex 18



lactone. This actually constitutes a new reactivity in the dimerization of enals, and it proceeds 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 PPh₃ 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.

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 by the silver ion at the alkene π -system.

3.6. Metallo-salen with Halides

We here touch at the border for this review, since mineral halides do not strictly belong to the field of organocatalysis, the interest of the work justify this addition here. Li and co-workers¹⁶¹ 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 group¹⁶² 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 60. Carbonate Formation from CO₂ and Epoxides with Catalyst 46 and a Phosphorane Additive

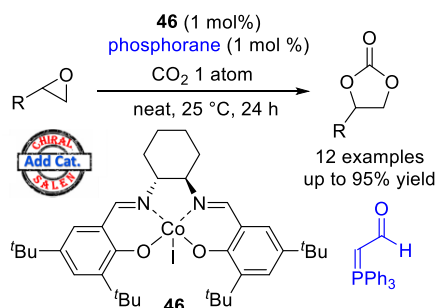


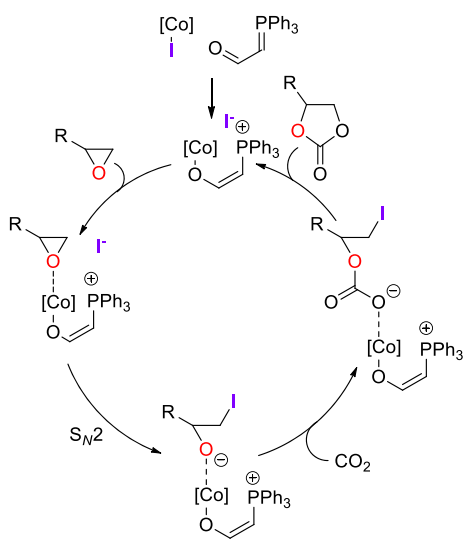
Table 21. Effect of Phosphorane Additives in the Synthesis of Carbonates from Epoxides and CO₂^a

Ph ₃ P=CH-R Phosphorane	Conv. (%)	σ _p ¹⁶⁴
none	0	-
R = CO ₂ Et	trace	0.45
R = Ph	trace	0.43
R = Me	9	0.50
R = H	27	0.42

^aConditions: (salen)AlCl (2.5 mol %), phosphorane (2.5 mol %).

Addition of lithium iodide was found to be beneficial for both the reaction rate and the chemical yield. Screening of the reaction conditions revealed that 20 mol % chiral (*R,R*)-(salen)AlCl and 1 equiv 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

Scheme 61. Proposed Mechanism for the Catalytic Synthesis of Carbonates with 46 and a Phosphorane Additive



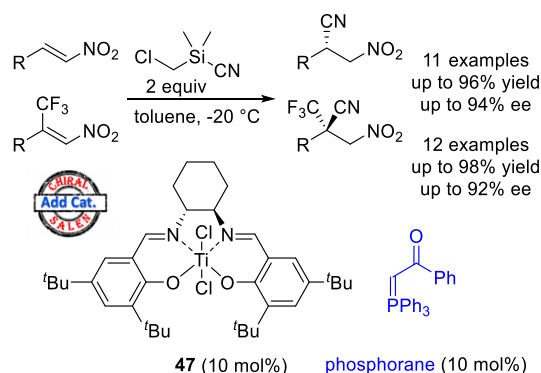
and form a transient iodo-allenoate, which subsequently attacks the aldehyde under electrophilic activation by the aluminum catalyst; final silylating quench of the aldolate anion by TMSI liberates an iodine ion, which is thus regenerated. This new catalytic system showed good substrate scope in which 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 Zhou¹⁶³ made an unconventional use of Wittig reagents in the preparation of cyclic carbonates from epoxides with incorporation of carbon dioxide. The most

Scheme 62. Hydrocyanation of Nitroalkenes with 47 and Phosphorane Additive

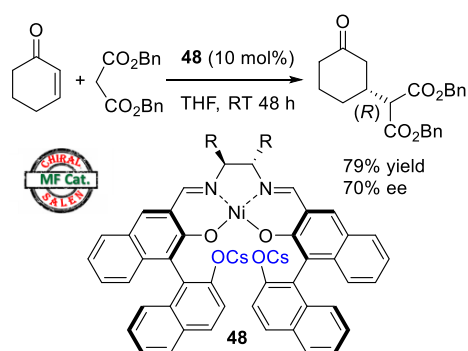


efficient system relies on (salen)Co-I 46 and (triphenylphosphoranylidene)acetaldehyde (Scheme 60).

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).

The crucial role of the halide counterion was also revealed while comparing (salen)CoX differential efficiencies in the process, the conversion increasing from 50% to 80% and then to 100% in the Cl, Br, and 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 63. Bifunctional Ni Salen Naphthoxide Catalyst in the Enantioselective Michael Addition Reaction



The zwitterionic, 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.

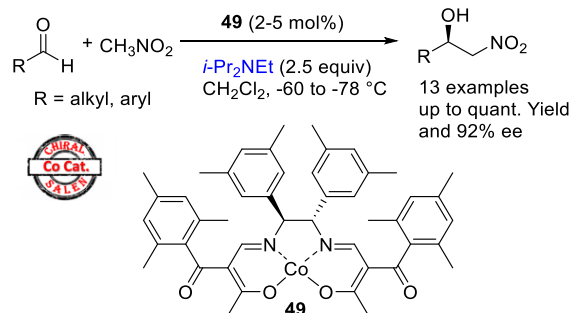
The same synergistic combination of a salen complex with a phosphorane was then exploited by the same group¹⁶⁵ to perform highly enantioselective hydrocyanations of nitroalkenes.

For this transformation, optimization led to identification of the (salen)TiCl₂ **47** as the best catalyst, in combination with the phenyl-substituted phosphorane additive as ligand, leading to highly effective conversions and selectivities (Scheme 62).

4. METALLO-SALEN AND BRØNSTED BASES

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

Scheme 64. Henry Reaction Catalyzed by Complex **49**



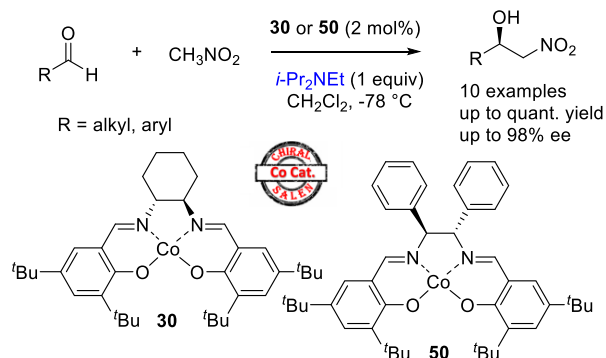
4.1. Addition of Malonates to Enones

The enantioselective addition of benzyl malonate to enones was investigated by DiMauro and Kozlowski.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-Cs₂ catalyst **48** (R = Ph) gave the best results.

The optimal “matched” combination of chiralities on the two active sites (salen and BINOL) was identified, allowing the reaction 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 attacks 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-workers¹⁶⁷ then reported in a second paper an extension of their initial study. Other well-

Scheme 65. Catalytic Enantioselective Henry Reaction with Complex **30** or **50** and DIPEA



characterized salen metal complexes incorporating two chiral BINOL moieties were synthesized and used as Lewis acid/

Table 22. Influence of Bases as Additives on the Catalytic Enantioselective Henry Reaction^a

base	yield (%)	ee (%)	pK _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

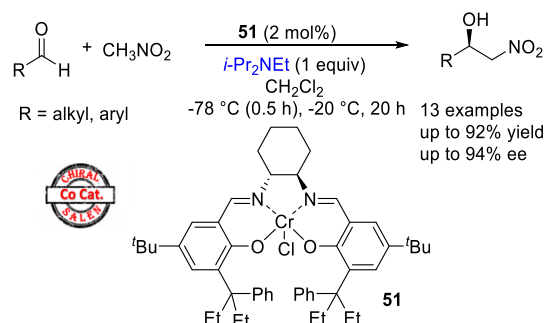
^aConditions: 2 mol % SalenCrCl, 1 equiv of base, CH₂Cl₂, −78 °C. pK_a given in ACN, except for DABCO and quinine in DMSO, and DIPEA in THF.

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 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,

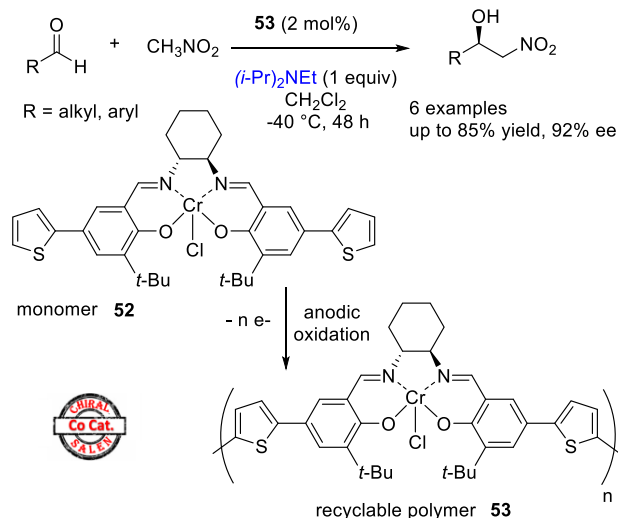
Scheme 66. Henry Reaction with Catalyst **51** with Very Congested 2,2' Positions



primary, secondary, 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 aldolization is then protonated by the ammonium salt of *N,N*-diisopropylethylamine (DIPEA). This bicatalytic system could be applied to a large variety of aldehydes.

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

Scheme 67. Chiral Thiophene (Salen)Cr Catalysts **52 and **53** Developed by Schulz and Co-workers¹⁷²**



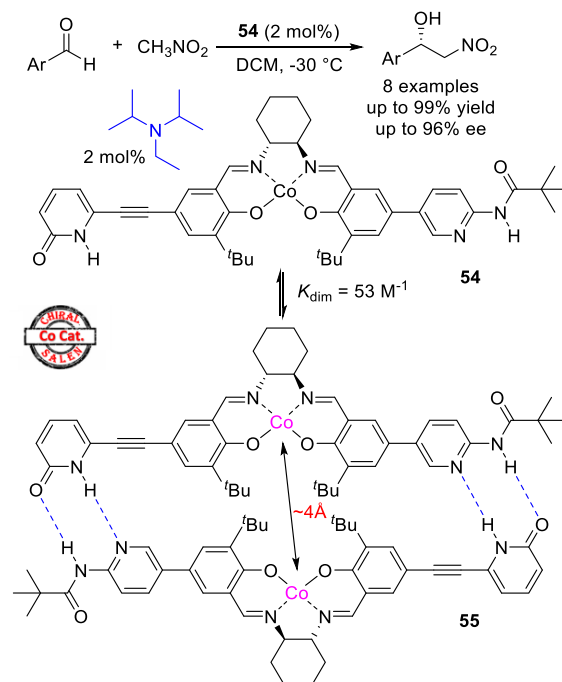
Examination of several salen-cobalt complexes revealed that the commercially available Jacobsen (salen)Co^{II} complex **30** and its derivative **50**, bridged by 1,2-diphenylethane-1,2-diamine worked best in this reaction. The role of the base was not discussed nor the choice of this tertiary amine.

Three years later, the group of Skarzewski¹⁷⁰ 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).

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 group¹⁷¹ later extended their studies on asymmetric Henry reactions, with broader optimization, 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 when the catalyst 2,2'-positions bear $C(Et_2)Ph$ 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

Scheme 68. Self-Assembled (Salen)Co **55, Catalyzing Asymmetric Henry Reaction in the Presence of DIPEA as Co-catalyst**

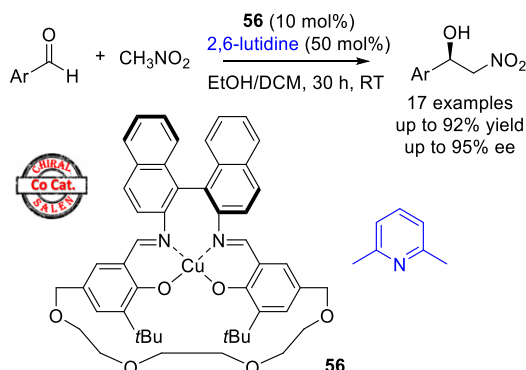


reports, a stoichiometric amount of DIPEA was used combined with only 2 mol % of chromium complex to produce the nitro alcohols in up to 92% yield and 94% ee.

About the same time, chiral thiophene-salen chromium complexes were investigated in the enantioselective Henry reaction, in both their monomeric and polymeric forms, by Schulz and co-workers.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).

The desired nitroaldols were obtained with enantiomeric excesses up to 92%. 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 excess up to 77%. The polymerized catalyst **53**

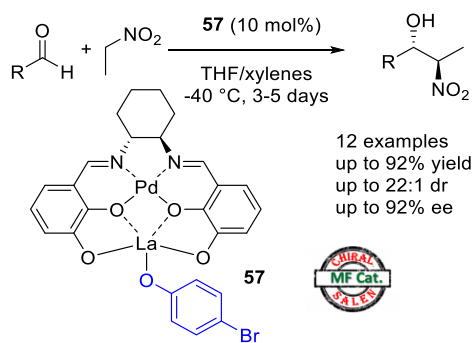
Scheme 69. Asymmetric Henry Reaction Catalyzed by **56 and 2,6-Lutidine**



could be recovered and reused in an original multisubstrate procedure. The 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 substantial improvement in ee (34% to 69%) when the amine loading was decreased from 1 equiv to 5 mol %, although at the expense of an important conversion decrease.

Then in 2008, Hong and colleagues¹⁷³ exploited the catalytic system used by Yamada in a supramolecular setting. The initial (salen)Co^{II} promoter was modified to give catalyst **54**, which allowed head-to-tail dimerization through a quadruple hydrogen-bond interaction (see **55** in Scheme 68). Hence, the catalyst design features two 2-pyridone/amino-pyridine hydrogen bonding pairs to create self-assembled

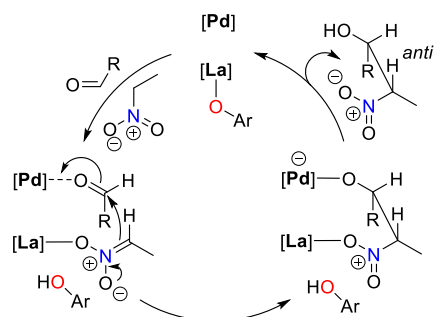
Scheme 70. Asymmetric Henry Reaction Catalyzed by Catechol–Salen Pd/La Complex and 4-Bromophenol



dimers of type **55** in solution. Dimerization was confirmed in the solid state by X-ray structure and ¹H NMR experiments in solution.

The dimeric species **55** proved 48-fold faster than the monomeric catalyst **54** in Henry reactions, again in the presence of DIPEA as base, loading of which could be decreased from 1 equiv to 2 mol %; moreover, the dimer exhibited improved yields and enantioselectivities. This remarkable result may 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 obtained X-ray diffraction analysis of the parent (salen)nickel^{II} complex, which showed a metal–metal distance of about 4 Å. The reaction scope was evaluated by using the bimetallic (salen)Co^{II} complex **55** and varying

Scheme 71. Mechanism of Henry Reaction with Trisfunctional Catalyst 57

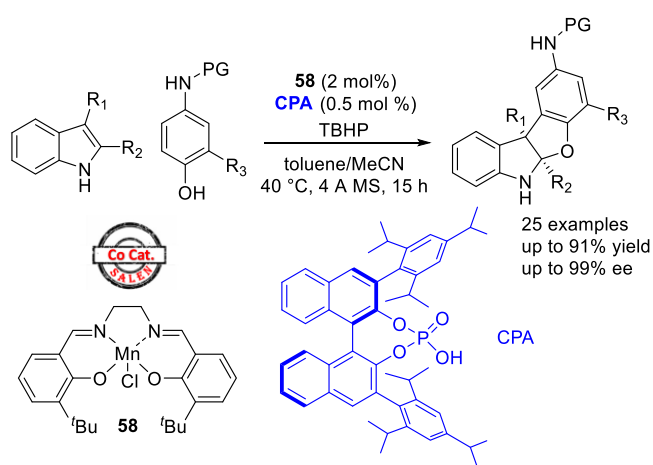


aromatic aldehydes. The resulting nitroaldols were obtained in good to excellent yields and with high enantiomeric excesses (81–96% ee).

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

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 copper(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

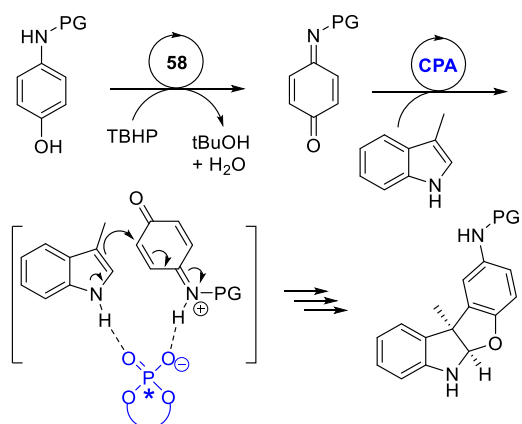
Scheme 72. Enantioselective Indole/Aminophenol Oxidative [3 + 2] Cycloaddition Catalyzed by Achiral 58 and CPA



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 section with an elegant protocol involving a trifunctional catalyst, **57**, developed by the group of Shibasaki in 2008.¹⁷⁵ A series of metallic catalysts was investigated in Henry reactions with aldehydes and nitroethane; the

Scheme 73. Mechanism Proposal for the Indole/Aminophenol Oxidative [3 + 2] Cycloaddition with 58 and CPA



complexes were formed *in situ* by mixing of a catechol–salen ligand with various transition metals and rare earth cations, as well as different additional phenols (Scheme 70).

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, 4-bromophenol being identified as the most suitable. The resulting complex **57** proved efficient in terms of yield, enantioselectivity, and diastereoselectivity for the *anti*-Henry product (12 examples, up to 92%, 92% ee, and 22:1 d.r.).

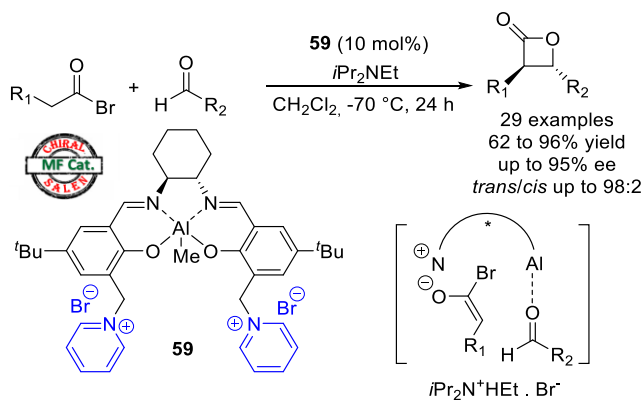
The speculated mechanism involves the double and selective chelation of both reagents, the aldehyde by the palladium center and nitroethane by the lanthanum center (Scheme 71). The phenolate ligand is then able to deprotonate the nitro substrate to lead to a liganded nitronate after liberation of bromophenol. 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 trifunctional catalyst.

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 Zhong¹⁷⁶ 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

Scheme 74. Formation of *trans*- β -Lactones Promoted by a Cooperative Ion Pair/Lewis Acid Catalyst, **59^a**



^aIntermediate simplified for clarity.

cycloaddition triggered by a chiral phosphoric acid (CPA) (Scheme 72).

In a one-pot protocol, the protected aminophenol is oxidized into an aminoquinone by *tert*-butyl hydroperoxide (TBHP) under the auspices of the (salen)Mn^{III}Cl catalyst (Scheme 73). This aminoquinone is then protonated by the CPA catalyst to form a quinone-iminium, which 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).

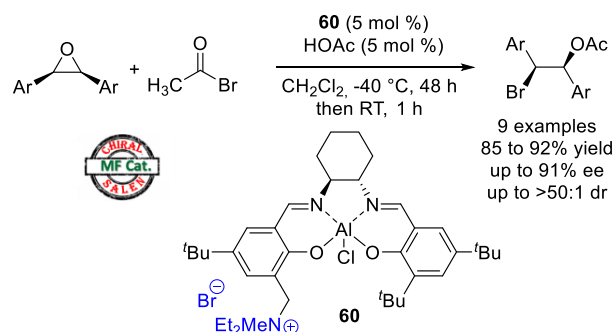
Both catalytic cycles are independent, and no deleterious interaction seems to occur between the active intermediates.

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 section 2.2, 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 quaternized heteroatom serves as an anchor for various nucleophilic anions that are kept in close proximity by Coulombic interactions.

Scheme 75. Desymmetrization of *meso*-Epoxides with a Bifunctional (Salen)Al/Ammonium Salt Catalyst



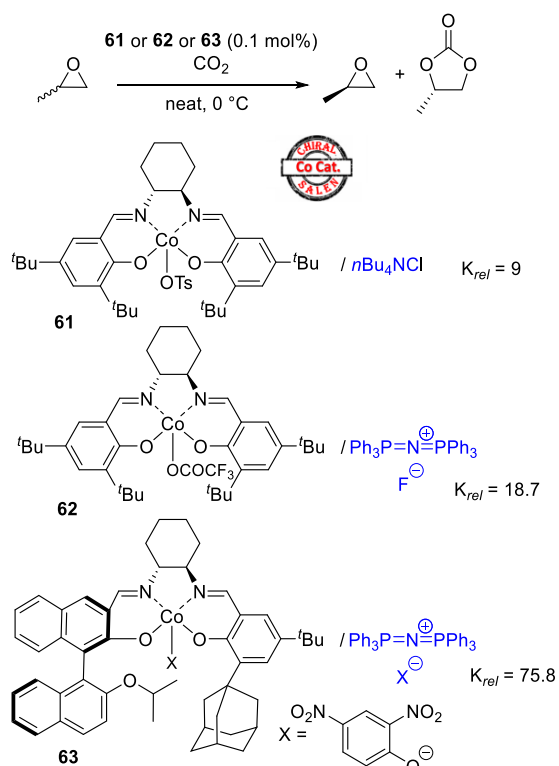
This strategy was also employed for asymmetric synthesis of *trans*-configured β -lactones by the group of Peters.^{177,178} A bifunctional catalyst, **59**, was devised to combine a Lewis acid with an ion-pairing moiety in order to trigger the [2 + 2] cyclocondensation between acyl halides and aliphatic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

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 hand, 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 d.r. and ee values; NBO calculations nevertheless ruled out a significant impact of the effective charges within the heterocycle to explain this result.

The same authors¹⁸⁰ were also able to exploit this dual activation mode to carry out the desymmetrization of *meso*-

Scheme 76. Synthesis of Chiral Carbonates with (Salen)Co Complexes and Ammonium Additives

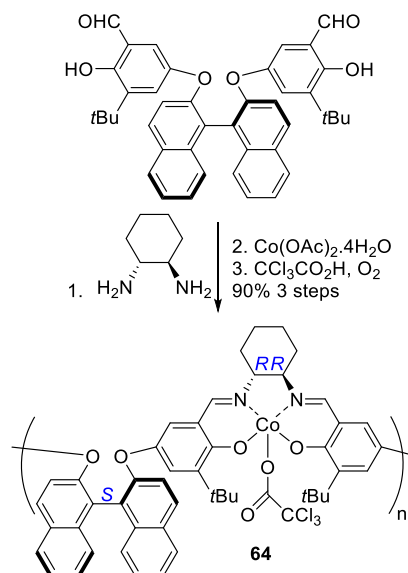


epoxides, by promoting their opening with bromide ions in the presence of acetyl bromide, a reactivity rarely described in prior literature. In this case again, the aluminum Lewis acidic center allows strong activation of the *meso*-epoxide, while the enantioselective nucleophilic attack of the bromide 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 deoordinated alcohol is finally esterified by acetyl bromide, regenerating both acetic acid and bromide anion.

In this case, although active, the pyridinium substituted complexes **59** proved less selective than the quaternary alkyl ammonium ones, 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 *n*Bu₄NBr. 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 to the metal center.

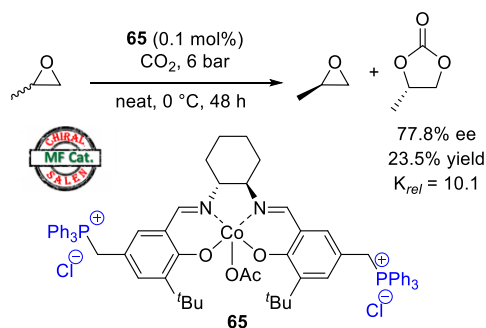
Preparation of chiral carbonates following this procedure remains challenging, because exploitable conversions are generally obtained only at high temperatures and under high CO₂ pressures, which remains experimentally unfavorable; furthermore competitive polycarbonate formation still as to be

Scheme 77. Synthesis of Chiral Polymeric (BINOL-salen) Co Catalyst **64**



minimized, leaving room for improvement in this particular field. For instance, Lu et al.¹⁸¹ in 2004 successfully performed

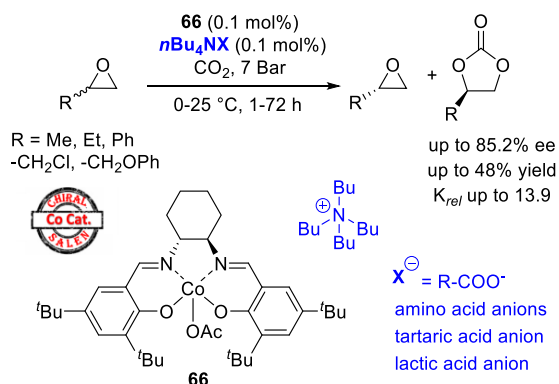
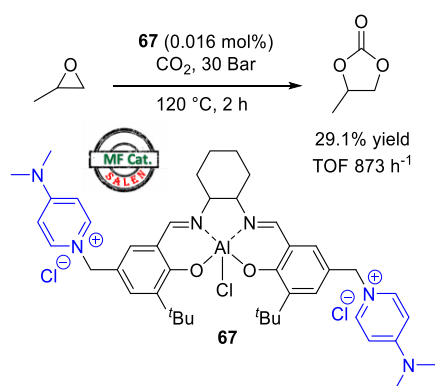
Scheme 78. Synthesis of Chiral Carbonates with Complex **65** Bearing an Appended Phosphonium Salt



catalytic kinetic resolution of racemic epoxides through their coupling with CO₂ 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.

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 the presence of tetrabutylammonium chloride and 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 and Brandenburg¹⁸² discovered in 2006 that the use of catalyst **62** with bis(triphenylphosphoranylidene) ammonium halides (PPNX) as co-catalysts delivered better selectivities (70% ee with the chloride and 75% ee with the fluoride); optimization 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 polycarbonate, which slowly converts into the desired monocyclic carbonate.

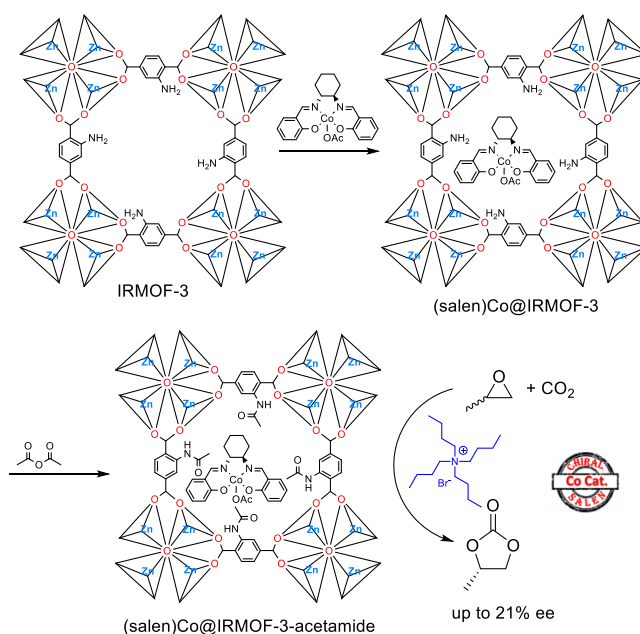
Scheme 79. Asymmetric Cycloaddition Reaction of CO₂ and Epoxides with **66 and Chiral Ionic Liquids****Scheme 80. Cycloaddition Reaction of CO₂ and Epoxides with **67** Bearing Appended Pyridinium Salts**

Yan and Jing¹⁸³ in 2009 developed a polymeric catalyst, **64**, prepared through polycondensation of BINOL–bis-salicylaldehyde with cyclohexyldiamine, delivering (salen)Co^{III} species after complexation, that was active in the aforementioned reaction in the presence of tetrabutylammonium fluoride (see Scheme 77).

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

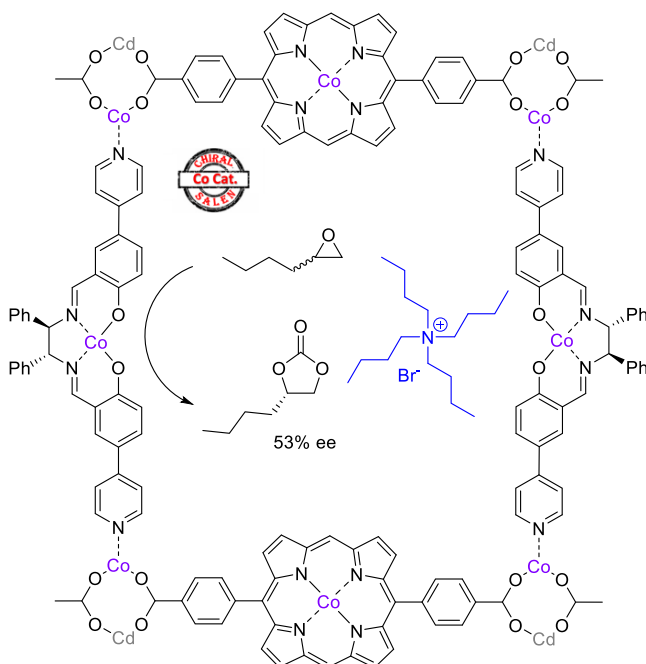
About the same time, the same group¹⁸⁴ obtained a similar level of selectivity by using (salen)Co^{III} bifunctional catalyst **65** incorporating quaternary phosphonium salts in its structure (see Scheme 78). The catalyst could be easily recovered and reused, showing interestingly almost no loss of activity and even slight increase in selectivity over the next four runs.

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, CO₂ 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

Scheme 81. Schematic Description of Imprisoning of Homogeneous Chiral (salen)Co^{III} Catalyst within the Cage of IRMOF-3 in Two Steps

acid anions were employed with the (R,R)-salen catalyst, a negative effect being observed with the diastereomeric combination: (S) + (S,S) (Scheme 79).

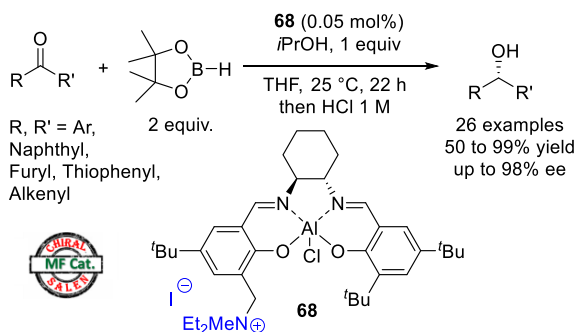
Liu, Darensbourg, and co-workers¹⁸⁶ in 2012 investigated the use of modified (salen)Al catalyst **67**, substituted at the 5,5' positions with various pyridinium and imidazolium moieties (Scheme 80). Without consideration of chirality, the authors identified the bifunctional catalyst (salen)AlCl flanked with two 4-dimethylaminopyridinium chloride to be the most active, reaching turnover frequency of 873 h^{−1}.

Scheme 82. Porphyrin–Salen Based Chiral MOF

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 with PPN salt and an anion with poor leaving-group ability (see Scheme 77). Hence, best results were observed with (triphenylphosphoranylidene)ammonium-2,4-dinitro-phenoxyde (PPN-DNP) reaching 97.1% ee corresponding to an 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 counteranion by postulating that the cobalt center 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 enantiomer 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 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 postmodification of the MOF walls upon acylation. Condensation of CO₂ with epoxides to obtain optically active cyclic carbonates occurred successfully at room temperature with these heterogeneous catalysts (up to 41% ee).

Scheme 83. Asymmetric Hydroboration of Ketones with Complex 68 Bearing an Appended Ammonium Salt



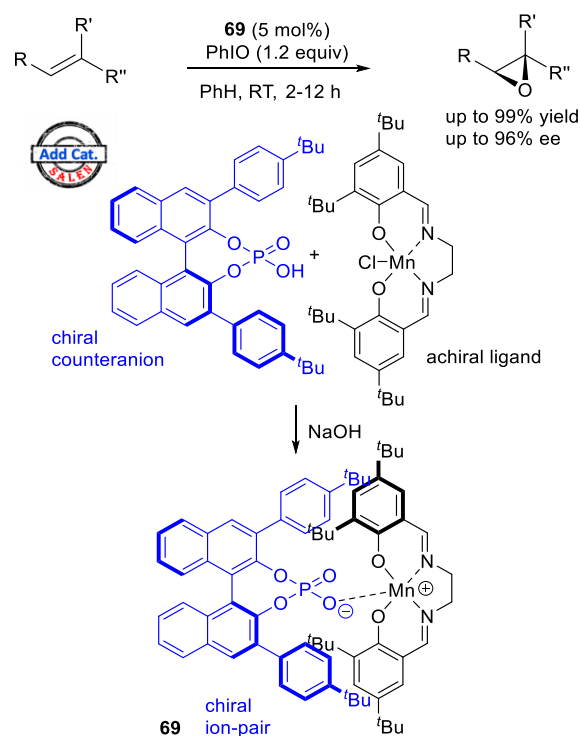
Control experiments confirmed that the reaction occurred inside the pores, and bulky substrates were poorly converted due to their low diffusion rate. The catalytic system was reused three times with constant values in terms of activity and selectivity.

Ren, Jiang, and co-workers¹⁸⁹ 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 metalation based on single-crystal to single-crystal transformation (Scheme 82). After impregnation with TBAB, the material could catalyze 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.

In 2015, North and collaborators¹⁹⁰ reinvestigated the field using a catalyst of type 66, but where the cobalt is replaced by aluminum with the idea of limiting polymerization side reactions, as well as the hydrolysis of the starting epoxide, and therefore increasing 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 section 3.1.2 with the work of Pasquale's group,⁸⁴ tetrabutylammonium bromide is crucial to perform the CO₂ incorporation into epoxides to produce cyclic carbonates. We have previously seen that a very complex triple-activation

Scheme 84. (Salen)Mn^{III}/Chiral Phosphate Ion Pair for Catalytic Asymmetric Epoxidations of Unfunctionalized Olefins



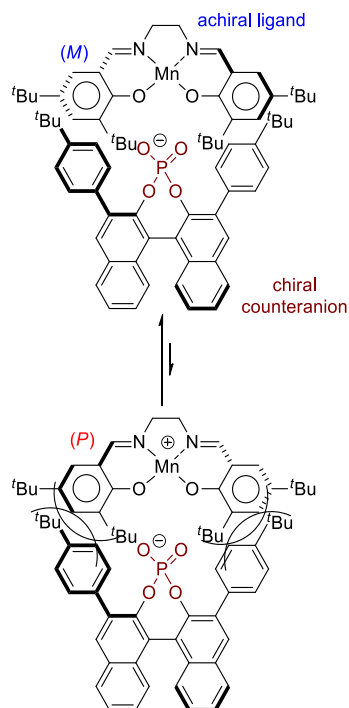
setting is at play in which the quaternary ammonium serves as bromide anion carrier into the organic phase where the reaction takes place.

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 highly efficient cooperativity within the bifunctional (salen)AlCl complex appended with an ammonium iodide 68 (Scheme 83).

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

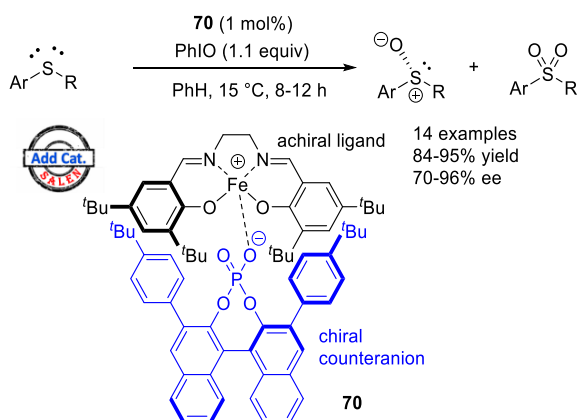
mechanism, with the reagents accurately positioned between the aluminum and ammonium centers, the latter keeping the

Scheme 85. (Salen)Mn^{III}/Chiral Phosphate Ion Pair Equilibrium Confirmed by VCD Spectroscopy



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.

Scheme 86. (Salen)Fe^{III}/Chiral Phosphate Ion Pair for Catalytic Asymmetric Oxidation of Sulfides



7. METALLO-SALEN AND CHIRAL ANIONS

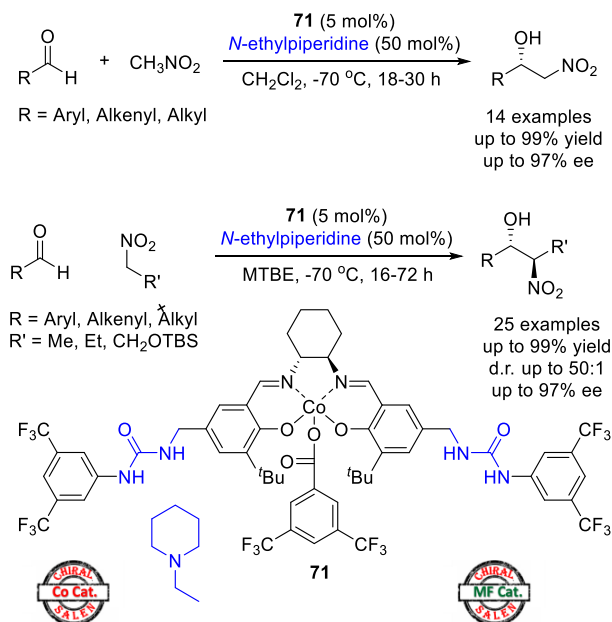
7.1. Epoxidation Reactions

In 2010, Liao and List¹⁹² 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 enantioselectivity of 96% ee.

With this ion-pair catalyst **69**, various olefins, chromenes, and other noncyclic alkenes were epoxidized with good functional group tolerance. In general, (*Z*)-alkenes were preferred substrates. In this way, they demonstrated that an enantiopure anion could impose 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.

In order to understand the mechanistic and structural aspects of this catalytic transformation, the same group, in collaboration with Merten's group,^{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 were able to demonstrate how a chiral anion forces the achiral cation of the ion-pair catalysts to adopt an enantiomeric conformation

Scheme 87. Henry Reactions with (Salen)Co-OBz^Fbisurea Catalyst 71



responsible for the observed asymmetric induction (Scheme 85).

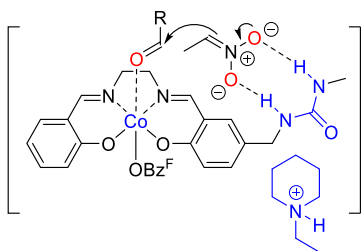
The authors showed that depending on the solvent, the intensity of the VCD signature correlates with the enantioselective induction observed in the same solvent, tight ion-pairs leading to more distorted conformations, corresponding to higher enantioselection.

7.2. Sulfide Oxidations

In parallel, still in 2012, the same group¹⁹⁵ got interested in enantioselective oxidations of sulfides using this type of ion-pair catalyst. In this investigation, 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, oxidation of prochiral sulfides, the produced chiral sulfoxides were obtained in high yields and enantioselectivities.

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)Fe^{III}

Scheme 88. Proposed Activation Pattern for the Henry Reactions with (Salen)Co-OBz^Fbisurea Catalyst **71**



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 evaluated 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-workers¹⁹⁷ 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 used a monometallic catalyst, **71**. It is bifunctional as the (salen)Co^{III} core is flanked by two urea groups, a versatile activating moiety through H-bonding^{198–201} (Scheme 87).

The bis-urea (salen)Co^{III}-based catalyst **71** with bis-(trifluoromethyl)benzoate as counteranion gave excellent yields when used with *N*-ethylpiperidine as ancillary base in methyl *tert*-butyl ether (MTBE) at $-70\text{ }^{\circ}\text{C}$. 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 Henry reactions with nitroethane, retaining excellent enantioselectivities and yields, and moreover 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

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 enantioselectivities. 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 coupled amine/salen complex for which the nucleophilicity of the amine exerts 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 that 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 of a good balance between Lewis basicity and steric hindrance of the additive has been clearly demonstrated for 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 proven 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 their 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 additive as multiple roles; 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 proven in the case of olefin 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 reactions, such as avoiding over-oxidation 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 and 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, and neither moiety alone was able to trigger the reaction nor was 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 toward 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 growth, halogen-bonding offers complementary opportunities to H-bonding but has not been 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 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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Author Contributions

The manuscript was written through contributions of all authors and all authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Yu-Chao Yuan obtained his M.Sc. degree in organic chemistry in 2016 under the supervision of Professor Min Shi (Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences (CAS), China). Then he received his Ph.D. degree in organic chemistry in 2019 under the supervision of Dr. Christian Bruneau and Dr. Rafael Gramage-Doria (Université de Rennes 1, France) before carrying out his postdoctoral research with Dr. Emmanuelle Schulz and Dr. Olivier David at Université Paris Saclay (2019–2020). He is presently working in Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, School of Pharmacy (Xuzhou Medical University, China). His current research mainly deals with transition metal-catalyzed C–H bond functionalization, synthesis of pharmaceutical intermediates, and green asymmetric catalysis.

M. Mellah received his Ph.D. degree from the Université Paris 12 in 2001 for electrochemical organic synthesis studies, under the supervision of Prof. J. Périchon. After an industrial postdoctoral position at EDF for the development of electrosynthetic processes and an academic postdoctoral stay at Université Rennes 1, he joined E. Schulz's group in Orsay in 2003 as assistant professor (University Paris Saclay). His research expertise focuses on the development of more environmentally friendly catalysis based on the use of electrochemistry instead of chemical reductants or oxidants, usually used in excess. He notably developed the electrochemical synthesis of polymers based on chiral salen complexes for asymmetric heterogeneous catalysis and samarium-based electrocatalytic procedures for chemoselective reductions.

E. Schulz graduated from ESCIL in Lyon and received her Ph.D. degree in 1992 for studies concerning the total synthesis of strigol (Prof. P. Welzel, Ruhr-Universität Bochum/Université de Lyon). After an industrial postdoctoral experience (RP Agro), she joined the group of Prof. M. Lemaire in Lyon and obtained a permanent position at the CNRS. Since 2000, she has been working in the Institut de Chimie Moléculaire et des Matériaux d'Orsay (Université Paris Saclay). Her research interests are mainly directed towards asymmetric catalysis. She particularly explores the enantioselective hydroamination reaction promoted by chiral rare-earth based catalysts. New procedures for the easy recovery and reuse of chiral organometallic catalysts, specifically with enantiopure salen complexes, are also developed in her group.

O. R. P. David, was born in 1974 in Paris; he studied chemistry at the Université Pierre et Marie Curie in Paris where he earned his Ph.D. under the guidance of Prof. G. Lhommet. He joined the group of Prof. H. Hiemstra in Amsterdam to work with Dr. J. van Maarseveen as a postdoctoral fellow. After one year at the Ecole Normale Supérieure de Cachan, he was appointed assistant professor at the Université de Versailles, now Paris Saclay. He is interested in asymmetric heterocyclic chemistry, nucleophilic activation processes, molecular cage compounds, and the chemistry of odorants.

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