Asymmetric synthesis with "privileged" ligands*

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Abstract: Different types of chiral "privileged" ligands **1** and **2** in promoting enantioselective addition of allylating agents to aliphatic and aromatic aldehydes are described. Here, a new concept in the asymmetric allylation reaction is presented. Redox [Cr(Salen)] mediated addition of allyl halides to carbonyl compounds is described, and mechanistic investigations are discussed. These results open access to the fascinating area of the catalytic redox processes mediated by metallo-Salen complexes.

INTRODUCTION

Enantiomerically pure compounds are in widespread use nowadays. Pharmaceuticals, vitamins, agrochemicals, flavors, and fragrances are often multifunctional molecules bearing stereocenters. The enantioselective catalysis appears as one of the most attractive strategies to obtain enantiomerically pure molecules, because the chiral information could be transferred only using a substoichiometric amount of optically active promoting agent. Our group is currently engaged in a fare-front development of new catalytic chiral methodologies. The following account documents our recent findings in the asymmetric C–C bond-forming processes area. In particular, we want to present an overview of our progress in the field of asymmetric allylation reaction of carbonyl compounds performed by using chiral catalysts [1]. Several organometallic complexes of two classes of "privileged" ligands (Binol **1** and Salen **2**, Fig. 1) were successfully tested as promoting agents in such a process. It is well known in fact, that complexes of **1** and **2** with several metal salts are capable of transferring chiral information in a highly efficient way, in a large variety of asymmetric reactions [2].
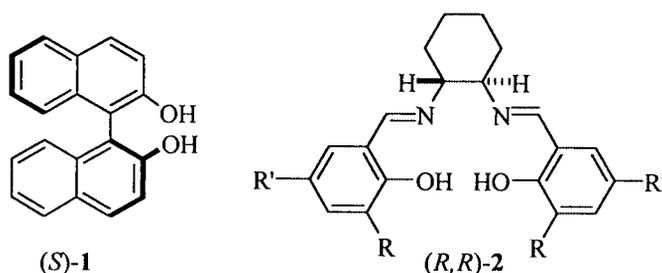
Fig. 1 The privileged ligands discussed in this overview.

BINOL

Asymmetric allylation of carbonyl group is a useful synthetic methodology. In fact, the homoallylic alcohols provided by this reaction are easily transformed in a variety of optically active functionalized compounds. In this contest, we introduced the use of new Binol-Ti and Binol-Zr catalysts **3** and **4** [3] prepared from $Ti(OiPr)_2Cl_2$, $Zr(OiPr)_4 \cdot iPrOH$ and ligand (*S*)-**1**, in the enantioselective addition of allyl-tributyltin to aldehydes. These metallo-Binol catalytic systems (20 mol %) afforded excellent results in terms of ee in the presence of 4 Å molecular sieves (Scheme 1).
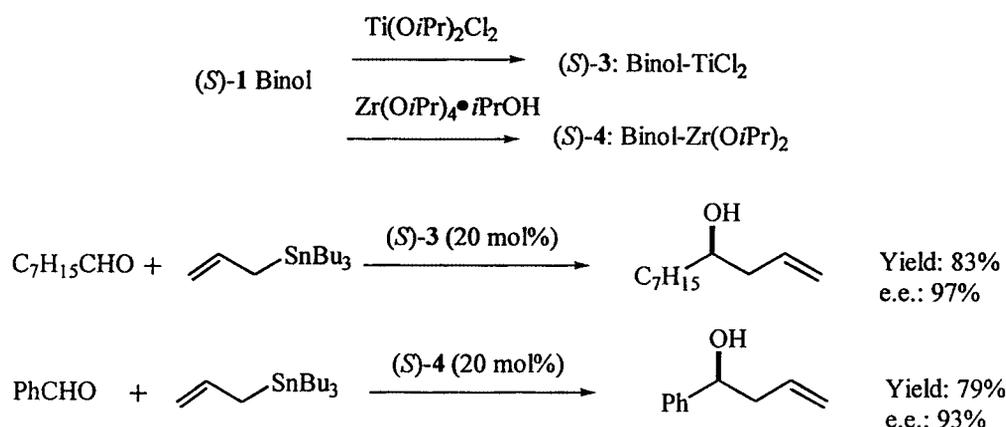
Scheme 1

With the Binol-Zr catalytic system, the reaction rate observed was higher in comparison with that of (*S*)-**4**, and the enantioselection recorded was excellent (ee up to 93% with the benzaldehyde). However, in some cases, a partial decrease of the chemical yields was observed due to the reduction of the aldehyde via Meerwein–Ponndorf–Verlay type reaction. The catalytic systems (*S*)-**3** and (*S*)-**4** appear complementary. In fact, while Binol-Ti furnishes better optical and chemical yields with aliphatic aldehydes, the chiral zirconium complex is more effective with aromatic substrates. In further studies, a class of achiral ligands such as calix[4]arenes emerged as promising activators for the **1**-Zr system [4]. The remarkable aspect of this procedure is that, even without the use of molecular sieves, it was possible to isolate the desired homoallylic alcohol with an excellent enantioselectivity (up to 96% with linear aldehydes) employing less then 2 mol % loading of chiral catalyst. With the purpose of investigating the influence of binaphthyl core on the stereochemical outcome of the allylation reaction, we set up a simple approach for the synthesis of disubstituted binaphthols [5]. Particularly, 3,3´-, 6,6´-, and 7,7´-disubstituted Binols were synthesized in optically active form and tested as chiral ligands in the addition of allyltributyltin to aldehydes.

High enantioselectivity was recorded using the optically active catalyst derived from 7,7´-dibenzyloxy ligand complexed with $Ti(OiPr)_2Cl_2$ that proved to be superior to the parent Binol catalyst **3** in the allylation of the benzaldehyde (ee = 92%). Moreover, of particular interest is the 7,7´-dibromobinol, which constitutes an ideal starting material for the preparation of a library of different Binols and polymer-bound (pb) binaphthols.

SALEN

Unfortunately, titanium and zirconium Binol systems were not able to promote the addition of sterogenic stannanes to aldehydes with good levels of chemical and optical yields. At the present time, a

general solution of this problem is still lacking with chiral Zr or Ti catalysts. We searched to solve this drawback moving away from the allylstannanes and allylsilanes and using more accessible and easily prepared stereogenic reagents. In exploring new concepts in allylation reaction, we focused our research interests into an enantioselective variant of a Barbier reaction [6]. A catalytic Barbier-type allylation reaction would involve a redox cycle in which an active metal, capable of performing an oxidative addition with an allyl halide, is constantly recycled by a stoichiometric amount of reductant. Catalytic redox processes showing these features have recently emerged in the organometallic synthetic community [7]. In particular, we took advantage from the work described by Fürstner [8] on the Nozaki–Hiyama–Kishi (NHK) reaction mediated by catalytic amount of chromium.

This protocol involves the use of Mn as the stoichiometric reducing agent and the Me_3SiCl (TMSCl) as the scavenger. During the reaction course the Mn is responsible to reduce the Cr(III) to Cr(II), and the Me_3SiCl is predisposed to liberate the Cr(III) species from the highly stable chromium-alkoxide by the formation of silylethers. To determine the optimal redox system we spent a considerable amount of time searching for the right ligand. The ligand has to guarantee the following requests: it must stabilize the chromium species in both its oxidation states (II/III) and secondly the ligand-exchange-labile Cr(II)-complex should be inert in the presence of an excess of Mn, MnX_2, and Me_3SiCl. *To find out the answer for all these questions at the same time was a really demanding issue!* The enantiopure **2** [(*R*,*R*,)-*N*,*N'*-bis(3,5-di-*t*-butyl-salicylidene)-1,2-cyclohexanediammine] ligand ensured all our requests. Avoiding the manipulation of the high sensitive $CrCl_2$, $CrCl_3$ was reduced *in situ* by an excess of Mn, and the resulting Cr(II) species were complexed with (*R*,*R*)-**2** in CH_3CN [9] in the presence of Et_3N.

Scheme 2

The resulting [Cr(Salen)] (10 mol %) was used in catalyzing the addition of allyl chloride to a number of aromatic, aliphatic, and heterocyclic aldehydes (Scheme 2).

The results in terms of ee were excellent (ee up to 89% for CyCHO) and the yields of the process satisfactory (41–67%), because the reaction suffers from side processes such as the pinacol coupling and the reduction of the aldehyde.

The procedure here described represents the first effective catalytic version of the Nozaki–Hiyama reaction. The synthetic utility of this C–C bond-forming reaction appears obvious because the features of the [Cr(Salen)] complex make the preparation of a large variety of chiral chromium reagents possible. However, applying our standard protocol in the addition of stereogenic organo halides to the PhCHO (model reaction), we obtained disappointing results in terms of diastereo- and enantioselection (*anti:syn* 67:33, ee$_{anti}$ = 5%). After a considerable amount of trials, we serendipitously discovered that using a 10 mol% excess of free Salen ligand (chromium:Salen ratio 1:2), interesting results were recorded [10]. The modified protocol appeared general, and remarkable levels of enantio- and diastereoslection were recorded in the addition of crotyl bromide to aromatic aldehydes (Table 1).

However, *we observed the complete switch of the simple diastereoselction of the reaction from* anti *to* syn. In fact, it is well known that the addition of stereogenic chromium reagents normally furnishes high levels of simple *anti* diastereoselection, via a cyclic Zimmermann–Traxler transition state

Table 1 Results of the diastereo- and enantioselective addition of crotyl bromide to aromatic aldehydes using [Cr(Salen)] catalyst.

Entry	ArCHO	Yield (%)	*Syn:Anti*	ee_{syn} (%)	ee_{anti} (%)
1	PhCHO	56	83:17	89	36
2	p-MeC$_6$H$_4$CHO	48	74:26	85	26
3	p-FC$_6$H$_4$CHO	53	74:26	90	27
4	p-ClC$_6$H$_4$CHO	46	61:39	82	24
5	p-BrC$_6$H$_4$CHO	43	72:28	82	28
6	p-PhC$_6$H$_4$CHO	47	71:29	84	16

[11]. The unusual behavior of our reaction was the stimulus for performing mechanistic studies. Firstly, we tried to understand the role played by the single components of the reaction mixture. The stoichiometric addition of the chiral [Cr(Salen)allyl] reagent to the benzaldehyde afforded the same level of chemical and optical yields of the catalytic version. This result points out that Me$_3$SiCl is not involved (i.e., activating the aldehyde) in the enantio-discriminating step of the redox catalytic cycle. Moreover, the Mn salts generated during the complexation step and the reaction course appear of fundamental importance. In fact, their absence causes the complete failure of the reaction. The role of the Mn salts is probably that to aggregate the [Cr(Salen)] molecules, giving the catalytically active species. Moreover, the influence of the chromium concentration over the diastereoselectivity of the reaction shows that aggregating phenomena are involved in the stereo-differentiating step of the process. As a matter of fact, the reaction appears more diastereoselective at the highest Cr concentration ([Cr] = 25.0 mM, de = 67%; [Cr] = 5.0 mM, de = 10%).

A tentative explanation for the *syn* simple stereoselectivity obtained should consider an open transition state, in which nonbonding and/or sterical intereactions play a key role. We previously suggested that a specific noncovalent binding of the chiral organochromium species **5** with another molecule of **2**, derived by the presence in solution of manganese salts, is responsible for the switch of the simple diastereoselection from *anti* to *syn* [10].

With such a catalytic species, in fact, a cyclic transition state (chair-like) should be denied. Acyclic transition states could require the synergic action of two molecules of chiral Salen complex, one of them acting as Lewis acid. Is a bimetallic transition state operating in our catalytic system? To answer this intriguing question we performed some careful kinetic analyses, and the obtained results showed that the reaction rate is a function of the square root of the [Cr] [12]. In the light of these results, we suggest that a dimeric [Cr(Salen)] aggregate is involved in the transition state of our reaction. Probably, one molecule of [Cr(Salen)] bearing the allyl organometallic reagent and the other acting as Lewis acid could be responsible for the *syn* diastereoselection observed [13].

These studies are of remarkable importance because they open the access to an unexplored area of the catalytic enantioselective redox reaction. Cooperative mechanism, Lewis acid behavior, and aggregation phenomena are strictly connected in these metallo-Salen-mediated reactions.

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12. Reaction rate $\propto$ to $[Cr_{total}]^{0.59}$.
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