FEATURE ARTICLE

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[Cr(Salen)] as a 'bridge' between asymmetric catalysis, Lewis acids and redox processes

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An overview focused on the synthesis, structural features and catalytic applications of chiral [Cr(Salen)] complexes is presented. Key aspects of modern organic chemistry such as Lewis acids, asymmetric catalysis and redox processes are strictly connected with chronium–Schiff base complexes. Among the asymmetric transformations mediated by [Cr(Salen)] complexes, Diels–Alder and hetero-Diels–Alder reactions, ARO of epoxides, kinetic resolution of *meso*-epoxides and Nozki–Hyama reactions are taken into account.

Introduction

The biological activity of many pharmaceutical compounds and agrochemicals and the nature of many fragrances and flavours is associated with their absolute configuration.[1] The demand of the pharmaceutical industry to make chiral drugs in enantiomerically pure form is growing. In this context, chemical industries are increasingly more engaged in 'Chirotechnology': innovation is a business survival imperative![2] Asymmetric catalysis is an economical way to introduce asymmetry and most asymmetric catalysts consist of metal complexes with chiral ligands. Discovering new asymmetric promoting agents is a challenge and is an interdisciplinary research effort that combines organic, inorganic, organometallic and bio-mimetic chemistry. In the construction of an efficient transition metal catalyst, the following issues must be taken into account: design and synthesis of chiral ligands, matching of ligands with the right metal or suitable substrate and searching for the appropriate reaction conditions. The ability to carry out such an exploratory work represents a critical aspect for developing highly efficient chiral catalysts.

Although no universal chiral ligand exists for solving all the demands in asymmetric catalysis some interesting ligands have been developed. A few ligands belonging to a 'privileged' class are able to transmit chiral information in a very effective manner.[3] 2,2′-Dihydroxy-1,1′-binaphthyl (BINOL), 2,2′-diphenylphosphino-1,1′-binaphtyl (BINAP), bis-oxazoline (Box), TADDOL, ethylenbistetrahydroindenyl (EBTHI) and phosphonyldihydrooxazole (PHOX) are active members of such a class and many different reactions with a large variety of metals are effectively catalysed by these 'privileged' ligands.[4]

In this paper, we will focus our attention on one of the most powerful chiral ligands nowadays utilised in asymmetric processes: Salen (*N*,*N*′-bis(3,5-di-*tert*-butylsalicydene)-1,2-cyclohexanediamine, **1**). The abbreviation Salen was initially introduced to indicate diimines derived from the condensation of salicylaldehydes and 1,2-ethylenediamine, however, nowadays all the structurally correlated chiral and achiral Schiff bases of such a class of compounds are commonly indicated by the word Salen.

Schiff bases are appealing frameworks for a tailored catalyst design (Fig. 1).[5] Chiral Schiff bases[6] resembling porphyrins are sterically well defined and kinetically non-labile. Unlike porphyrins the synthesis of a large variety of chiral Schiff base is easy, and the introduction of stereogenic centres near the coordinated metal makes the transmission of the stereochemical

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Professor Pier Giorgio Cozzi graduated (Laurea) in Milan with Professor Gennari in 1989. After four years as research associate in organometallic chemistry with Professor C. Floriani (Lausanne, Switzerland) he was appointed Assistant (1994–2001) then Associate Professor in Bologna University (Bologna, Italy). Among his research interests homogeneus enantioselective catalysis has the pre-eminent position. He was visiting research scientist with Professors S. Regen (Lehigh, USA), A. Pfaltz (Basel, Switzerland), K. A. Jørgensen (Aarhus, Denmark) and S. Gambarotta (Ottawa, Canada) and also with Drs P- van der Schaaf (Ciba Speciality Chemicals) and A. Hafner (Ciba Inc., Switzerland).

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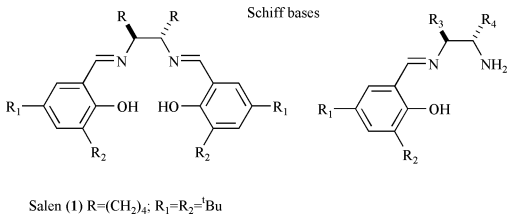


Fig. 1

information more feasible. Generally, chiral Salen ligands have C_2 symmetry and are readily prepared in excellent yields from the condensation of appropriate optically active 1,2-diamines with variously substituted salicylaldehydes.[7] Normally, the synthesis of metallo–Salen complexes is accomplished simply by mixing the chiral ligand with the desired metal–salt. However, for the synthesis of the [Cr(Salen)] complex several synthetic methods have been reported.

Synthesis of [Cr(Salen)]

Metallo–Salen complexes have attracted the interest of chemists since more than eighty years ago. Evidence of such scientific attraction is demonstrated by several reviews published in the middle 1960s.[8] However, the pioneering study reported by Coggon *et al*. on the synthesis of Cr(III)-Schiff base complexes was published only in 1970. The procedure involved the use of $Cr(OTf)_2$ in coordinating solvents adopting strictly anhydrous conditions.[9] Such a synthetic protocol involves the oxidation of the intermediate [Cr^{II}(Salen)] complex by air (Fig. 2).

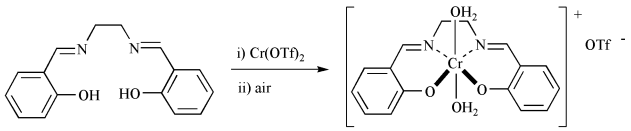


Fig. 2

More recently, Jacobsen *et al*. described an alternative approach to the preparation of chromium–Schiff base species with the aim of obtaining a high level of reproducible catalytic activity in several asymmetric reactions (*vide infra*).[10]

Since the highly air-sensitive commercially available $CrCl_2$ contains molecules of water coordinated to the metal,[11] an alternative route to the preparation of Cr complexes is desired. In this context, Gilheany and coworkers published a protocol for asymmetric epoxidation of olefins, based on [Cr(Salen)] complexes as catalysts. In this case, reproducible asymmetric inductions were observed when the chromium complex was obtained by aqueous reduction of Cr(III) salts with Zn amalgam.[12]

Finally, a variant of the aforementioned reductive procedure was adopted by us, using manganese as the stoichiometric reductant, in the catalytic asymmetric allylation of carbonyls (*vide infra*, Fig. 3).[13] Moreover, since we usually performed the heterogeneous redox process and further complexation step in anhydrous CH_3CN (Salen is scarcely soluble in CH_3CN), 2 equiv. of freshly distilled Et_3N had to be added to guarantee the formation of the [Cr(Salen)] complex **2**. At the present, we are developing a more direct and controlled synthetic approach avoiding handling Cr(II) salts which starts from $CrCl_3(THF)_3$. The desired [Cr(Salen)Cl] complexes **3** can be readily obtained by reaction of $CrCl_3(THF)_3$ with the Na or K salts of the Schiff bases in rigorously anhydrous conditions.[14]

Although effective procedures for the preparation of [Cr(Salen)] catalysts have been published, in order to get a high chemical/optical yield and reproducible results in organic reactions, the synthetic protocol to obtain chromium complexes must be optimised each time.

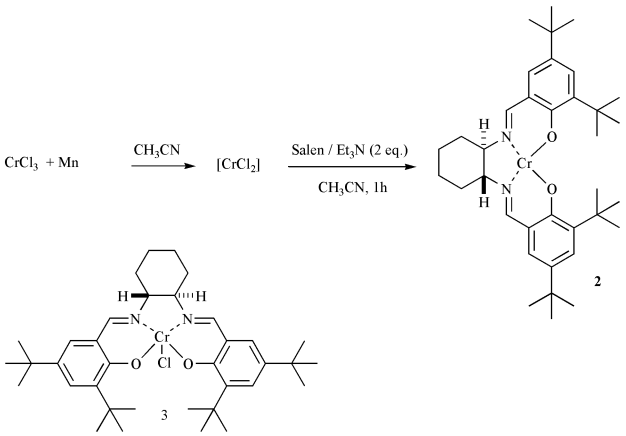


Fig. 3

[Cr(Salen)]: structure and catalytic activity

In 1983 Kochi and coworkers reported the first application of chromium–Salen as the promoting agent in catalytic reactions.[15] In this work achiral cationic [Cr(oxo)Salen] complexes were utilised in catalysing the epoxidation of simple olefins with iodosylbenzene. The structural relationship between the Cr(V) complex and its chromium(III) precursor was also notable. In fact, in each complex the metal shows a square planar coordination geometry, but the presence of the oxygen in the Cr(V) system displaces the metal by 0.5 Å above the Salen ligand. In 1990, Jacobsen, Wu and Katsuki independently published a development of this effective catalytic system focusing their attention on the asymmetric epoxidation of unfunctionalised *cis*-di- or tri-substituted olefins in the presence of the cationic [Mn(Salen)] complexes **4** and **5** (ee 80–95%, Fig. 4).[16] For this purpose, chiral Schiff bases derived from optically

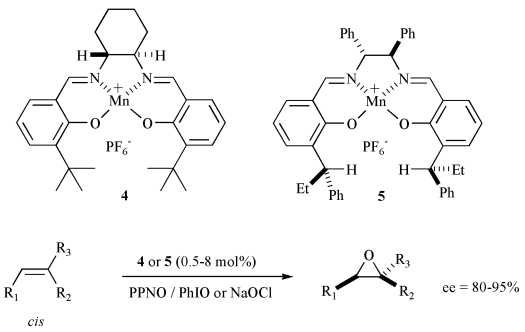


Fig. 4

pure 1,2-diamines, were utilised as the backbones for the chiral ligands. The stereochemical induction was further optimised by the introduction of *tert*-butyl substituents in the positions 3-(3′) and 5-(5′) of the aromatic rings.

On the other hand, chiral [Cr(Salen)] complexes were considered less effective in performing enantioselective epoxidation reaction until Gilheany and coworkers discovered that the epoxidation of *trans*-olefins could be efficiently carried out in the presence of stoichiometric and catalytic amounts of stable oxo Cr(Salen) **6** complexes and iodosylbenzene as oxygen source (ee up to 77%, Fig. 5).[17] This behaviour is clearly in contrast to the Mn complex and to metallo–porphyrin complexes. To understand this different behaviour some structural and mechanistic considerations are required.

Essentially, the epoxidation that is taking place is considered to be related to the approach of the olefin on the reactive oxo metallo–Salen species: [Mn(O)(Salen)] and [Cr(O)(Salen)].[18] Potential energy surface calculations for the [Cr(O)Salen] epoxidation showed that the Cr system has a doublet electronic state with a stepped conformation[19] while the Mn system may

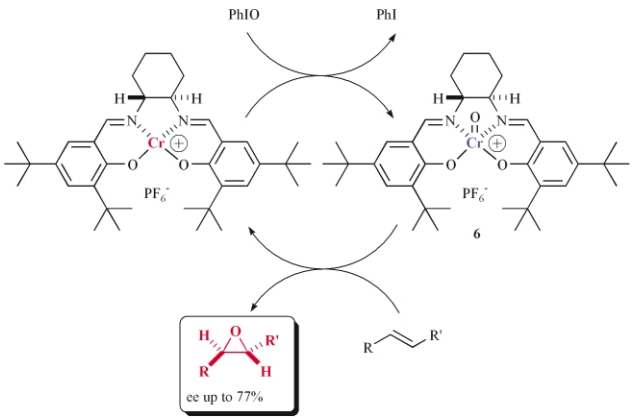


Fig. 5

be a quintet or triplet and the corresponding oxo complexes may display a bowl or stepped shaped conformation.[20] Such features may be responsible for the complementary catalytic activities in the epoxidation of alkenes.

The importance of the molecular conformation is also shown by the fact that, while in the case of [Mn(Salen)] only the presence of bulky substituents on position 3-(3′) of the ligand guarantees high enantiomeric excesses, for the [Cr(Salen)] complex no particular effects are displayed by the hindrance of the substituents on the aromatic portions.[21]

Katsuki and coworkers have introduced a new class of chiral metallo–Salen complexes in which the Salen units are folded.[22] This folding amplifies the asymmetric induction in the catalytic reactions. The chirality induced by the folding of the Salen skeleton is controlled by the stereogenic centres of the ethylenediamine moiety. The metallo-chelate conformational structure (five-membered) has one methine carbon above the plane and one methine carbon below to relieve the steric interactions between all the substituents (Fig. 6). The C=N

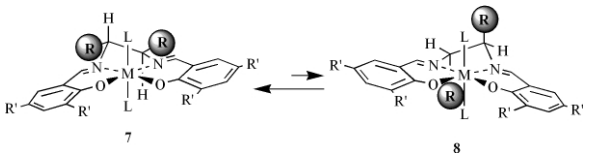


Fig. 6

double bonds incline up- and down-ward, causing ligand folding. The degree of folding is also determined by secondary weak bond interactions such as OH–π attractions which take place between aromatic substituents in C3-(C3′) and apical aqua or other ligands.

The folding of the complex is important in the enantiodescriminating step of the asymmetric transformations and its degree depends also on the presence of donor ligands coordinated to the metal. In fact, upon the addition of the appropriate donor ligand some of the weak intramolecular interactions derived from the presence of the apical aqua ligand are eliminated and the folding of the molecular conformation can be controlled.[22a] Finally, it is important to mention that [M(Salen)] complexes exist in an equilibrium conformers (**7**, **8**, Fig. 6), and such an equilibrium is shifted toward the conformation with the substituents in the more stable pseudo-equatorial orientation.[23]

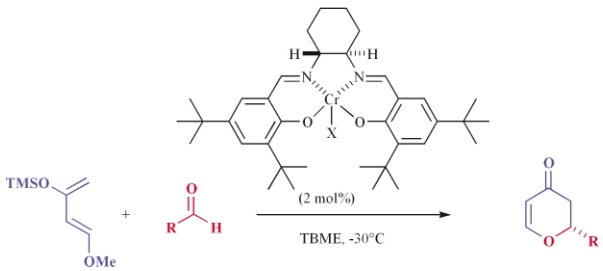
Recently, the importance of the sixth coordination site of metal–Salen complexes in the rate and enantioselectivity enhancement of the Jacobsen–Katsuki epoxidation was elegantly shown by Wiest, Plattner and coworkers.[20b] In this computational study the influence of an axial ligand such as $(CH_3)_3NO$ on the Mn=O length and on the conformation of the [Mn(O)(Salen)] complex was taken into account. The calculated structures for the hexacoordinate complexes are in agreement with the statement that a class of non-planar enantiomorphic conformations are in equilibrium. Moreover, the presence of a strongly bound axial ligand leads to weaker Mn=O bond, increasing the oxygenation reaction rate of olefins.

A number of asymmetric catalytic oxidation reactions can be controlled by the presence/absence of coordinating additives and this fact shows the importance of weak bonding interactions on the effectiveness of Salen and [M(Salen)] frameworks.

[Cr(Salen)] as chiral Lewis acids

Although cationic [Cr(Salen)] complexes can be utilised as precursors for the synthesis of chromium–oxo species,[24] their utility in promoting other asymmetric catalysed reactions was demonstrated in Lewis acids mediated processes. For instance, chiral cationic tetradentate [Cr^{III}(Salen)] complexes are able to catalyse the asymmetric hetero Diels–Alder (HDA) reaction between 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene ('Danishefsky's diene') and carbonyl compounds in a highly stereocontrolled manner (Table 1, entries 1, 2).[25]

Table 1 Asymmetric hetero-Diels–Alder reactions catalysed by cationic [Cr(Salen)] complexes[a]



Entry	R	X	Yield (%)	Ee (%)
1	Ph	Cl (**3**)	96	56
2	Ph	BF_4 (**9**)	85	87
3	Ph	N_3 (**10**)	86	81
4	C_6H_{11}	**9**	71	93
5	*n*-C_5H_{11}	**9**	86	83
6	2-furyl	**9**	89	76

[a] Reactions carried out at 5.0 M in TBME.

In this context, [Cr(Salen)Cl] **3**, [Cr(Salen)BF_4] **9** and [Cr(Salen)N_3] **10** were described as efficient catalysts. However, cationic [Cr(Salen)] systems bearing other non-coordinating counterions such as PF_6 and $B(Ar_f)_4$ [Ar_f = 3,5-$(CF_3)_2C_6H_3$] have proved to be less efficient. This behaviour can be related to the presence of coordinated water, as a matter of fact, the addition of 4 Å molecular sieves is important to achieve completion of the reactions. For this process Jacobsen and coworkers have investigated the reaction mechanism that seems to point toward a concerted [4 + 2] process.[25] Later, Jacobsen and coworkers reported that even a new class of chiral tridentate chromium(III) catalysts (**11**) were able to furnish a high level of chemical and optical yields in the HDA reaction between aldehydes and substituted electron-rich dienes (Fig. 7).[26]

The influence of the complex conformation of the catalyst, that we have already discussed for [M(O)(Salen)] catalysed epoxidation of olefins, was also detected in this Lewis acidic chromium–Salen mediated hetero-Diels–Alder reaction. In fact, the diastereomeric (*R*,*R*)-[Cr(Salen)] (**12**) and (*R*,*S*)-**13** complexes show opposite senses of enantioselectivity (Fig. 8).[27] However, although it is widely accepted that the coordination of the carbonyl to the metal centre is involved in the reaction mechanism, at the present time it is still unclear how the

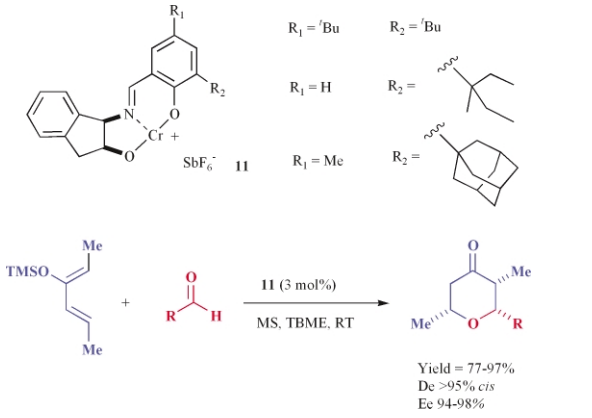


Fig. 7

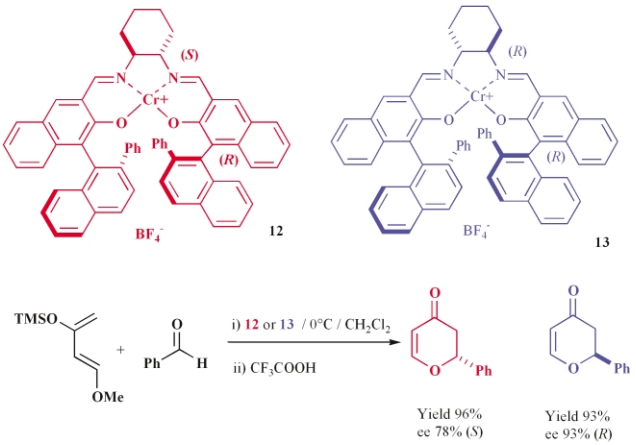


Fig. 8

approaching trajectory of the incoming diene is effected by the ligand conformation.

Comparable levels of stereoselectivity were obtained by the use of cationic [Cr^{III}(Salen)] complexes in the diastereo- and enantioselective Diels–Alder (D–A) reaction between 1-amino-3-siloxy-dienes and various acroleins (yield 78–94%, ee 79–93%).[28] This procedure allows the synthesis of highly functionalised cyclohexene derivatives in the presence of activated molecular sieves (Fig. 9).

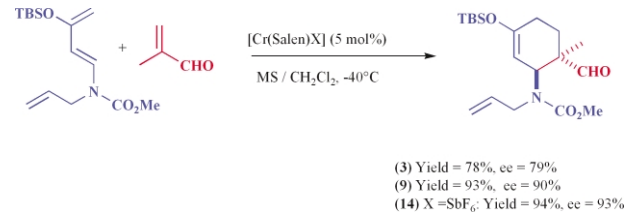


Fig. 9

By contrast, it is important to note that only the second generation [Mn(O)(Salen)] complexes described by Yamashita and Katsuki are able to promote D–A reactions in a highly stereocontrolled way.[29] In fact, cationic [Mn^{III}(Salen)] systems catalysed this reaction with significantly lower levels of enantioselectivity.[28]

A great advantage in using [Cr(Salen)] complexes in catalysed processes in comparison to other HDA methodologies is the straightforward preparation of the active complex and the possibility of readily designing of the coordination core of the catalyst by tuning steric and electronical features of the ligand. Continuing in the field of the Lewis acidic metal–Salen mediated reactions, the effectiveness of [Cr(Salen)Cl] **3** in promoting the asymmetric ring-opening (ARO) of *meso*-epoxides by $TMSN_3$ [ee 42–97%, Fig. 10(a)] is evident.[30] The reason that prompted Jacobsen to develop such a catalytic transformation was the strict relationship between the supposed transition state of the epoxidation with the ground-state structure of the epoxy–[M(Salen)] complex [Fig. 10(b)]. In fact, the supposed ARO mechanism involves an activated epoxide coordinated to the [M(Salen)] complex. Among all the organometallic systems screened, [Cr(Salen)] emerged naturally as the more efficient catalyst even if coordination geometries of the analogous [Al(Salen)Cl] and [Ti(Salen)Cl_2] complexes are quite similar.[9,31]

In this study the synthesis of the catalyst can be effectively performed *via* air oxidation of [Cr^{II}(Salen)] and exchange of the axial ligand with Cl anion during the work up. Traces of water are essential in producing HN_3 by hydrolysis of Me_3SiN_3: HN_3 is indeed the active reagent. On the other hand, a careful exclusion of water by adding strong dehydrating organometallic reagents gave an inactive system. Such experimental evidence is in agreement with the assumption that the real active catalyst is the [Cr(Salen)N_3] complex **10** obtained *in situ* after the first turnover.[32]

A focus for the perspective of [Cr(Salen)] chemistry was the singular and interesting mechanistic analysis performed by Jacobsen and coworkers. The ring-opening reaction of cyclopentene oxide with HN_3, in the presence of catalytic amounts of preformed **10** shows a second-order dependence on the catalyst, indicating that two molecules of catalyst are involved in the rate determining step.[33] In particular, the chiral chromium complex is capable of activing both reaction partners in a bimetallic rate determining step accelerating the formation of new stereocenters. As a partial support for the proposed cooperative mechanism a positive non-linear effect (NLE) was observed.[34] Several nucleophiles were shown to open epoxides with appreciable stereoselectivity.

Intimately connected with the use of Salen are certain molecular recognition phenomena determined by self-assembly processes. In fact, Breinbauer and Jacobsen have recently discovered that assembling the [Cr(Salen)] in a dimeric[35] and [Co(Salen)] in a dendridic architecture,[36] the transmission of chiral information was benefial in the ARO by $TMSN_3$ and in the hydrolytic kinetic resolution (HKR) of terminal epoxides (Fig. 11).[37] The arrangement of the supramulecolar Salen aggregate is crucial as well. In fact, while a linked 'head-to-head' alignement of two Salen frameworks is poorly enantioselective, the analogous 'head-to-tail' dimer with the appropriate tether displays a reactivity two orders of magnitude greater than the monomeric catalyst.[35] It is notable that in order to oligomerise Salen units maintaining the C_2 symmetry a specific synthetic strategy was designed.[38]

An extention of the ARO reaction was the kinetic resolution of terminal epoxides by using of [Cr(Salen)N_3] complex in catalytic amount.[39] This methodology was efficiently applied to the preparation of biologically active compounds such as 2-(*S*)-propranolol **15** and (*R*)-9-[2-(phosphonomethoxy)propyl]adenine **16** in high enantiomeric excesses (Fig. 12).

Finally, the effectiveness of Cr(III) complexes of tridentate Schiff bases in catalysing the enantioselective ring opening of *meso*-aziridines was recently described.[40]

Enormous possibilities are still open in this area, in fact, the design of particular architectures that constrain the Salen units in cooperating actions should enhance the stereochemical communication. In theory a chiral space suitable for any kind of reaction could be created.

[Cr(Salen)] and redox catalysis

An important characteristic associated with metallo–Salen systems is their capability to undergo redox processes. However a distinction needs to be made in relation to other metallo-

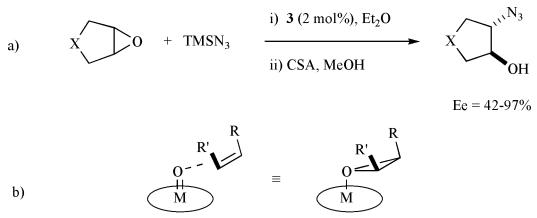
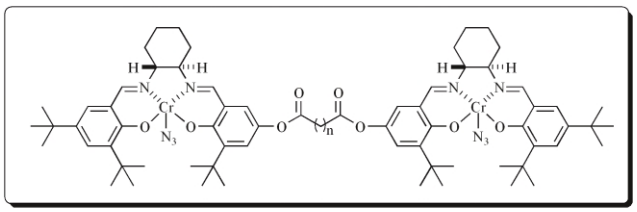


Fig. 10



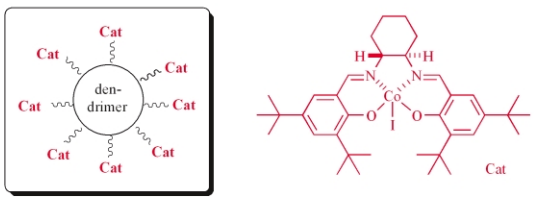


Fig. 11

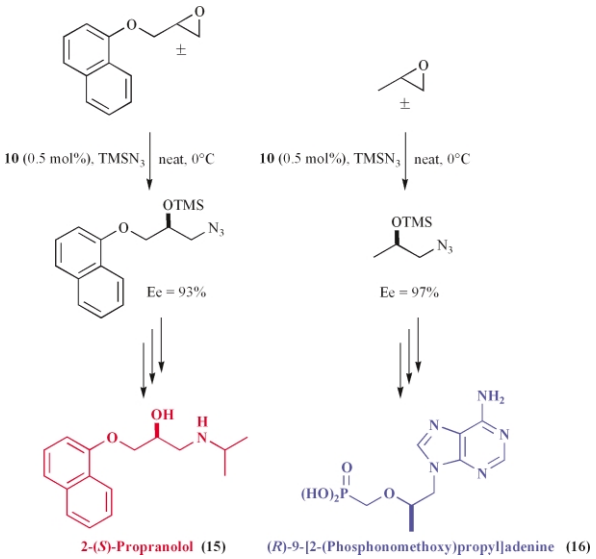


Fig. 12

mediated redox transformations. As a matter of fact, while in the usually employed catalysts of redox processes the electron transfer step concerns exclusively a change of oxidation state of the metal centres, in the case of M–Schiff base species the ligand frameworks can play an active role as well. On the other hand, [M(Salen)] complexes can act as 'molecular batteries' storing electrons by the formation of intermolecular C–C and M–M bonds *via* a reversible reductive coupling of two imino groups of the Schiff base (Fig. 13).[41]

This chemistry was exploited with a number of redox active metals.[42] It is quite interesting to remark that in the coupled Schiff base compounds a 'head-to-tail' arrangement was observed in the solid state, as evident from several crystal structures.[42] Molecular recognition and steric interactions guide the two units of the Schiff base allowing the formation of the new C–C bond.

On the other hand, organometallic reagents prepared by the Barbier[43] protocol have found numerous applications in organic

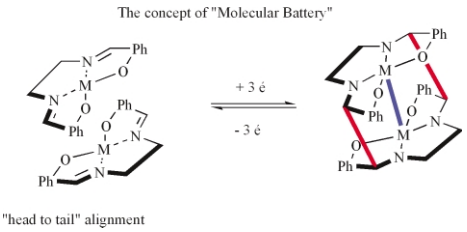


Fig. 13

synthesis. Titanium, zinc, samarium and chromium reagents have been exploited in the modern organic synthesis in many applications.[44,45] In general, the organometallic reagent is prepared *in situ* by an oxidative addition reaction between a reactive organohalide and more than stoichiometric amount of the redox active metal (Fig. 14).[46] However, environmental and atom economy demands require the switch to catalytic processes.

Fig. 14

A catalytic redox process can be designed employing a couple of metals one of them being the stoichiometric reductant (Fig. 15). However, only a handful of catalytic redox processes

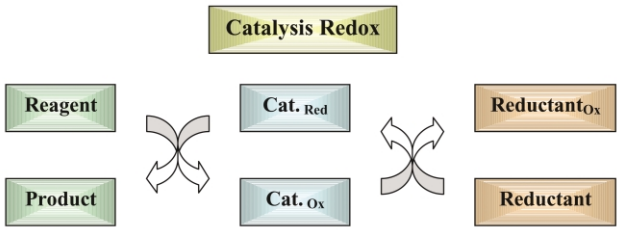


Fig. 15

based on titanium, chromium, samarium and vanadium have been described.[33] These systems are based on two concepts, namely the use of a reductant (usually a metal) capable of restoring the catalytic active species and the use of a 'scavenger' able to liberate the organic product by cleaving a stable metal–oxygen bond.

In this context, one of the most powerful methodologies for the construction of new C–C connections is the Nozaki–Hiyama–Kishi (NHK) reaction.[47] Such a procedure consists in the chemo- and regio-selective addition of organo-chromium complexes to carbonyls compounds [Fig. 16(a)]. The protocol

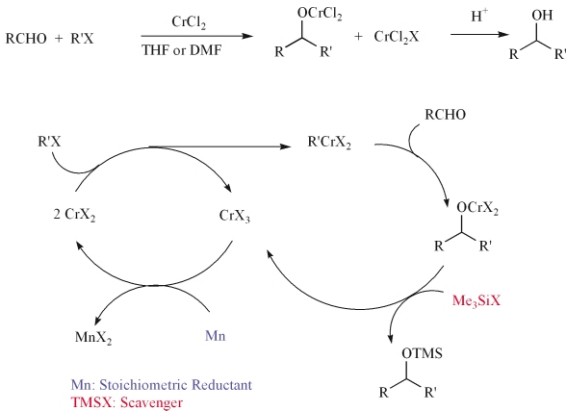


Fig. 16

was effectively applied in some crucial steps of the synthesis of several natural compounds such as palytoxin, ophiobolin C and halichondrin B.[48]

A catalytic version of the NHK reaction was published by Fürstner and Shi in which the use of Mn powder as stoichiometric reductant and Me_3SiCl as the scavenger allows the utilisation of the chromium source only in catalytic amounts [Fig. 16(b)].[49] Other versions of the NHK transformation employing an organic reducing agent [tetrakis(dimethylamino)-ethylene: TDAE][50] or electrochemical driving forces[51] were described. The Ultimate goal of a general catalytic redox process is the use of *just electrons!*

As already stressed, one of the most effective way to prepare [Cr(Salen)Cl] complexes starts from anhydrous $CrCl_2$. In other words, the redox couple Cr(III)/Cr(II) is not able to perfom an intermolecular coupling of the imine functions. The redox active chromium metal surrounded by the Schiff base can be exploited as a general method for making new C–C bonds. Due to the large variety of C–C bond forming reactions mediated by chromium redox systems and due to the possibility of the fine tuning of the Schiff bases, redox reactions based on chromium–Salen catalysts have enormous possibilities. On the light of these considerations, we have recently published the first catalytic and enantioselective version of the NH reaction in the presence of catalytic amounts of [Cr(Salen)] (Fig. 17).[13,52] With

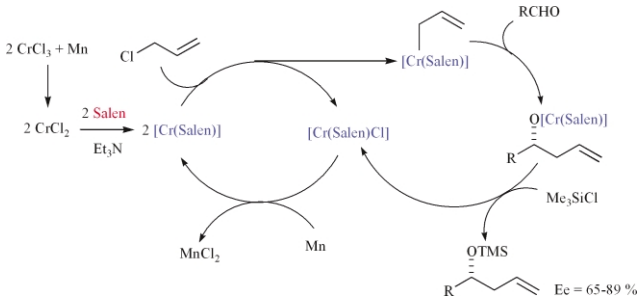


Fig. 17

the aim to optimise the enantiomeric excess in the catalytic addition of allyl halides to aldeydes, the crucial issue of the catalyst preparation was examined. By detailed experimental work we have reached a good compromise between synthetic accessibility, reproducibility and good enantiomeric excess.

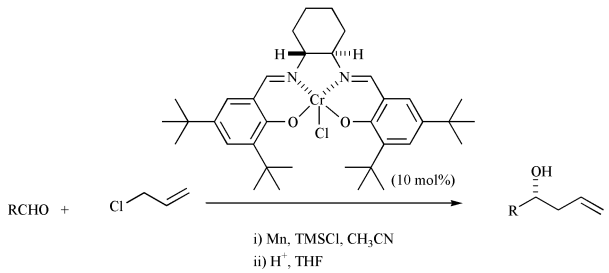
Batches of $CrCl_3$ and Mn by different vendors gave different results in terms of the fast reduction Cr(III) → Cr(II) (heterogeneous reaction). Because the reduction is taking place between two solid surfaces intimate contact is important. However we have recently found that addition of small amount of Me_3SiCl (15 mol%, compared to aldehyde) in the early stage of the reaction significantly speeds up the reduction making the protocol more reproducible.[53]

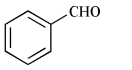
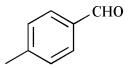
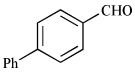
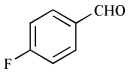
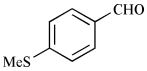
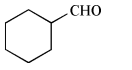
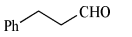
The addition of non-stereogenic organo halides to aliphatic, aromatic and heterocyclic aldehydes takes place in satisfactory yields and good enantiomeric excesses (yield 40–67%, ee 77–90%, Table 2). By contrast, ketones appeared completely unreactive and only the formation of the corresponding silyl enol ether was observed. Moreover, the catalytic nucleophilic addition of other substituted halides[54] and propargyl halides[55] afforded the products in moderate enantiomeric excesses.

Particularly notable is the fact that all the processes reached good enantioselectivity at room temperature while for other catalytic enantioselective allylation methodologies low temperatures are normally necessary in order to effectively discriminate between the diastereomeric transition states.[56]

The facile oxidative addition allowed the use of stereogenic allyl halides. It is well known that both the stoichiometric and catalytic chromium mediated addition of crotyl halides to carbonyls furnishes the *anti* diasteroisomer as the major product.[57] A cyclic transition state (Zimmermann–Traxler) is often invoked in order to explain the observed simple diastereoselection, that is also independent of the configuration

Table 2 Asymmetric addition of allyl chloride to aldehydes catalysed by [Cr(Salen)][a]

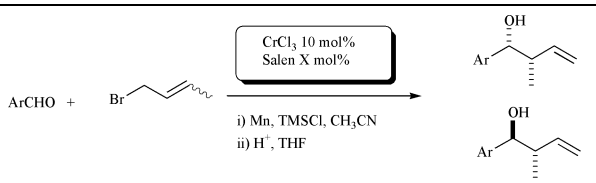


Entry	RCHO	Yield (%)	Ee (%)	Conf.
1		67	84	*R*
2		67	78	*R*
3		54	82	*R*
4		41	77	*R*
5		46	78	*R*
6		42	90	*R*
7		45	77	*S*

[a] Reactions carried out at RT in CH_3CN.

(*Z* or *E*) of the starting crotyl halide.[49] Applying our redox [Cr(Salen)]/Mn/TMSCl protocol in the addition of crotyl bromide to PhCHO, we were able to isolate the desired homoallylic alcohol in satisfactory yield (50%) but with a low degree of diastereoselection, *anti*:*syn* 67:33, ee_{anti} = 5%, ee_{syn} = 78% (Table 3, entry 2).

Table 3 Effect of the amount of Salen in the simple diastereoselection of the chromium catalysed addition of crotyl bromide to PhCHO and to ArCHO[a]



Entry	Salen (%)	ArCHO	Yield (%)	*Syn*:*anti*	Ee_{Syn} (%)	Ee_{Anti} (%)
1[b]	—	PhCHO	85	10:90	—	—
2	10	PhCHO	50	33:67	78	5
3	20	PhCHO	56	83:17	89	36
4	20	*p*-FC_6H_4CHO	53	74:26	90	27
5	20	*p*-MeC_6H_4CHO	48	74:26	85	26
6	20	*p*-PhC_6H_4CHO	47	71:29	84	16
7	20	*p*-BrC_6H_4CHO	43	72:28	82	28

[a] The reactions were carried in the presence of 10 mol% of $CrCl_3$ as the chromium source. [b] The reactions were carried in the presence of 7 mol% of $CrCl_3$ as the chromium source.

However, the aforementioned ability of Salen ligands to produce complex aggregate systems and bimetallic reagents by self-assembly phenomena can afford interesting surprises in terms of simple diastereoselection. In fact, we discovered that the diastereoselectivity can be significantly altered by changing the amount of Salen ligand. For instance, using a 10 mol% of

free chiral Salen ligand (molecular ratio Salen:Cr = 2:1) the simple diastereoselection can be completely switched from *anti* to *syn* (Table 3, entries 2 and 3).[58]

The chiral switch observed is a function of the amount of free Salen ligand and depends on the structure of the Salen (Fig. 18).[53] In fact, only structurally correlated Salen skeletons are

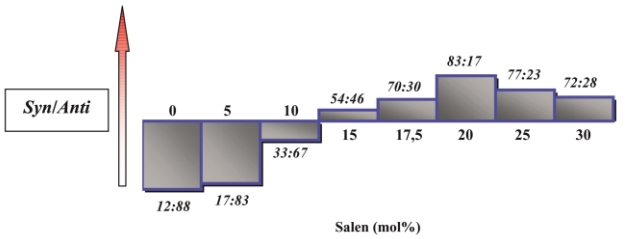
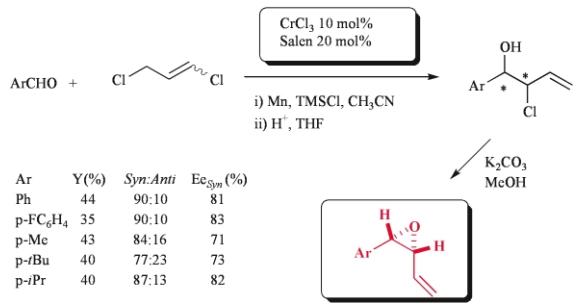


Fig. 18

able to give this chiral switch. The *syn* diastereoselection observed is quite unusual for chromium mediated crotylation of carbonyl compounds and suggests that a cooperative mechanism may be involved. In the presence of an excess of chiral Salen the *syn* diastereoselection was generally obtained for a large variety of functionalysed stereogenic crotyl bromide and aromatic aldehydes (Table 3, entries 4–7). Moreover, we have applied this methodology to devise a practical access to optically active chloridrines, key precursors of vinyl epoxides with good levels of diastereo- and enantio-selectivity (Fig. 19).[59]



Ar	Y(%)	*Syn:Anti*	Ee_{Syn} (%)
Ph	44	90:10	81
p-FC_6H_4	35	90:10	83
p-Me	43	84:16	71
p-*t*Bu	40	77:23	73
p-*i*Pr	40	87:13	82

Fig. 19

This peculiar 'chiral switch' prompted us to examine further details about the reaction mechanism.[60] We first examined the role of the scavenger (TMSCl). Its hypothetical Lewis acid activity was excluded by the fact that using stoichiometric amount of [Cr(Salen)] (no TMSCl is then required in this case) the homoallylic alcohols were obtained with the same stereoselectivity.

Moreover, it is important to stress that the preparation of the catalytic complex is a key issue. In fact, (a) using Jacobsen's methodology, *i.e.* starting from $CrCl_2$, lower levels of enantiomeric excess were obtained in the catalytic procedure;[10] (b) using stoichiometric conditions starting from anhydrous $CrCl_2$ (no Mn is required), no reaction between allyl chloride and benzaldehyde was recorded at all and (c) small traces of water in our allylation procedure (added before or after the complexation step) completely stop the reaction.

Point (a) can be easily explained considering that commercially available $CrCl_2$ contains water, therefore it is not surprising [in the light of point (c)] that the results collected preparing the catalyst with the Jacobsen's protocol were inferior. Instead, the higher enantiomeric excess recorded by using our particular procedure indicated that the presence of Mn salts derived from the oxidation of Mn (*i.e.* $MnCl_2$) are playing a crucial role.

The reaction was more diastereoselective in higher concentration, showing that aggregation phenomena were involved [Fig. 20]. A more direct evidence of such an hypothesis comes

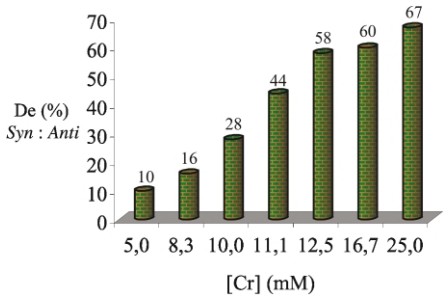


Fig. 20

from NLE studies. In our reactions (both allylation and crotylation) a peculiar negative effect was recorded. This behaviour suggests that multimetallic catalytic species can be involved in our reactions. In fact a kinetic study performed on the standard asymmetric addition of crotyl bromide to benzaldehyde showed that the reaction rate was proportional to $[Cr]^{0.5}$.[60,61] This reaction order suggested that in the rate determining step two *linked* molecules of [Cr(Salen)] are involved. However such a conclusion should not be confused with the proposed mechanistic of the ARO with $TMSN_3$. In fact, while Jacobsen proposes the presence of two molecules of [Cr(Salen)] in the enantiodescriminating step, in our redox reactions the catalytic chromium aggregate seems derived by more complicated self-assembly and organometallic aggregation events. In fact, the oxygen atoms of a Schiff base metal complex can act as coordinating bases for other metal species.[62] Therefore, the MnX_2 salts produced during the catalytic turnovers are likely responsible for the formation of the bimetallic aggregate. The dimeric $[Cr(Salen)]_2{\cdot}MnX_2$ species is our working hypothesis to explain our results, but more careful studies are necessary (Fig. 21).

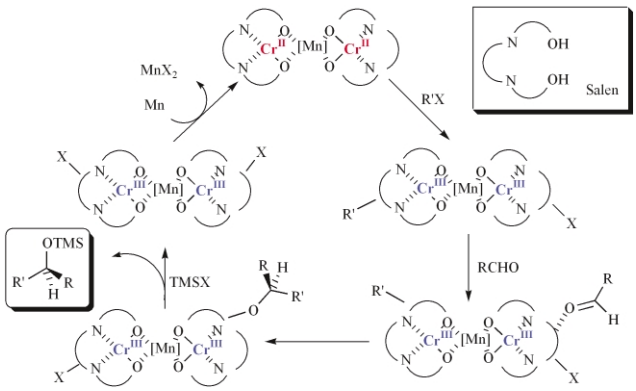


Fig. 21

Using [Cr(Salen)] catalysts for the construction of other C–C skeletons seems to be possible as well as exploiting other motifs in aggregation by using the concepts of supramolecular chemistry. Finally, the wide scenario of possible applications of such an area of the enantioselective catalytic redox processes is obvious because the properties of the metallo–Salen complexes make the preparation of a large variety of chiral organometallic reagents possible.

Conclusions

In this brief excursion on [Cr(Salen)] chemistry we have shown some peculiar behaviours of this flexible catalyst. Ligand design and non bonding interactions can enhance and reduce the folding of Salen complexes moduling the transmission of chiral information. Self-assembled or tethered catalysts with optimal geometry serve as bimetallic frameworks for enantioselective catalytic reactions working cooperatively in the activation of

nucleophiles and electrophiles. Finally molecular recognition and aggregation shown by other metals can be used in redox mediated reactions. In our opinion the [Cr(Salen)] complexes represent a clear example of how a chiral organometallic species can reunite concepts belonging to supramolecular chemistry. These concepts can be further expanded finding new possibilities for [Cr(Salen)] mediated reactions.

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