CHIRAL Ti(III) COMPLEXES FOR CATALYTIC PINACOL COUPLING AND RELATED REACTIONS

BY

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A THESIS

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BY

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DEDICATED

TO

MY PARENTS

DECLARATION

The research work incorporated in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. N. N. Joshi**, Division of Organic Synthesis, National Chemical Laboratory, Pune – 411008. This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in thesis entitled "**Chiral Ti(III) Complexes for Catalytic Pinacol Coupling and Related Reactions**" has been carried out under my supervision and is a bonafide work of **Mr. Anamitra Chatterjee**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune

October 2005

(Dr. N. N. Joshi)

Research Guide

Acknowledgement

The most cherished dream one bears in mind since the first day of thesis writing comes true when he writes the acknowledgement. This is one of those rare moments one gets in his life to express gratitude for all the persons responsible in completing the thesis. The first name that appears on the top of the list is of course my supervisor, Dr. N. N. Joshi. He has not only showed me the glimpse of excitement in the field of asymmetric synthesis but also influenced me in every walk of life. His indepth knowledge, intuitions, sympathetic and principle centered nature, have touched my mind. His enthusiasm and integral view in the field of research have made a deep impression on me. I also find it hard to express my thanks in words for his help at the time of my personal crisis. I owe him my deepest sense of gratitude. The runners for the whole innings were my labmates. It was a privilege to have colleagues like Kartick, Madhuri, Mayur, Mukesh, Manoj, Manmath, Sashi, Ravindra and seniors like Sushil and Bennur. It was a pleasure to work with them. It is needless to mention that their helpful discussion and cheerful company made my stay enjoyable.

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(Anamitra Chatterjee)

CONTENTS

Pinacol coupling, one of the older reactions, is still recognized as an important carbon-carbon bond forming reaction. Indeed it provides the most direct way to synthesize *vic* diols, recognized as a very important class of compounds in organic chemistry. Initial bottleneck of diastereoselectivity although overcome by using stoichiometric reagents, the enantioselectivity remained elusive. Attempts were made to induce enantioselectivity using chiral complexes, but in most cases only a moderate selectivity has been observed. Titanium complexes have drawn considerable attention in this regard. The present work describes the designing and synthesis of various ligands and their application in catalytic pinacol coupling reaction.

The first chapter describes the background to the present work by reviewing literature thoroughly.

In the second chapter the logic of designing ligands of varying sterics and electronics has been presented. Based on the scheme a variety of bidentate, tridentate and tetradentate ligands starting from optically active alcohols, aminoalcohols and diamines have been synthesized. Titanium complexes were prepared using a novel method, which can be operated even in multigram scale.

The third chapter deals with a systematic study of these ligands for catalytic pinacol coupling reaction. Benzaldehyde was chosen as a model substrate, TMSCl as the catalyst generator and zinc dust as a reductant. Most of the complexes failed to furnish good result. Gratifyingly, one of the tetradentate SALEN ligands furnished exciting result. Any further modification on the ligand framework was found detrimental. The catalyst structure was established through all probable analytical techniques. On optimization of the reaction parameters, the enantioselectivity went up to 96%. A variety of aromatic aldehydes were examined. In all the cases high yield and diastereoselectivity has been observed. The enantioselectivity was found sensitive to the nature of the substituent.

To extend the general applicability of our catalyst various other coupling reactions e.g. ketone coupling, imine coupling were also tried. Unfortunately, the present catalyst was not effective in these cases.

To summarize, we are able to establish a catalytic protocol for the enantioselective pinacol coupling of aromatic aldehydes. Good to excellent results were obtained in all the cases. Based on the experimental results, a plausible mechanism has also been proposed.

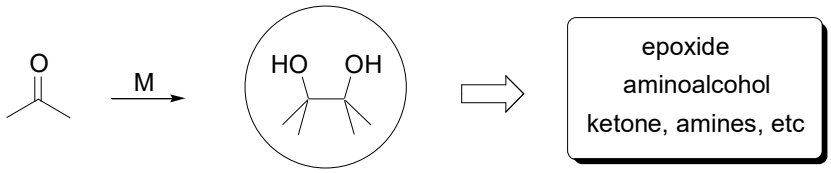
CHAPTER-1

A Review in Pinacol Coupling Reaction

1. Introduction:

Carbon-carbon bond forming reactions are pivotal to organic synthesis. Chemists in many cases have succeeded in achieving a good control over a number of such reactions. Pinacol coupling, an old timer can be placed in this category. Ever since the pioneering work by Fittig et al in 1859,[1] this reaction has remained as a challenging target to the organic chemists due to the need for dual control of diastereoselectivity and enantioselectivity in a single step. A slow and sustained evolution took place over about hundred and fifty years through a number of stages. An exponential growth being noticed in the last ten years. The popularity of this reaction stems out from its intrinsic ability to furnish 1,2-diols which are a very important class of compound. They can serve the structural motif in total synthesis, as chiral auxiliary, chiral ligand and so on. The diols can be even converted to a number of compounds such as amino alcohol, epoxide, ketone etc (Figure 1).

Figure 1.

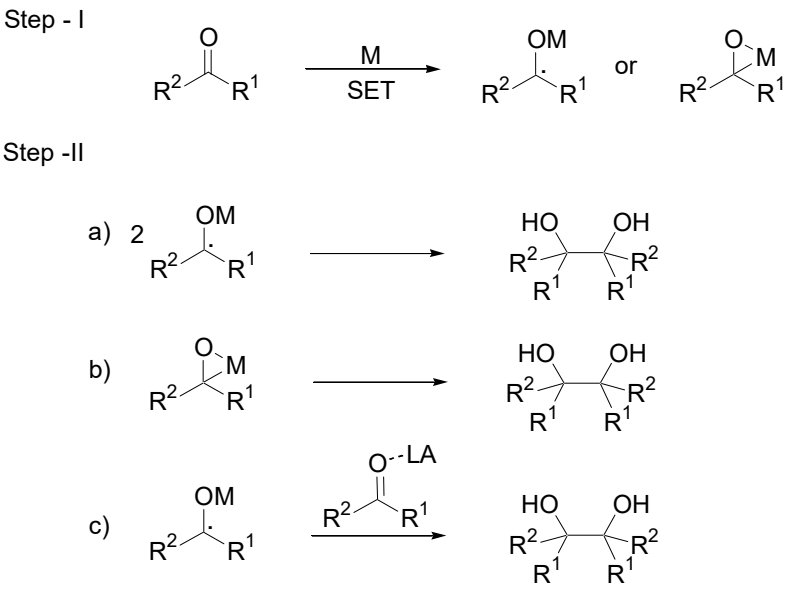


A variety of methods have been applied to perform this reaction. Of these, the most reliable is the use of various low valent metals or metal complexes in stoichiometric or catalytic amount. Although the reaction path that has been followed in pinacol coupling is described in literature, the origin of enantioselectivity is not clear till today.[2] In this present review we will emphasize on the different protocols adopted to pursue pinacol coupling in both diastereoselective and enantioselective fashion. A glimpse of the various compounds prepared using pinacol coupling as the key step will also be provided.

The most general way of presenting the mechanism of pinacol coupling reaction could be as shown in the figure 2. The first step of this reaction is the generation of a ketyl radical, generally achieved through the homolytic cleavage of the carbonyl bond in the presence of a metal. A simultaneous electron transfer from the metal atom (SET) furnishes the metal bound ketyl radical which can have several fates depending upon its stability. When the dimerization of two such radical takes place through a pseudo-bridged metal atom, the *dl* selectivity in the product predominates owing to a steric reason. On the other hand, when two such species couple through a non-bridged intermediate the formation of

the *meso* product is favoured. However in case of intramolecular pinacol coupling the *syn* product is formed in a higher ratio through a metal bridged intermediate. In case of transitional metals, the metal insertion into the carbonyl group generates an oxirane. Thus the carbonyl character is umpoled to initiate the attack by another molecule. The last possibility is the dimerization of a ketyl radical with an activated carbonyl group.

Figure 2.



2. Reagents for pinacol coupling:

Since its early days, pinacol coupling has been achieved using alkali metals or alkaline earths. Latter several transitional metals, lanthanides or p-block elements were also used successfully. Although the diastereoselectivity in a stoichiometric protocol has been achieved through ligand modification, for enantioselectivity the only reliable source was a chiral complex or a chiral auxiliary. The reagents have been therefore categorized in two classes. The first part, describes the stoichiometric use of metal or metal complexes for achieving diastereo and enantioselectivity respectively. The next part, deals with the catalytic protocols.

2.1. Stoichiometric protocols

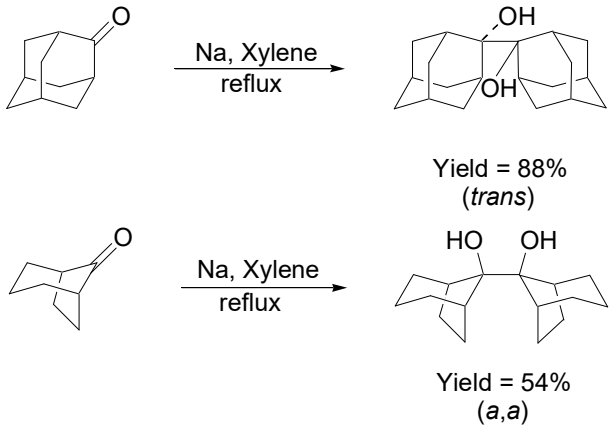
2.1.1. Diastereoselective

Alkali and alkaline earths

Sodium: The use of sodium in the pinacol coupling is an age old process probably started with the discovery by Fittig during his synthesis of pinacols.[1] Sodium in amalgamated form[3] or in combination with liquid ammonia[4], was also used for the coupling. All these

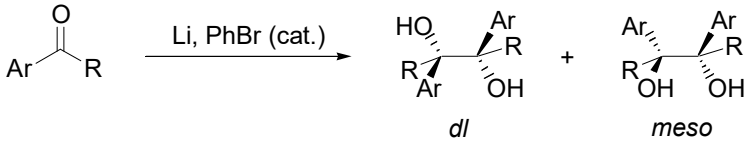
methodologies proved to be equally poor owing to their unsatisfactory yield and selectivity and sometimes drastic conditions. A moderate yield with *trans* selectivity was observed in the coupling of few hindered ketones using sodium in boiling xylene (Scheme 1).[5, 6]

Scheme 1.



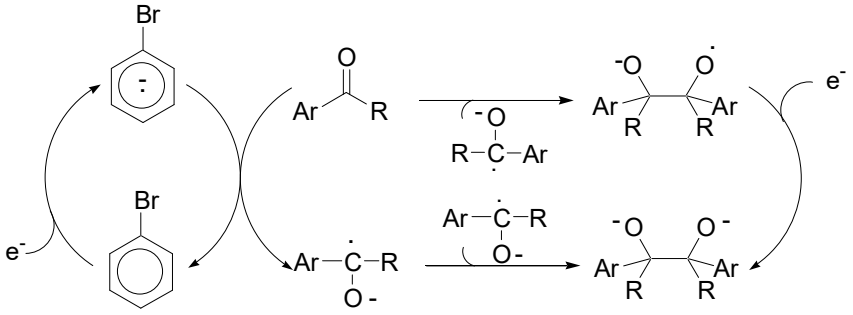
Lithium: Among other alkali metals, lithium in combination with stoichiometric amount of TMSCl provided pinacols from aliphatic aldehydes in moderate yield with a very poor selectivity.[7] Li/liquid NH_3 is also another old method found in literature.[8] Recently, Guo et al reported a novel solvent free system where a high diastereoselectivity has been achieved using lithium and a catalytic amount of bromobenzene as the electron carrier (Scheme 2).[9] Aliphatic ketones showed less reactivity to this protocol but the selectivity obtained in cases of aromatic aldehydes were quite high (Table 1). A high diastereoselectivity was also achieved using amalgamated lithium.[10]

Table 1.



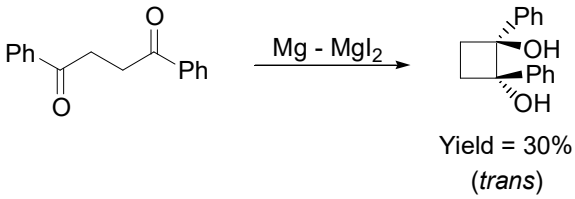
Entry	Substrate	Yield	*dl*:*meso*
1.	PhCHO	84%	99:1
2.	2-ClC_6H_4CHO	81%	100:0
3.	2,4-$Cl_2C_6H_3CHO$	90%	100:0
4.	$PhCOCH_3$	87%	74:26
5.	$PhCH{=}CHCOCH_3$	75%	100:0

Scheme 2.



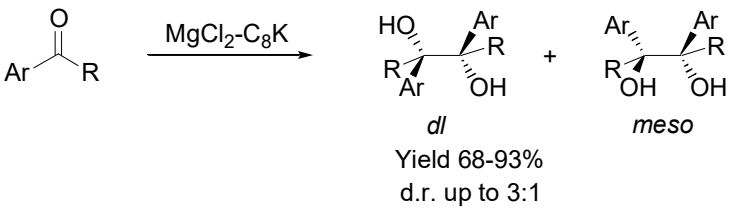
Magnesium: Magnesium is the only alkaline earth which found its early application in pinacol coupling reaction in an amalgamated form.[11] An equimolar mixture of Mg-MgI_2, introduced by Gomeberg and Bachman gained popularity as a coupling agent for aromatic ketones or hindered aromatic aldehydes.[12] Simple aromatic aldehydes were reduced rather than coupled by this reagent.[13] 1,2-Dibenzoyl ethane was coupled to *trans* 1,2-diphenylcyclobutanediol selectively using Mg-MgI_2 (Scheme 3).[14]

Scheme 3.



In the presence of stoichiometric amount of TMSCl, magnesium can also couple aromatic aldehydes in good yields.[15] The above protocol was effective in the cases of keto-aldehyde or with cyclic aldehydes.[16] However the selectivity remained low in all the cases. Magnesium, as a fine dispersion on graphite can couple aldehydes or ketones in moderate selectivity.[17] A variety of aldehydes were coupled in high yields. The intramolecular cyclization also proceeded smoothly (Scheme 4).

Scheme 4

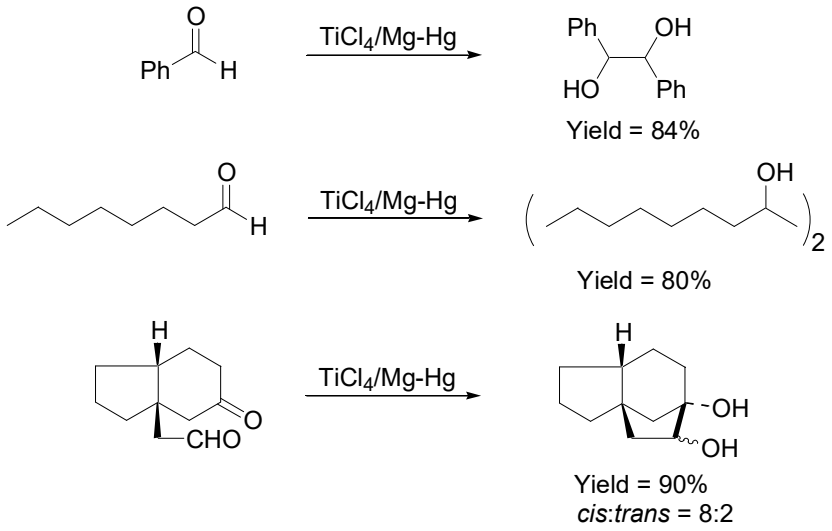


Transition metals

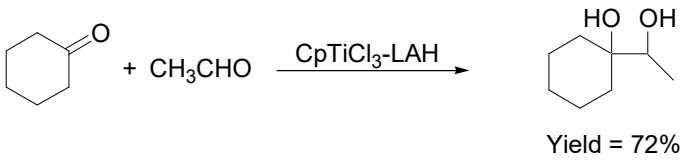
Titanium: Titanium is the most popular reagent for pinacol coupling. The reducing ability of titanium was established long ago, for example reduction of ethylenic acids with aqueous Ti(III) solution.[18] The development on the titanium chemistry proliferated in early 80's following three independent discoveries by Tyrlik,[19] Mukayama[20] and McMurry[21] to generate low valent titanium species for the reductive coupling of ketones/aldehydes. All these investigations unveiled the synthetic utility of low valent titanium and opened new vistas in organometallic chemistry.

***Titanium(II)*:** A number of reducing agents have been employed so far for the generation of Ti(II) or Ti(III) species, thought to be efficient reagents for the pinacol coupling reaction. Initially Ti(II) based coupling agents were used for this reaction which met with significant success.[22] One of the most efficient precursor was developed by Corey et al using $TiCl_4$ and magnesium amalgam.[23] It was further modified to $CpTiCl_3$-LAH for the cross coupling of ketones with aldehydes (Scheme 5 & 6).

Scheme 5.



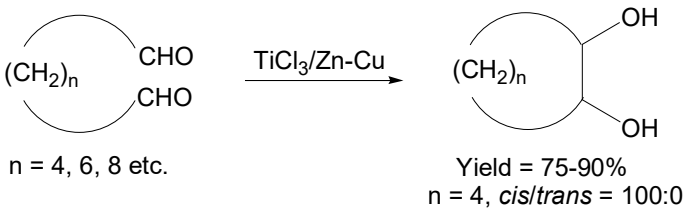
Scheme 6.



The combination of $TiCl_3$/Zn-Cu, introduced by McMurry was also used successfully for the intramolecular coupling of various aldehydes.[24] The *cis* isomer

dominated in the small rings whereas the *trans* isomer became prominent with rings containing ten or more carbon atoms (Scheme 7).

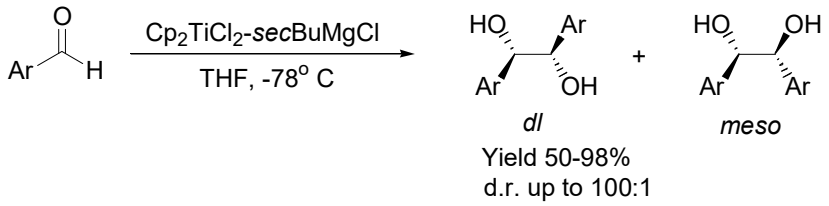
Scheme 7.



A number of other reagents like $TiCl_3$-K/I_2,[25] $TiCl_3$-Li/Napthalene,[26] Ti(II)-porphyrin complex,[27] $TiCl_2$-Zn[28] to generate low valent titanium were also employed for the pinacol coupling reaction.

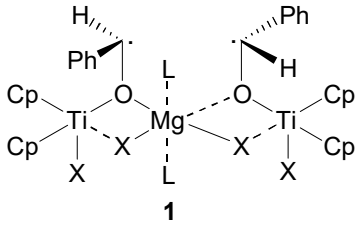
Titanium(III): Till the early 80's there were hardly few reports of performing pinacol coupling using well defined Ti^{+3} species.[29] Inanaga in 1987 reported a cyclopentyl bound Ti^{+3} reagent, generated by the reduction of Cp_2TiCl_2 with *sec*BuMgCl for the coupling of aromatic aldehydes.[30] Aldehydes containing an electron donating group were coupled in excellent selectivity (Scheme 8).

Scheme 8.



Aliphatic aldehydes showed poor selectivity. The stereochemical outcome was attributed to a dimeric structure (**1**) as shown in figure 3.

Figure 3.

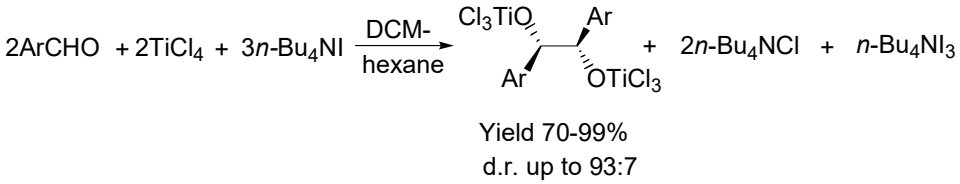


1

X = halogen, L = solvent

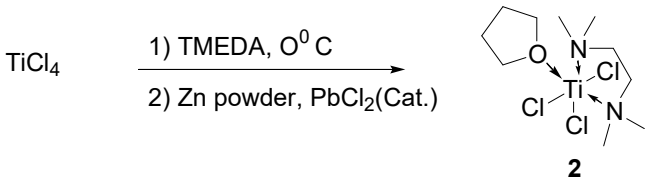
The high *dl* selectivity originated from the repulsion of the aromatics groups. This assumption was reinforced by the experimental finding of a decrease in *dl* selectivity with an electron withdrawing substituent in the aromatic ring. Porta et al showed that an anhydrous $TiCl_3$ solution in dichloromethane can provide pinacols with high selectivities.[31] Various other combinations e.g. $Ti(O^iPr)_4/EtMgBr$,[32] $TiCl_4/Zn$,[33] Cp_2TiCl_2/SmI_2,[30] Cp_2TiCl_2/Zn[30], $Cp_2TiCl_2/^iPrMgI$[30] were also used for pinacol coupling with good success. In most cases a stoichiometric reductant was used to produce the low valent titanium with a concomitant generation of a metal halide. This caused the undesired paths to operate simultaneously resulting in a poor selectivity. To avoid this possibility, Oshima et al used tetrabutylammonium iodide as a stoichiometric reductant (Scheme 9).[34] The tetrabutylammonium iodate generated as the side product, did not interfere in the reaction. The newly generated Ti(III) was found to be very much efficient for both aliphatic as well as aromatic aldehydes. The mechanism proposed was proved by further experimental studies.

Scheme 9.



Addition of TMEDA and zinc to $TiCl_4$ in the presence of catalytic amount of $PbCl_2$ provided [$TiCl_3$.(TMEDA).(THF)] (**2**) in quantitative yield. Employing the aforesaid complex (**2**) with aromatic aldehydes a very high yield and excellent selectivity was observed in the pinacols (Scheme 10).[35]

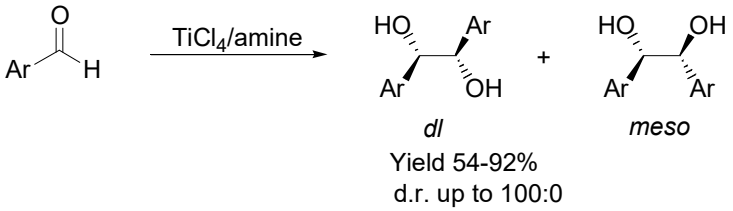
Scheme 10.



2

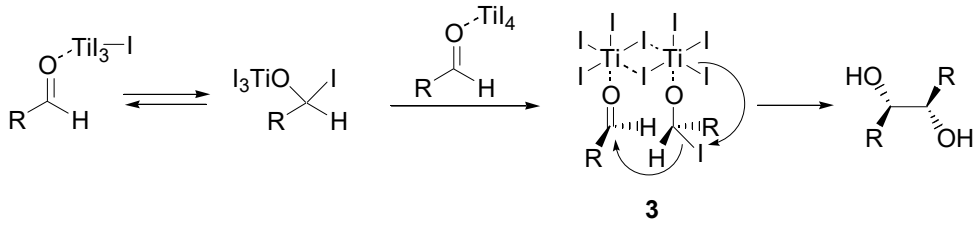
Addition of non chelating amines e.g. TEA,[36] DIPEA[37] to $TiCl_4$ proved to equally effective in generating a Ti^{+3} species.

Scheme 11.



Titanium(IV): Pinacol coupling has also been achieved with Ti^{+4} species avoiding the use of any stoichiometric reductant. Titaniumtetraiodide in propionitrile under argon atmosphere provided hydrobenzoins in excellent yields and selectivities.[38] Aliphatic aldehydes were found inert to this reagent. To circumvent this problem, *β* halogenated or *α*, *β* unsaturated aliphatic aldehydes were employed.[39] The mechanism was believed to involve an iodination in the first step. This intermediate on reacting with another activated molecule formed (**3**) and finally the pinacol (Scheme 12).

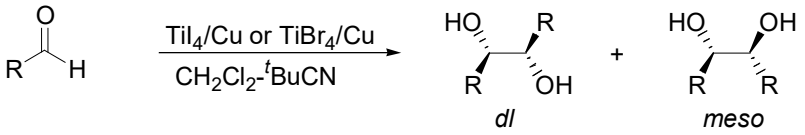
Scheme 12.



3

Other low valent halogen derivatives were also employed for pinacol coupling reactions. Indeed a low valent titanium iodide generated by mixing TiI_4 and copper was found to provide better results than titaniumdibromide or dichloride.[40] The superiority of the iodide derivative was explained by its monomeric nature due to its bigger size. Thus the inhibition of cluster formation resulted in higher solubility and in turn a better selectivity.[41] The use of pivalonitrile as a co-solvent increased the solubility through coordination of the nitrogen lone pair (Table 2).

Table 2.

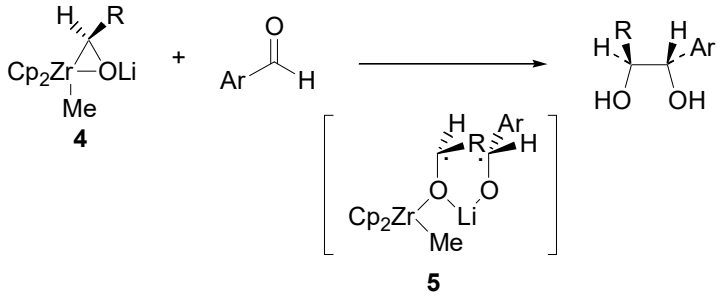


entry	R	TiI_4/Cu		$TiBr_4$/Cu	
		Yield	*dl*:*meso*	Yield	*dl*:*meso*
1.	Ph	94%	>99:1	95%	96:4
2.	4Cl-C_6H_4	93%	>99:1	97%	99:1
3.	4MeOC_6H_4	76%	98:2	74%	94:6
4.	PhCH=CH	76%	99:1	80%	91:9
5.	C_6H_{11}	98%	85:15	75%	75:25
6.	$(CH_3)C$	92%	85:15	n.r.	-

n.r. No reaction

Zirconium: Pinacol coupling was also achieved through dimerization of anionic zirconaoxiranes (**4**) with aromatic aldehydes or ketones.[42] The cross coupled products were produced in high yield with the selectivity up to 19:1 for *dl*:*meso* in case of *p*-tolualdehyde. The higher selectivity was explained by a lithium bound intermediate **5** (Scheme 13).

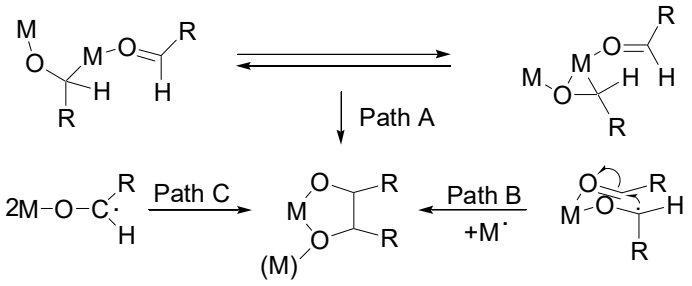
Scheme 13.



Vanadium: Among other early transitional metals, vanadium found wide application in the stereoselective pinacol coupling reactions. In 1989 Pederson et al prepared a low valent vanadium complex using $VCl_3(THF)_3$ and Zn. It showed a coupling ability towards aryl aldehydes with good yield and selectivity.[43] Aldehydes containing a chelating group in aromatic ring was found to be more suitable as a substrate. The reaction is believed to

proceed via either path **A** or path **B** (Scheme 14) furnishing a cross coupled product with two aldehydes of different reactivity in moderate yield, but poor selectivity.[44]

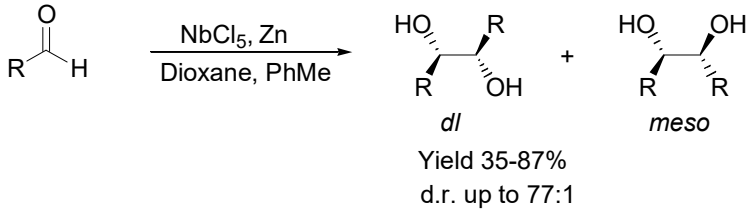
Scheme 14.



Aldehydes containing a sulfide or sulfone group were also coupled by employing this reagent. The effect of the size of the sulphur substituent was found to be optimum at a certain limit.[45]

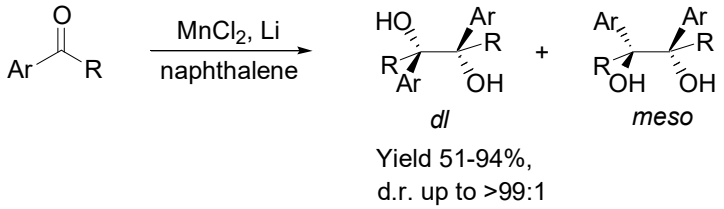
Niobium: The efficiency of niobium as a reductant was realized with the success for coupling an imine with an aldehyde.[46] Later this reagent proved effective for coupling aliphatic aldehydes in high selectivity. Even the intramolecular coupling proceeded with a high *cis*/*trans* ratio.[47] The in situ generation of Nb(III) by reducing $NbCl_5$ with Zn has proved to be an excellent methodology for the pinacol coupling reaction (Scheme 15).[48] This reaction is believed to proceed through a niobiooxirane intermediate. Oshima et al used Bu_4NI to reduce $NbCl_5$ which also provide a very high de in the coupling of aromatic aldehydes.[34]

Scheme 15.



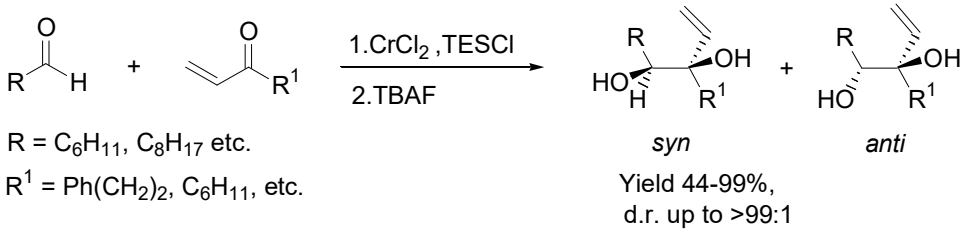
Manganese: Reduction of manganese halides with lithium in the presence of an electron carrier generates an active manganese which has been found to be an excellent promoter for pinacol coupling reaction of a variety of aromatic aldehydes.[49] The ratio of manganese to aldehyde was found to be extremely important for a good yield. This protocol was equally effective for aromatic ketones where a high selectivity was observed (Scheme 16).

Scheme 16.



Chromium: A chromium mediated cross-coupling between an α, β unsaturated ketone and an aldehyde was reported by Takai et al using an excess of $CrCl_2$ and TESCl.[50] The role of the silylating reagent was to trap the γ-siloxy-substituted allylic radical. This radical immediately reacts with Cr(II) to form γ-siloxy-substituted chromium complex which couples with the aldehyde. A cyclopropane derivative was recovered in the absence of silylating agent. The yield and selectivities were quite good (Scheme 17).

Scheme 17.

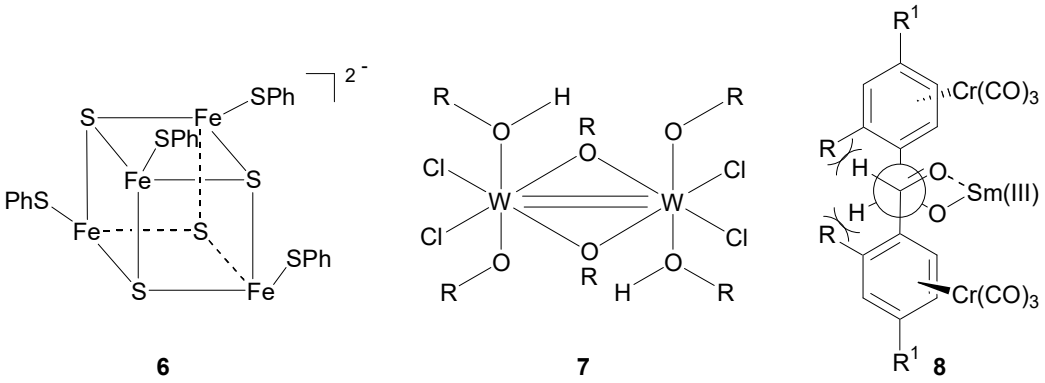


Zinc: Zinc in the presence of trimethylsilylchloride promoted pinacol coupling of aromatic aldehydes.[51] Though the yields were moderate, the selectivities were very poor.

Iron: Coupling of various aldehydes was also found to proceed in high yields using $Fe(CO)_5$ or $Fe_3(CO)_{12}$ and pyridine.[52] The reactive intermediate is believed to be a divalent iron complex of the molecular formula $[Fe(C_5H_5N)_n][Fe_2(CO)_8]$. Inoue et al used $FeCl_3$ and ^{n}BuLi to couple aromatic aldehydes and ketones. The yield and selectivity remained moderate.[53] The iron cluster **6** was also found to act as an efficient electron transfer carrier in combination with ^{n}BuLi. The yield and the selectivity varied with the molar ratios of ^{n}BuLi employed.

Tungsten: A doubly bound tungsten complex (**7**) was employed by Cotton et al for the reductive coupling of dialkyl ketones. The structure of the complex was confirmed by X-ray crystallography.[54] This multiply bound dinuclear complex was the first example in this category that showed a reductive coupling of ketones.

Figure 4.



6 **7** **8**

p-block elements:

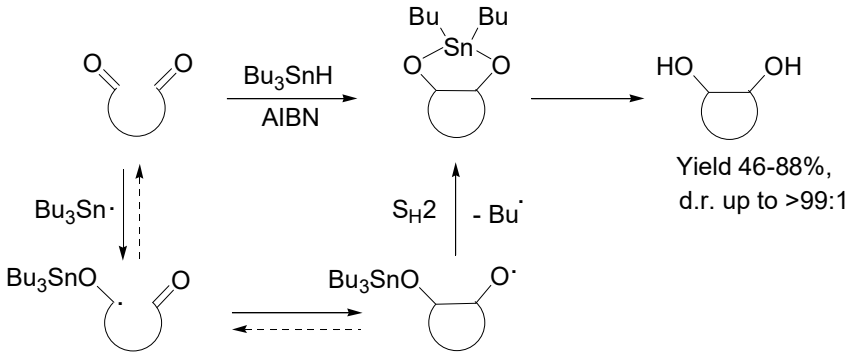
Very few p-block elements have been used in stoichiometric amount to perform pinacol coupling reaction.

Aluminium: Aluminium amalgam has remained a reliable tool since the early days of pinacolic coupling.[55] Schreibmann et al reported pinacol coupling of acetophenone using the same reagent in dichloromethane with a very high *dl* selectivity.[56]

Silicon: Hexamethyldisilane in combination with catalytic amount of CsF or TBAF afforded pinacols in moderate to good yield but poor selectivity.[57] Methyldiphenylsilyllithium was also able to couple benzophenone in low yield.[58]

Tin: Tributyltinhydride was found to promote intramolecular pinacol coupling in presence of AIBN.[59] This reagent with the ability to form five or six membered rings, showed an excellent selectivity for the *syn* isomer in a very good yield. A thorough study on the reaction mechanism was conducted using isotope labeling experiments. The key step was found to be an unprecedented addition of a tin ketyl radical to a carbonyl. A subsequent intramolecular homolytic substitution (S_H2) provided the pinacol (Scheme 18).

Scheme 18.



Lanthanides:

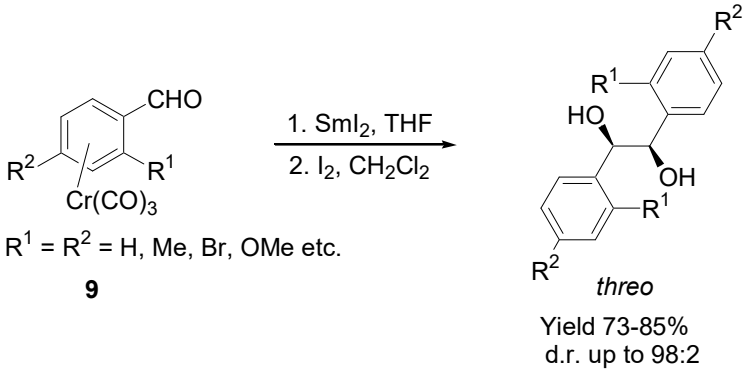
Among the lanthanides, samarium has been used most widely for both intra and intermolecular pinacol coupling reaction. However Hirao et al showed that it is possible to promote pinacol coupling by using almost every lanthanides in the presence of TMSCl under sonication.[60] The selectivities varied depending on the lanthanide employed.

Cerium: The use of cerium in pinacol coupling was first reported by Imamoto in 1982.[61] A varieties of combinations such as Ce-ICH_2CH_2I, CeI_3-K, Ce-C_6H_5I, Ce-$TiCl_4$ were tried for the in situ generation of low valent Ce(II). Finally an equimolar mixture of cerium and iodine was found to be the best. Applying this protocol, aliphatic or aromatic aldehydes and ketones were coupled in high yield. A variety of substituent in the aromatic ring were also tolerated.

Samarium *(Intermolecular)*: Kagan et al introduced SmI_2 in 1983 for the pinacol coupling of aromatic or aliphatic aldehydes.[62] The reaction proceeded smoothly in the absence of any protic solvent**.** Aliphatic ketones reacted at a very slow rate The addition of TMSCl although accelerated the reaction considerably, there was no improvement in the diastereoselectivity of the product.[63] Yamada et al later performed this reaction in protic solvents like MeOH without any improvement in the selectivity.[64] The in situ generation of low valent samarium was also achieved from metallic samarium using Sm/TMSCl/NaI[65] or Sm/Et_2AlI.[66] No improvement in the diastereoselectivity could be noticed.

Uemura et al reported *threo* selective pinacol coupling using a chromium bound benzaldehyde complex (**9**).[67] A very high yield and selectivity was observed with various aldehydes (Scheme 19).

Scheme 19.



$R^1 = R^2$ = H, Me, Br, OMe etc.

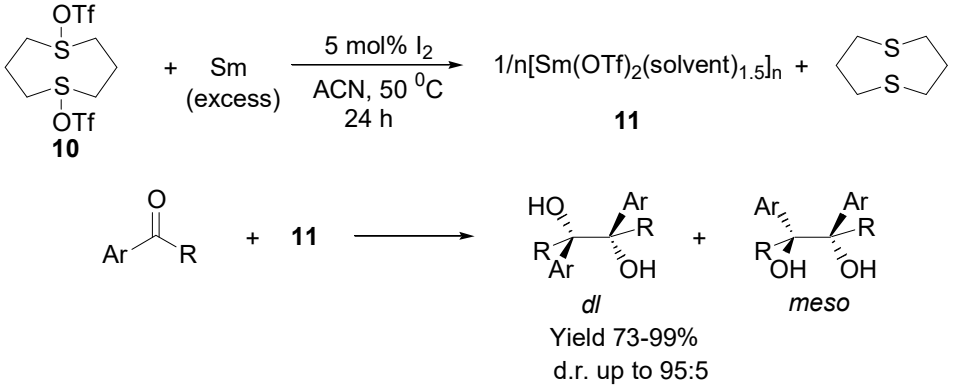
9

Surprisingly, the addition of HMPA reversed the selectivity. The rationale to this high selectivity was explained through a Newman model (**8**) where both the oxygen atoms

of the carbonyls were bound to the same samarium. This conformation was disrupted through coordination of a heteroatom or by an *o*-substituent. As a result of which a reversal in the selectivity was observed in case of *o*-bromo derivative.

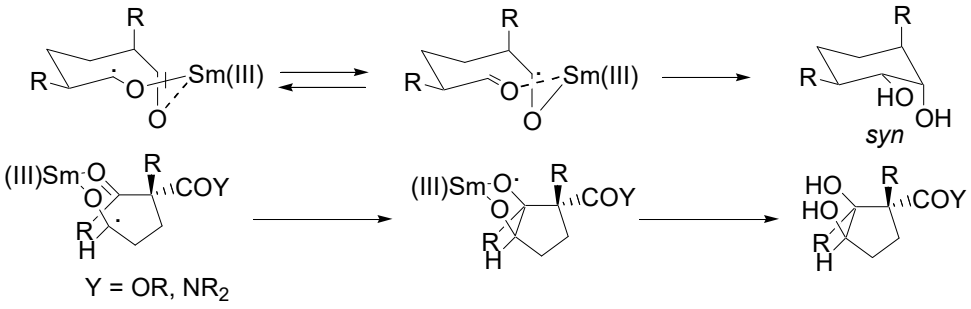
Beside samarium halides, divalent samariumtriflate were found to be excellent precursors. The in situ generation was achieved by reducing $Sm(OTf)_3$ with EtMgBr[68] or *sec*-BuLi.[69] The selectivity was very low in both the cases. An excellent diastereoselectivity with aromatic ketones was reported by Tani et al with a divalent samarium complex (**11**) prepared in situ from the hypervalent sulfur compound (**10**).[70]

Scheme 20.



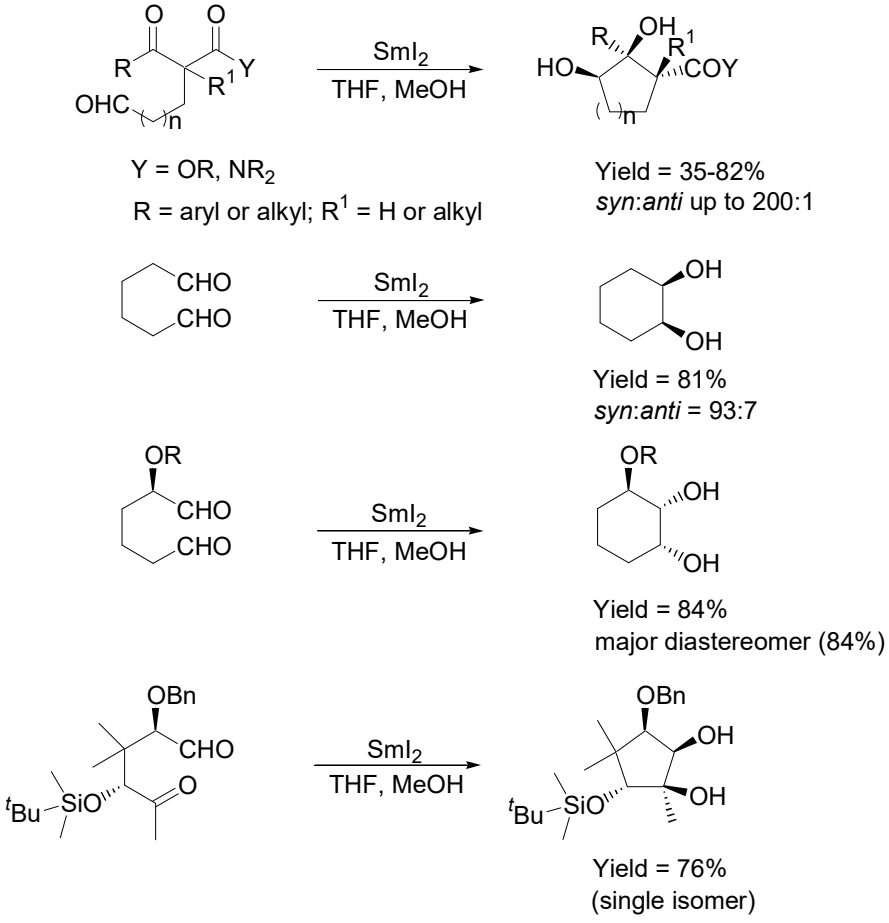
Intramolecular: The chemistry of samarium mediated intramolecular pinacol coupling is rather rich and well established. The first example in this category was reported by Kagan et al in the year 1983 during the synthesis of 1,2-diphenyl-1,2-cyclohexanediol.[71] Later on a number of publications appeared where a definite stereocontrol was achieved by the help of a neighbouring coordinating group. Hanessian et al prepared a number of cyclic diols from the corresponding dialdehydes or ketones in a high *syn* selectivity.[72] The stereochemical outcome was attributed to the inherent geometric preference for the coordination of the ketyl radical with the distal aldehyde carbonyl and the samarium (III) ion (Scheme 21). The most interesting part of this coupling reaction is that the presence of an alkoxy,[72] ester,[73] amide[73] or siloxy[74] group in the neighbouring carbon on either or one of the carbonyl groups forces an *anti* orientation of the hydroxyl group with respect to the substituent (Scheme 22).

Scheme 21.



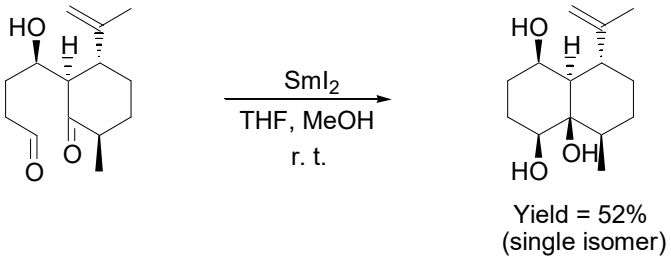
It is logical to assume that the dipolar repulsion (β substituent effect) plays a key role in this. To minimize the electronic as well as steric repulsion with the α-substituent, a *trans* orientation of the hydroxyl group is favored.

Scheme 22.



A free -OH group was also found to effect the selectivity through coordination (Scheme 23).[75]

Scheme 23.



Ytterbium: Ytterbium mediated pinacol coupling although known for a long time,[76] was not studied thoroughly till Fujiwara et al proposed a detailed mechanism for the umpoled behavior of the diaryl ketones for the formation of pinacols.[77] They also obtained a cross coupled product with this reagent. In the presence of TMSBr[78] or phenylthio-trimethylsilane,[79] metallic ytterbium was found to promote pinacol coupling efficiently. The former reagent was applied for cyclic aliphatic ketones whereas the latter was effective for aromatic systems. The ratio of *dl*:*meso* went up to 4:1 in case of *p*-chloro derivative. The yields were moderate in all the cases.

2.1.2. Enantioselective:

There are very few examples of enantioselective pinacol coupling using stoichiometric protocols. Enantioselectivity in most cases, has been achieved either by using a chiral auxiliary or by transferring the axial chirality to the central atom. However in true sense, the use of stoichiometric amount of chiral complexes proved to be the best and met with a better success.

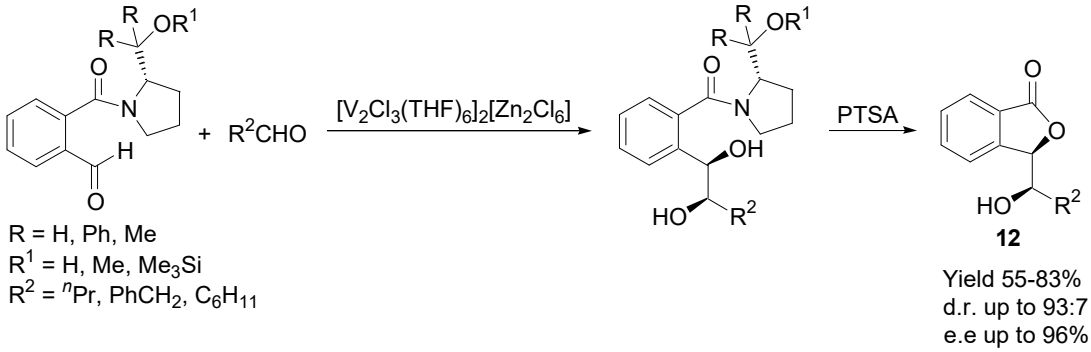
Alkali and alkaline earths

Lithium: The enantioselectivity in a lithium induced pinacol coupling of camphor originated from a selective coupling between two similar enantiomers. Pradhan et al reported that optically active or racemic camphor when subjected to pinacol coupling under same condition, only a single pinacol or racemate was produced respectively.[8] The stereochemistry of the single product formed was established to be *endo*:*endo*. The conclusion drawn from the above fact was that the reaction took place only between a (+) and (+) or a (-) and (-) enantiomers. The single isomer was produced in moderate yield but in high selectivity.

Transition metals

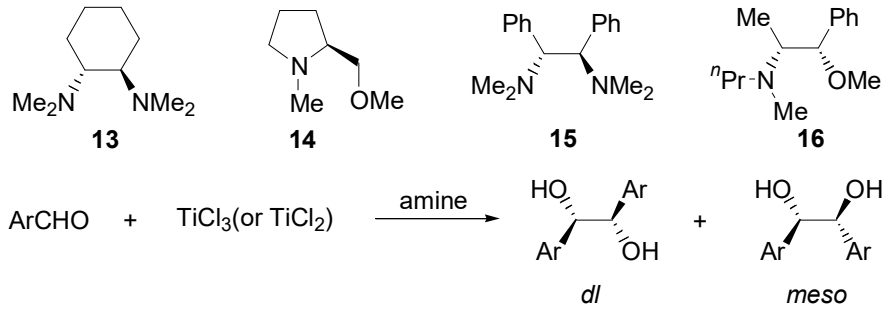
Vanadium: Using $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ for the cross coupling between an aliphatic and an aromatic aldehyde containing a chiral auxiliary, a high enantioselectivity in the final product (**12**) was obtained (Scheme 24).[80]

Scheme 24.



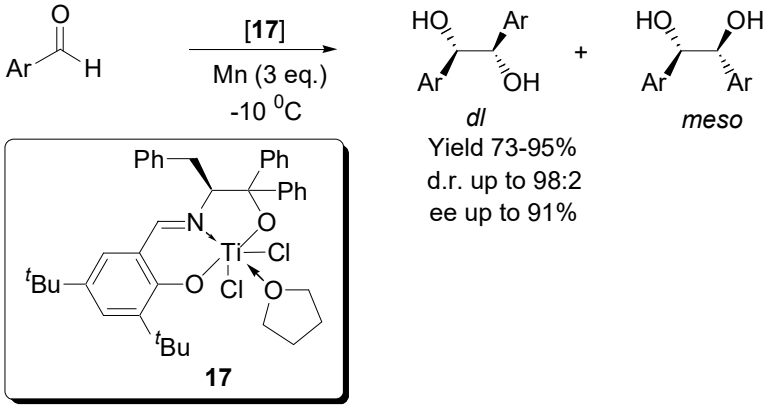
Titanium: Titanium is the most successful among all the metals in producing optically active pinacols from prochiral aldehydes. A preformed chiral titanium complex or in combination with a chiral ligand is used as the most reliable tool to perform enantioselective pinacol coupling reactions. Matsubara et al achieved a moderate enantioselectivity using a chiral amine with a low valent titanium.[81] Among the variety of chiral amines tried *N*,*N*,*N'*,*N'*-tetramethylcyclohexylamine (**13**) proved to be the best in combination with $TiCl_3$ inducing 40% ee in the hydrobenzoin. An insight into the reaction mechanism using SAXS measurement and AFM (Atomic Force Microscopy) revealed the presence of two kinds of particles in the solution. The cluster particle with the general formula $[(TiCl_3)_n(amine)_m]$ were inert and responsible for the drop of ee. Whereas the monomeric particles $[TiCl_3(amine)_{1\sim2}(THF)_{1\sim2}]$ were responsible for the coupling. The addition of cosolvent for the breaking of the cluster resulted in an increased ee of 58%.[82] In another report, Enders et al achieved 65% ee with a high *dl*:*meso* ratio using $TiCl_2$/amine **14** for the coupling of benzaldehyde.[83] No better selectivity was observed with other aldehydes (Scheme 25).

Scheme 25.



An enantioselectivity up to 91% was reported by Riant et al using a titanium hemi-SALEN complex **17** (Scheme 26).[84] A decrease in the ee was observed with electron withdrawing substituent at the para position.

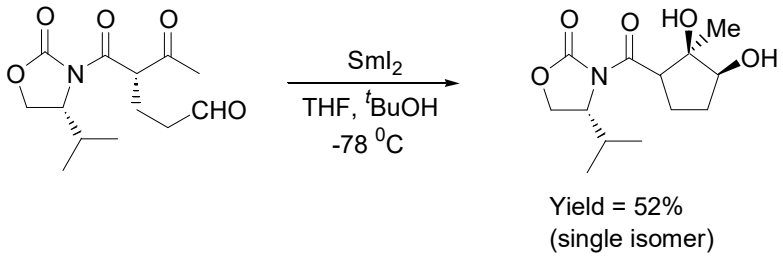
Scheme 26.



Lanthanides

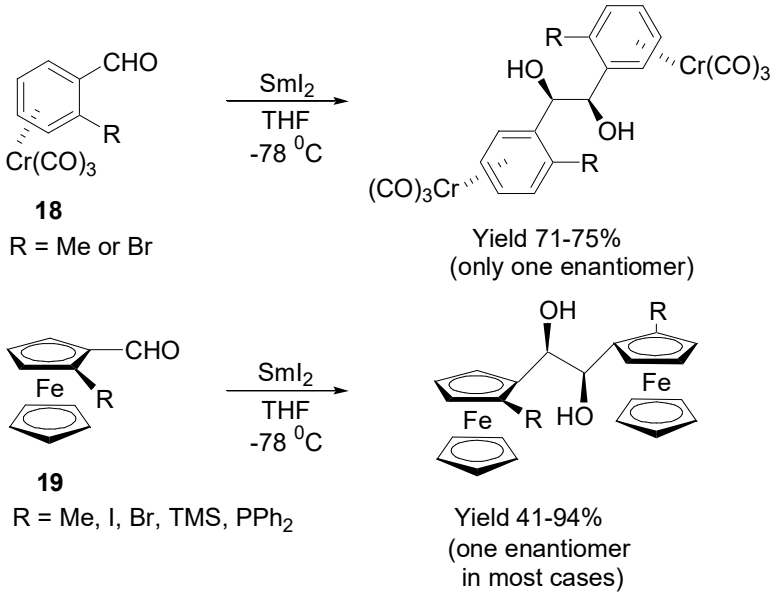
Samarium: With the knowledge of a preferential *syn* selectivity of samarium mediated intramolecular pinacol coupling reaction, a number of optically pure aldehydes were treated with SmI_2 to form an enantiomerically pure diols. One of the first example was set by Molander et al through an intramolecular cross-coupling reaction (Scheme 27).[85]

Scheme 27.



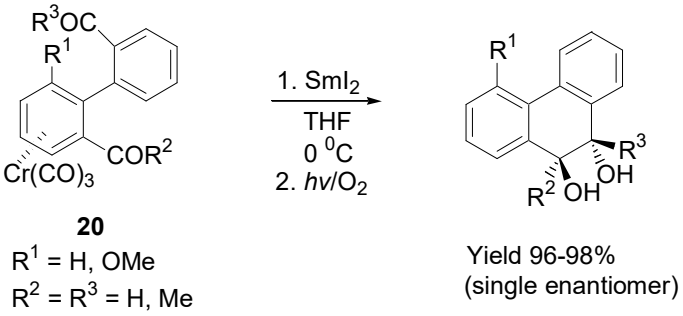
Kagan et al performed an intermolecular enantioselective pinacol coupling reaction between a camphor and benzophenone using $SmBr_2$. As predicted an optically pure diol was formed.[86] Uemura et al showed that an optically active chromium bound ortho substituted benzaldehyde (**18**) can be coupled in an enantioselective fashion using SmI_2.[87] The same methodology was further extended to optically active 2-substituted ferrocenecarboxaldehyde (**19**) (Scheme 28).

Scheme 28.



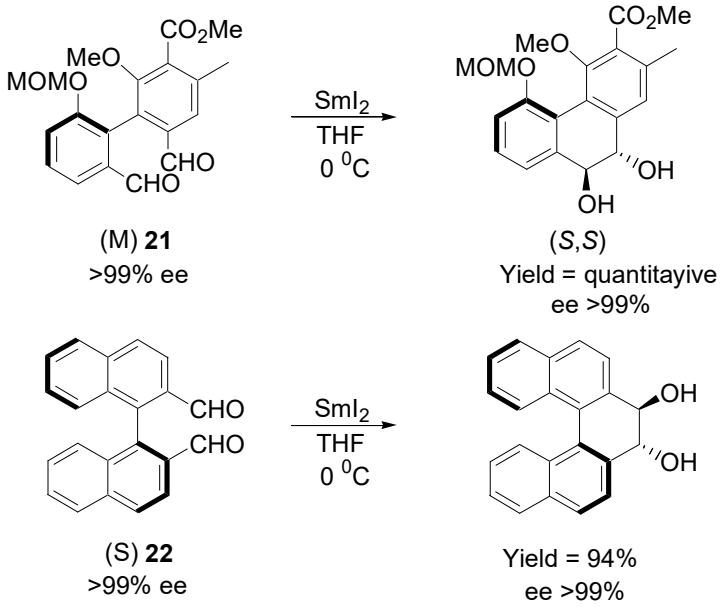
Applying a similar methodology, chiral 1,2 diols were prepared from a chiral mono $Cr(CO)_3$-complexed biphenyl derivative **20** (Scheme 29).[88]

Scheme 29.



Suzuki et al developed a new method for transferring axial chirality of biphenyl derivatives to the central chirality through pinacol coupling reaction.[89] After examining a variety of coupling agents, SmI_2 proved to be the best. The *trans* diols were obtained in optically pure form as a single diastereomer starting from the aldehydes **21** and **22** (Scheme 30).

Scheme 30.



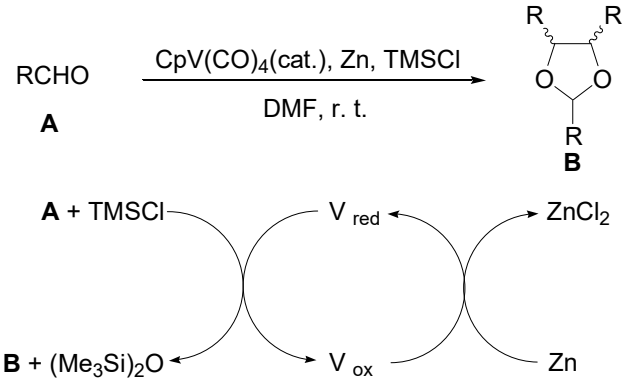
2.2. Catalytic protocols

2.2.1. Diastereoselective

Transition metals: Although the introduction of catalytic protocols in the pinacol coupling reaction is not very old, it has developed exponentially in the last ten years. Transition metals remained the most favoured reagent in this context.

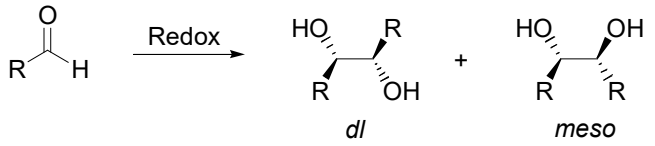
Vanadium: Hirao et al in 1996 described the first catalytic cycle for a vanadium mediated pinacol coupling reaction using Zn and TMSCl (Scheme 31),[90]

Scheme 31.



Soon after this report, various other methods were developed based on the similar reagents. e.g. $Cp_2VCl_2/Me_3SiCl/Zn$,[91] $VOCl_3/Me_3SiCl/Al$[92] etc. In most cases a good selectivity was achieved and was extended to imine coupling as well (Table 3).

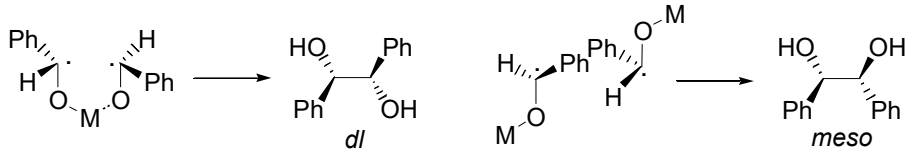
Table 3.



Entry	R	Redox	Yield	*dl*:*meso*	Ref
1.	C_6H_5	$VOCl_3$/Al/TMSCl	68%	>95:5	92
2.	4-ClC_6H_4	$VOCl_3$/Al/TMSCl	89%	>95:5	92
3.	4-MeC_6H_4	$VOCl_3$/Al/TMSCl	62%	>95:5	92
4.	C_6H_{11}	Cp_2VCl_2/Zn/TMSCl	66%	90:10	91
5.	$Ph(CH_3)CH$	Cp_2VCl_2/Zn/TMSCl	66%	94:6	91
6.	$(CH_3)_2CH$	Cp_2VCl_2/Zn/TMSCl	89%	91:9	91

The higher *dl* selectivity was attributed to a metal bridged intermediate. On the other hand, an acyclic intermediate was proposed for the *meso* product (Scheme 32).

Scheme 32.

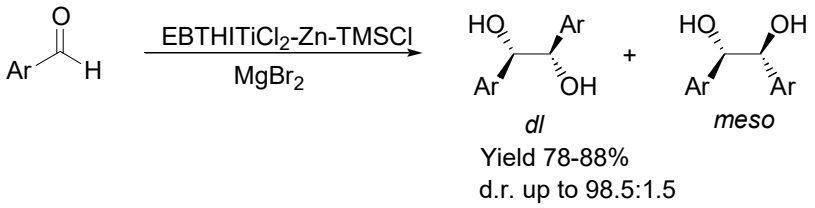


Instead of using TMSCl as the catalyst generator, acetic anhydride was also found to regenerate the catalyst.[93] The pinacols were obtained in more than 80% yield with a variety of substituent at ortho or para position of the aromatic ring. The diastereoselectivity went up to 94:6 for *dl*:*meso* in case of 2,6-$Me_2C_6H_3CHO$.

Titanium: The immense potential of titanium to promote a high diastereoselection in the pinacol coupling reaction was realized through its stoichiometric protocols. However a catalytic version is highly desirable for expensive complexes. The first break-through came after the report by Fürstner et al for recycling titanium using TMSCl.[94] The well documented Cp_2TiCl_2 prompted Gansäuer to pursue pinacol coupling with this reagent. As expected, a very good yield and diastereoselectivity was obtained with several aromatic aldehydes.[95] The preferential *syn* selectivity was attributed to a similar dimeric structure (**1**) as proposed by Inanaga.[30] The need of adding one equivalent of $MgBr_2$ as an additive was argued to contribute to a tighter trimeric species for a better steric tuning. The slow addition of the mixture of TMSCl and aldehyde was the key to a higher selectivity and

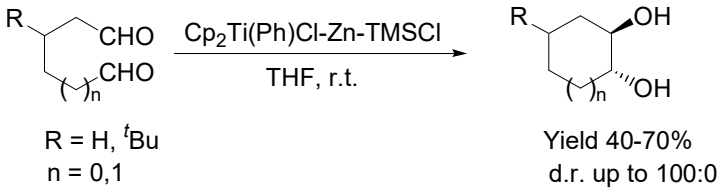
provided an evidence for the silylation step to be rate determining one. Hirao et al applied the same protocol for the pinacol coupling of aliphatic aldehydes and ketones.[96] A high diastereoselectivity of 96:4 for *dl*:*meso* was reported for cyclohexane carboxaldehyde, however, it remained low in cases of acyclic aldehydes and ketones. Slightly higher selectivity for the aromatic aldehydes was achieved using *rac*-ethylenebis(η^5-tetrahydroindenyltitanium)titaniumdichloride (EBTHITiCl$_2$) as a catalyst (Scheme 33).[97]

Scheme 33.



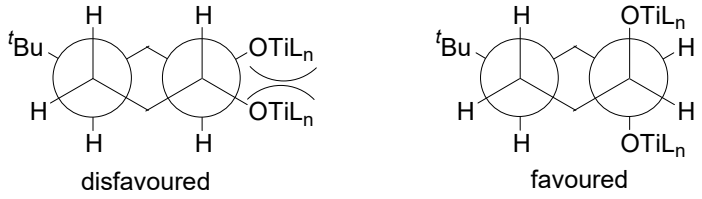
In most cases, the success of an organometallic complex depends on the monomeric nature of the reagent in the solution state. Probably this is the reason for different behavior of the newly generated titanium complexes from different sources. One of the easiest way of prohibiting dimerization could be to increase the sterics of the ligand. With this logic in mind, Itoh et al prepared a bulky Cp$_2$TiPhCl for the coupling reaction.[98] Though the selectivity was lower with aliphatic or aromatic aldehydes, the intramolecular pinacol coupling of dialdehydes containing five to six carbon atoms proceeded with an excellent selectivity (Scheme 34).

Scheme 34.



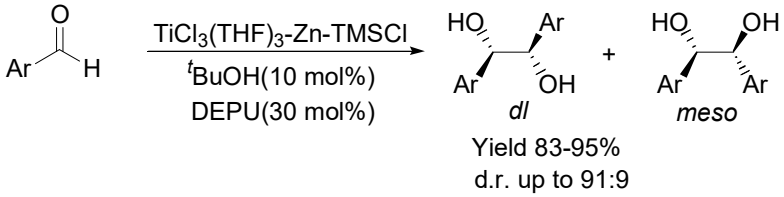
The high *trans* selectivity observed in this case was contrary to the report of McMurry using TiCl$_3$/Zn-Cu.[24] This was explained by the restriction of the bulky titanium radical to coordinate with another aldehyde moiety, unlike in McMurry's protocol. As a result of which the repulsion of the two bulky titanium insisted a *trans* orientation of the hydroxyl groups (Fig. 5).

Figure 5.



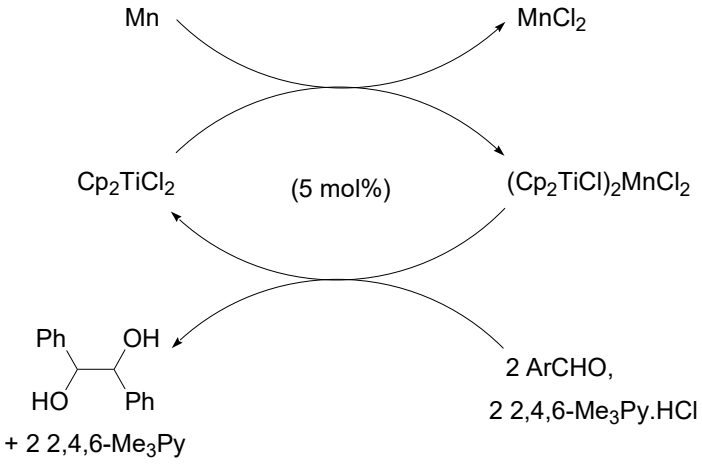
Nelson et al showed that instead of using complex ligands, it is possible to achieve high diastereoselection through a proper tuning of the catalyst architecture. $TiCl_3(THF)_3$-Zn-TMSCl redox in the presence of 10 mol% ^{t}BuOH and 30 mol% DEPU (1,3-diethyl-1,3-diphenylurea) furnished a high *dl* selectivity for various aromatic aldehydes.[99] In the optimized condition, the 1,5 dialdehyde was also coupled in a high selectivity (*syn*:*anti* = 89:11) (Scheme 35).

Scheme 35.



The catalytic cycle of titanium so far described was based on the stoichiometric use of TMSCl. Gansäuer et al achieved a catalytic turnover through protonation of the metal oxygen bond.[100] The catalytic cycle has been achieved using 2,4,6-collidine hydrochloride salt.

Figure 6.

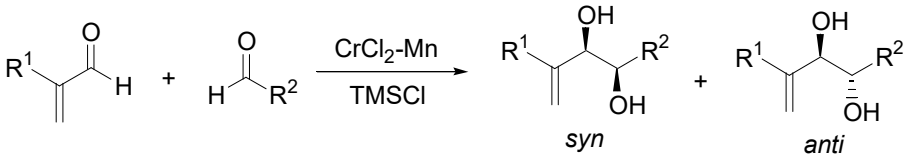


This new protocol was found to be very much effective for a variety of substituted aldehydes furnishing an excellent selectivity (>95% for *dl*) and a high yield.

Hirao et al established another catalytic cycle using acetyl chloride to cleave the metal-oxygen bond.[93] $TiCl_4$ in the presence of aluminium as a reductant and acetyl chloride as the catalyst regenerator provided a successful cycle for catalytic pinacol coupling of aromatic aldehydes. The yield were within a range of 78-94% and the diastereomeric ratio for *dl*:*meso* went up to 91:9 in case of *p*-$CF_3C_6H_4CHO$.

Chromium: Following the catalytic path established by Fürstner et al for "Nozaki-Hiyama-Kishi" reaction,[101] a number of publications appeared for the catalytic pinacol coupling of aldehydes or ketones using chromium.[102] A good yield and high selectivity has been achieved after optimizing solvent polarity, sterics of the silylating agent and the coreductant. Intramolecular pinacol coupling was also achieved in high *cis* selectivity. The selectivity was found to increase with an increase in the ring size.[103] 2-substituted acroleins were coupled with aldehydes in high selectivity using $CrCl_2$/Mn/TMSCl (Table 4).[104] With decrease in the steric demand, a fall of the selectivity was noticed. The change of the product conformation from *syn* to *anti* with changes in sterics was believed to be a consequence of the preferred conformation for the six membered transition state for the cross coupling reaction.[105] It is to be noted here that the reaction in this case doesn't proceed through a "classical" dimerization of two ketyl radicals, instead, a chromium allyl species attack another aldehyde.[106]

Table 4.



Entry	R^1	R^2	Yield (%)	*syn*:*anti*
1.	^{t}Bu	^{t}Bu	61	>98:2
2.	^{t}Bu	$Ph(CH_2)_2$	73	86:14
3.	Me	^{t}Bu	54	28:72
4.	H	^{t}Bu	52	22:78

Nickel: Tu et al proposed a similar catalytic method using nickel(II) chloride in combination with magnesium and TMSCl.[107] The catalytic cycle has been believed to

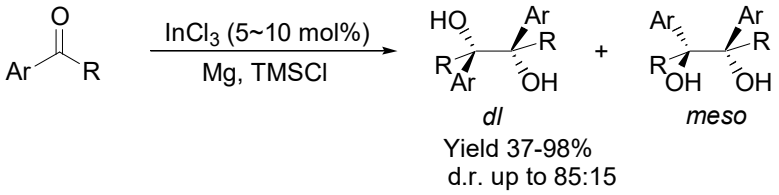
follow a similar path as describe for titanium. Although a variety of aromatic aldehydes were coupled in good yield, the diastereoselectivity remained low. Aromatic ketones and aliphatic aldehydes were also coupled with this protocol.

Ruthenium: A cationic thiolate bridged diruthenium complex [Cp*RuCl-(μ_2S^{i}Pr)$_2$Ru Cp*][OTf] (Cp* = η^5-C_5Me_5) was used for catalytic pinacol coupling reaction.[108] Unlike acetophenone, aromatic aldehydes were coupled in a quantitative yield. The selectivity was low in all the cases.

p-block elements

Indium: Among the p-block elements, only indium has been found to catalyze pinacol coupling reaction. $InCl_3$ in combination with Al[109] or Mg[110] and TMSCl was able to couple aromatic aldehydes and ketones (Scheme 36). The latter furnished a better result as compared to the former one. An electron withdrawing group in the aromatic ring was found to decrease both yield and selectivity whereas an electron donating substituent seemed to have a favourable effect.

Scheme 36.

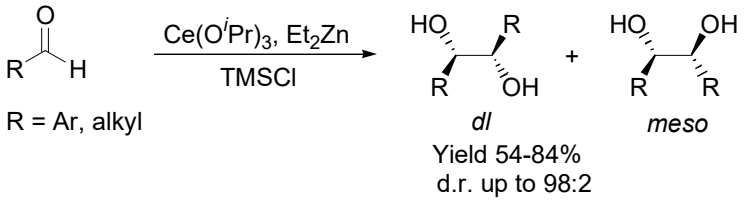


Lanthanides:

For catalytic pinacol coupling reaction, cerium and samarium are the only successful candidates from the lanthanide group.

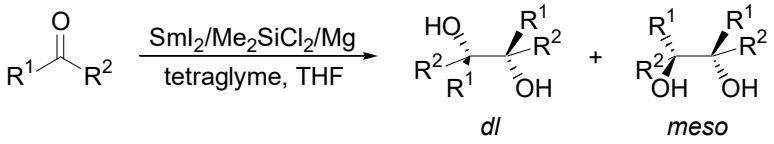
Cerium: Groth et al reported the first catalytic use of cerium in an analogous method described by Fürstner.[111] Diethylzinc was used in excess to generate the low valent cerium which was regenerated by TMSCl. The Protocol proved to be effective up to a 3 mol% loading. Various aromatic aldehydes were coupled in very high yield and excellent selectivity (Scheme 37). To overcome the need of a demanding sterics for a higher selectivity, reducing agents or the ligand framework has been modified.[112] Long chain aldehydes were also coupled, for the first time, in a high selectivity with this modified procedure. The author showed that with an increase in the ligand sterics, the selectivity as well as yield increased sharply.

Scheme 37.



Samarium: Endo et al established the catalytic cycle of samarium by avoiding the electrochemical route.[113] Thus SmI_2 in combination with Mg and TMSCl coupled aldehydes and ketones in a moderate to good yield albeit without any stereocontroll. Recently Greeves et al improved the selectivity through a little modification.[114] Tetraglyme as an additive and Me_2SiCl_2 as the catalyst regenerator afforded a selectivity as high as 95:5 for the *dl*/*meso* in cases of pivalaldehyde (Table 5).

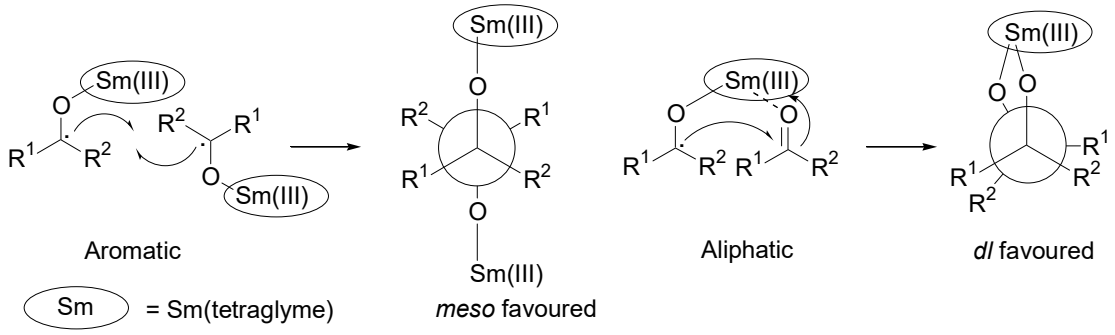
Table 5.



Entry	R^1	R^2	Yield (%)	*dl*:*meso*
1.	Ph	H	83	20:80
2.	Ph	CH_3	62	19:81
3.	C_6H_{11}	H	63	81:19
4.	$(CH_3)_3C$	H	76	95:5
5.	C_6H_{11}	CH_3	74	94:6

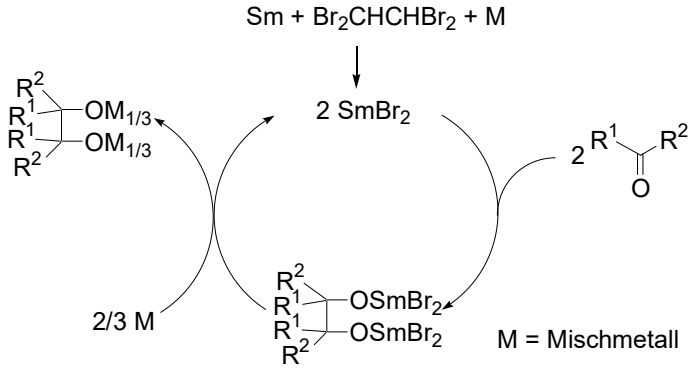
For intramolecular pinacol coupling also this protocol met with a good success. The reversal of selectivity was attributed to the ease of reduction in case of aromatic aldehydes as compared to the aliphatic one due to their low energy LUMO electrons. As a result of which the concentration of these radicals become sufficiently high to allow dimerization between two such species resulting in meso products. On the other hand, the aliphatic ketyl radicals being less in population, prefers to attach to another aldehyde through a pseudo-bridged transition state (figure 7).

Figure 7.



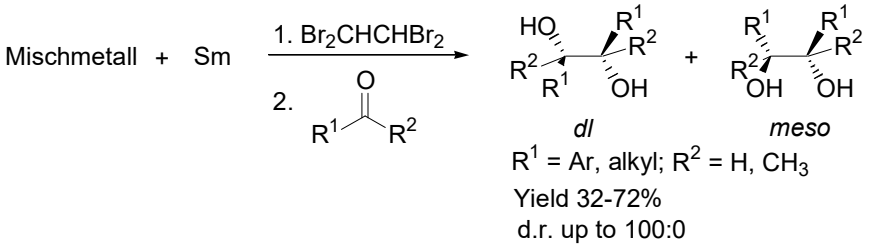
Namy et al established a catalytic cycle using a new approach.[115] The reduction of tri valent samarium as well as the cleavage of the Sm-O bond was achieved using Mischmetall (a cheap alloy of light lanthanoids used in large amounts for industrial application) (Figure 8).

Figure 8.



The *dl* selectivity went up to 100% in an highly demanding aldehyde.[116] The addition sequence and the addition time was found to be a determining factor towards high selectivity. Following this protocol, in optimized condition, a number of aldehydes and ketones were coupled in good success (Scheme 38).

Scheme 38.



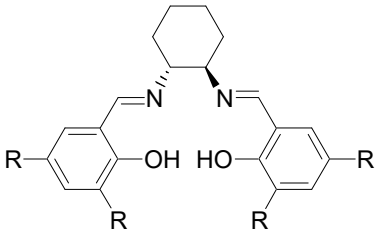
2.2.2. Enantioselective:

Achieving enantioselectivity through the use of a chiral catalyst is considered as the most modern way of synthesizing chiral compounds. For catalytic enantioselective pinacol coupling, titanium remained the most popular metal.

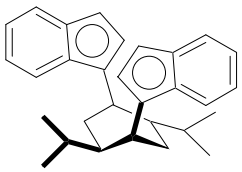
Transition metals

Titanium: Cozzi and Umani-Ronchi were the first to notice a low chiral induction in the pinacols while using Ti-Schiff base complexes.[117] After examining various Schiff bases, they found **23** induced 10% ee with high diastereoselectivity (*dl*:*meso* = 90:10). Taking the advantage of a high diastereoselectivity with *rac* Brintzinger's catalyst (ethylenebis(tetrahydroindenyl)titaniumdichloride), Nicholas et al tried its chiral version to catalytic pinacol coupling reaction.[118] They were pleased to see a moderate ee (60%) of the resulting pinacol in an unoptimized condition. To check the enantioselectivity of the pinacols using a similar ligand framework, *ansa* bis(indenyl) (Ti-**25**) and *ansa* bis(tetrahydroindenyl) (Ti-**26**) metal complexes were employed.[119] Unfortunately a racemic product was noticed in the bis(indenyl)complex (Ti-**25**) whereas a lower ee was obtained with the other complex (Ti-**26**). More recently Riant et al came with a complex (**17**) using the hemi-SALEN ligand (**27**) which induced up to 91% ee in a stoichiometric protocol. However it could induce only a moderate ee (64%) through a catalytic path.[84] This lower ee was rationalized through the inhibition of a proper catalytic path at a lower temperature. Later our group reported a Ti-SALEN complex (Ti-**24**) as a first successful catalyst for this reaction.[120]

Figure 9.



23, when R = ^{t}Bu
24, when R = H



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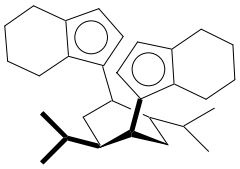

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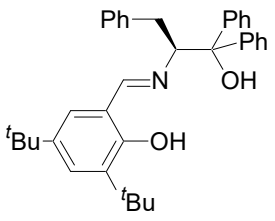
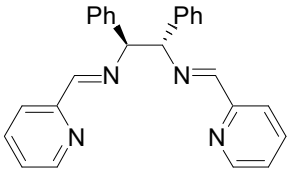
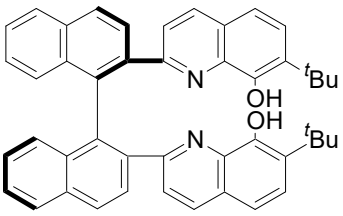


27



28

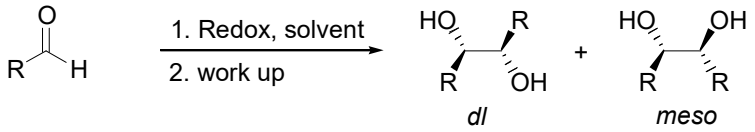


29 (TBOxH)

Recently You et al reported an in situ generation of Ti-Schiff base complex (Ti-**28**) which also showed a good enantioselectivity in most cases.[121]

Chromium: The most sophisticated and effective catalyst for enantioselective pinacol coupling has been designed by Yamamoto et al using a Cr complex of tethered bis(8-quinolinolato) (Cr-**29**).[122]

Table 6.



No.	R	Redox	Cat. loading	Temp.	Yield (%)	*dl*:*meso*	ee (%)	Ref.
1.	Ph	(Ti-**24**)-Zn-TMSCl	10 mol%	-10 ^{0}C	94	98:2	95	120
2.	4-$CH_3C_6H_4$	(Ti-**24**)-Zn-TMSCl	10 mol%	-10 ^{0}C	84	91:9	96	120
3.	2-MeC_6H_4	(Ti-**24**)-Zn-TMSCl	20 mol%	-10 ^{0}C	75	96:4	82	120
4.	2-Naphthyl	(Ti-**24**)-Zn-TMSCl	10 mol%	-10 ^{0}C	82	94:6	91	120
5.	Ph	(Cr-**29**)-Mn-TESCl	3 mol%	rt.	94	98:2	97	122
6.	3-$MeOC_6H_4$	(Cr-**29**)-Mn-TESCl	3 mol%	rt	92	98:2	97	122
7.	4-$CF_3C_6H_4$	(Cr-**29**)-Mn-TESCl	3 mol%	rt	89	92:8	95	122
8.	1-Naphthyl	(Cr-**29**)-Mn-TESCl	3 mol%	rt	92	96:4	98	122
9.	-$(CH_2)_6$-	(Cr-**29**)-Mn-TMSCl	3 mol%	rt	44	93:7	84	122

The chromium complex was prepared in three steps in very high yield starting from optically active 2,2'-diiodo-1,1'-binaphthyl. X-ray crystallographic study of the racemic catalyst revealed a *cis-β* configuration of TBOxCrCl. The catalyst proved to be quite

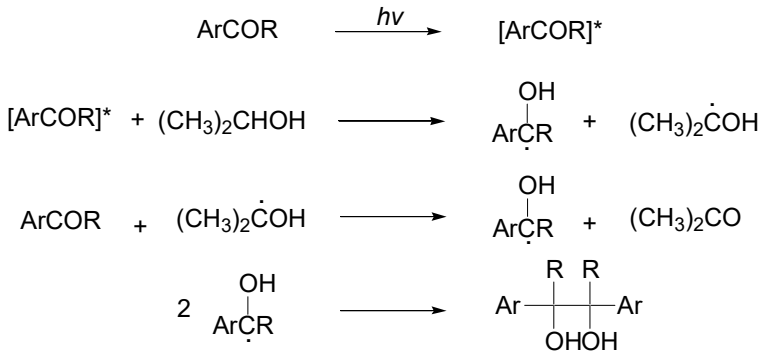
insensitive to the change of sterics as well as electronic of the aromatic ring. The enantioselectivity remained >95% in all the cases. Indeed the author also reported the first enantioselective coupling of aliphatic aldehydes.

3. Other methods

3.1. Photochemical irradiation

The formation of benzopinacols upon irradiation was noticed in the year 1900 by Ciamician[123] and about twenty years later a detail mechanistic study was conducted.[124] Since then the photo-irradiation through sunlight has become a reliable way to prepare benzopinacols.[125] Inspite of the slow rate, these reactions are encouraged due to their environmental friendly nature and cheap sources.[126] Recently Li et al reported the coupling of various aromatic aldehydes and ketones in excellent yields and in some cases, a very high selectivity.[127] The general mechanism involved in the reaction is the excitation of the aldehyde group followed by an extraction of a hydrogen from the solvent to form the α-hydroxybenzyl radical. Finally the dimerization of this radical furnishes the product (Figure 10).

Figure 10.



Seebach et al showed that irradiation of a solution of acetophenone in presence of a chiral amine at low temperature produced the pinacol in 58% yield with 6% optical purity.[128]

3.2. Sonication:

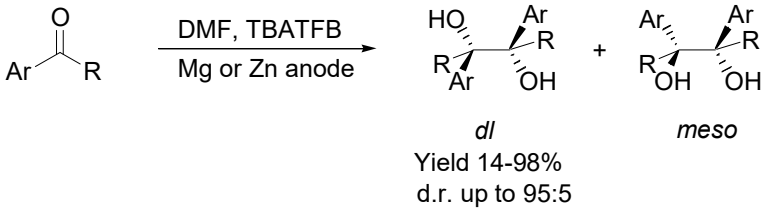
Sonical irradiation is also used for quite some time as a tool to achieve pinacol coupling in non-aqueous medium. Metals which are sluggish or do not react at all in normal condition, were found to furnish pinacols though ultrasound irradiation. The reason for such behaviour has been attributed to an active surface modification.[129] Alkali metals such as Na or Li[130] or a combination of Sm/NH_4Cl[131] provided pinacols of various aromatic

aldehydes and ketones in moderate to high yields, however with a poor selectivity. Recently Ranu et al achieved a very high selectivity using Li in THF under sonication.[132] Aromatic aldehydes and ketones were coupled in moderate to high yield with the selectivity ranging from 75:25 to 98:2 for *dl*/*meso*.

3.3. Electrolysis

Electrochemical reductions have been used since long time to prepare pinacols.[133] A number of examples appeared in literature for the preparation of the diols using a metal cathode (generally Hg) in aqueous, acidic or basic medium.[134] Indeed it is observed that the ratio of *dl* isomer increases in aqueous alkaline solution than in acidic condition.[135] Aprotic solvents in combination with a salt as an electrolyte has been employed for this reaction.[136] In most cases, a high yield of the product was obtained with low selectivity.[137] Coupling of unsaturated ketones[138] or cross coupling reactions[139] have found success in some cases. Using Zn or Mg anode and a stainless steel cathode in the presence of tetrabutylammonium tetrafluroborate (TBATFB) as a supporting electrolyte in DMF, a variety of aldehydes and ketones were coupled (Scheme 39).[140]

Scheme 39.



Duňach et al achieved a catalytic cycle of samarium in presence of 5 to 10 % of $SmCl_3$ based on the use of sacrificial anodes of Mg or Al.[141] A variety of aromatic aldehydes and ketones were coupled successfully in high yield but with a poor selectivity.

Seebach et al showed that it is possible to achieve some enantioselectivity, although to a very less extent by using an achiral supporting electrolyte in a chiral medium.[142] The hydrodimerization of acetophenone in a solution containing (+)-1,4-bis(dimethylamino)-2,3-dimethoxybutane (DDB) in combination with MeOH and LiBr proceeded in 95% yield of pinacol with a slight excess of one enantiomer. Dana et al also reported an enantioselective pinacol coupling of conjugated ethelenic ketones.[143] A maximum of 20% asymmetric induction was achieved in the electrochemical dimerization of acetophenone and its derivatives using chiral salts like (1*R*,2*S*)-HOCHPhCHMeN$^+$Me$_3$I$^-$.[144]

4. Reactions in aqueous medium

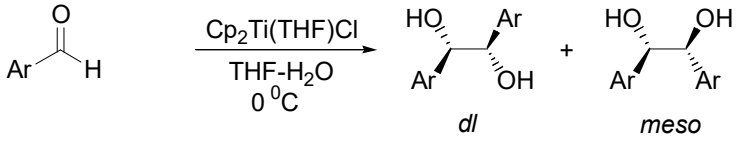
Alkali and alkaline earths

Magnesium: Magnesium is the only alkaline earth metal that can produce pinacol in a dilute aqueous solution of ammonium chloride with poor selectivity.[145] Sonication though increased the rate did not improve the selectivity.[146]

Transition metals

Titanium: Among the transitional metals, titanium remained the most successful in terms of selectivity. The reducing ability of titanium is very much dependent on the pH of the medium and it increases sharply with an increase of the pH value.[147] Aldehydes or ketones undergo a coupling in an acidic solution only if they contain an activated carbonyl group.[148] However, Porta and Clerici showed that they can be coupled easily in a basic medium.[149] But in all the cases, the selectivity remained very low. A reagent controlled highly selective pinacol coupling was reported by Schwartz et al using Cp_2TiCl in a mixed solvent of THF/H_2O for the α, β unsaturated aldehydes (Table 7).[150] The selectivity was very high with [$(EBTHI)_2TiCl$] for aromatic aldehydes.

Table 7.

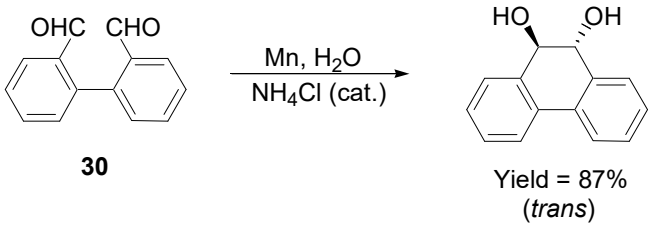


Entry	Ar	THF:H_2O	Yield(%)	*dl*:*meso*
1.	Ph	20:80	82	95:5
2.	4-FC_6H_4	80:20	85	94:6
3.	4-$MeOC_6H_4$	80:20	88	94:6
4.	Furfuraldehyde	80:20	75	95:5
5.	Cinnamaldehyde	80:20	83	98:2

Zinc: A combination of THF and aqueous ammonium chloride with Zn was found to be effective for the pinacol coupling of aromatic aldehydes and ketones.[151] The pinacols were obtained in moderate yield ranging from 32 to 82% but with a poor selectivity. Several other combinations such as Zn-Cu[152] or Zn-$ZnCl_2$[153] under ultrasonic irradiation were also found effective. Zinc in both aqueous alkaline[154] or acidic[155] solutions furnished diols in absence of any organic solvent.

Manganese: Aromatic aldehydes were found to react with manganese in an aqueous solution in presence of catalytic amount of acetic acid or in aqueous ammonium chloride.[156] Aliphatic aldehydes were inert. A variety of substituted aromatic aldehydes including 1-naphthaldehyde were coupled in good yield but with a poor selectivity. Surprisingly, the intramolecular coupling of **30** afforded only the *trans* diastereomer in 87% yield (Scheme 40).

Scheme 40.



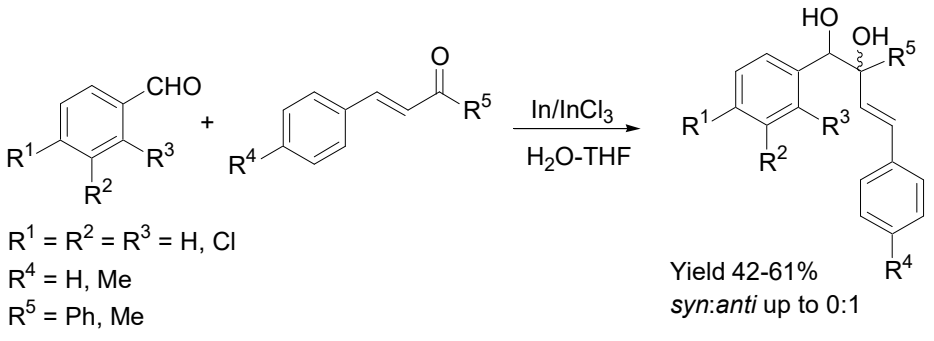
Cadmium: In situ generation of cadmium from $CdCl_2.H_2O$ in a DMF/ H_2O medium by reduction with samarium metal enabled coupling of aromatic aldehydes in good yield with a *dl*:*meso* ratio of 89:11 for *o*- bromobenzaldehyde.[157]

p-block elements

Aluminium: Among the p-block elements, aluminium has been widely used to promote pinacol coupling in aqueous medium. In aqueous alkaline solution, aluminium powder was found to produce *vic* diols through coupling of aromatic dialdehydes[158] in poor diastereoselectivity and moderate yield. Sonication seemed to have a beneficial effect in terms of yield and selectivity.[159] An increase in the *meso* selectivity was noticed in the presence of metal fluorides.[160] Aluminium in an amalgamated form can also promote pinacol coupling of cycloalkanones in mixed solvent of THF/H_2O.[161]

Indium: Indium under prolong sonication was found to promote pinacol coupling of substituted aromatic aldehydes in good yields but with a poor selectivity.[162]

Scheme 41.



Nair et al showed that the crosscoupling between an aromatic aldehyde and a chalcone can be nicely performed in aqueous THF in the presence of In/$InCl_3$.[163] the product yields were moderate and the *anti*-selectivity was high (Scheme 41).

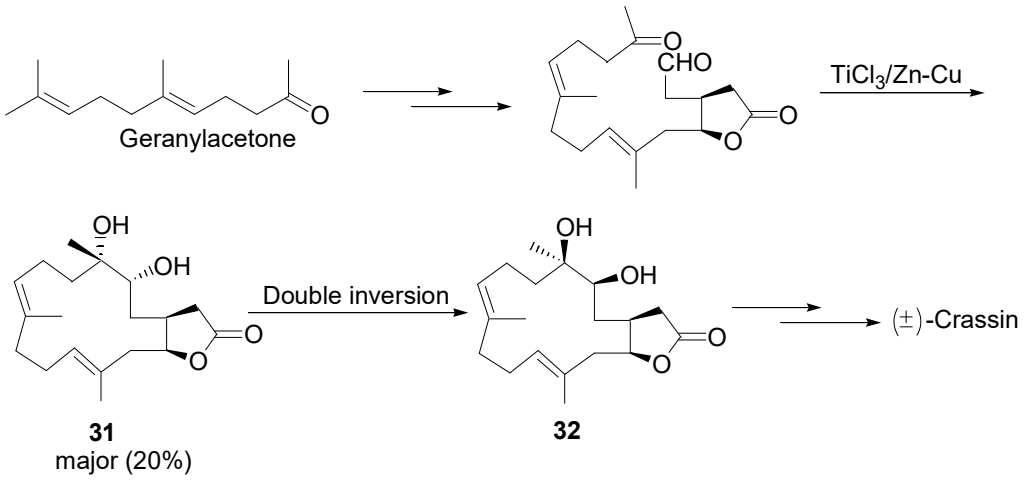
Lanthanides

Samarium: Samarium is the only lanthanide which has been used for pinacol coupling in aqueous medium. In aqueous acidic solution, samarium was found to couple aromatic aldehydes and diarylketones in high yield.[164] A binary combination of $SmCl_3$ with Sm or Mg was also equally effective.[165] In all the cases the selectivity was poor.

5. Synthetic application

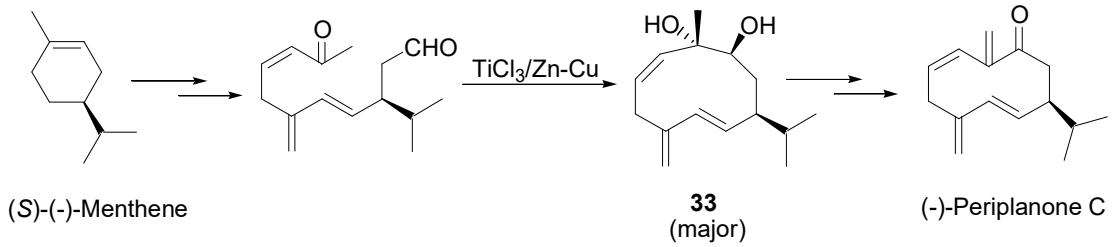
Terpenes: Pinacol coupling has been used successfully in many syntheses of di, tri or sesquiterpenes. McMurry et al prepared racemic Crassin, a diterpenoid, using $TiCl_3$/Zn-Cu to construct the 14-membered ring.[166] The keto-aldehyde coupling proceeded with 48% yield (including four isomers). As the yield of the desired isomer (**32**) was very low, the major isomer (**31**) was epimerized at C_3, C_4 center through double inversion (Scheme 42).

Scheme 42.



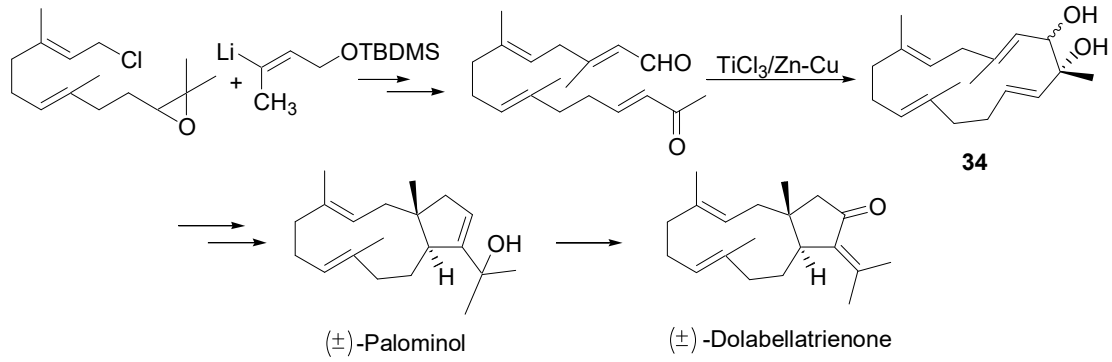
In another example, McMurry et al reported the synthesis of (-)-Periplanone C, a ten membered sesquiterpene, which is an insect pheromone.[167] The ten membered ring was constructed in a similar way. Unlike the previous case and contrary to mechanistic calculations, the *trans* diol (**33**) was formed as the major product. Further transformations lead to the final product (Scheme 43).

Scheme 43.



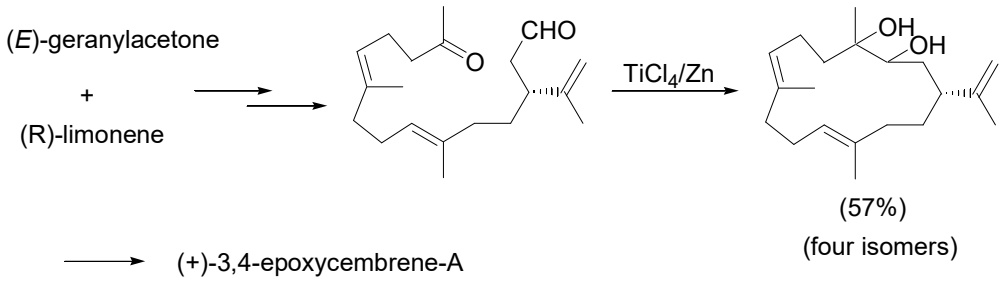
Corey et al prepared *rac* Palominol and Dolabellatrienone, a dolabellane class of marine diterpenoids using pinacol coupling as the key step for the ring formation.[168] The coupling with a low valent titanium gave a mixture of two diastereomers (**34**) in a ratio of 2.1:1 as a separable mixture (53% yield) (Scheme 44).

Scheme 44.



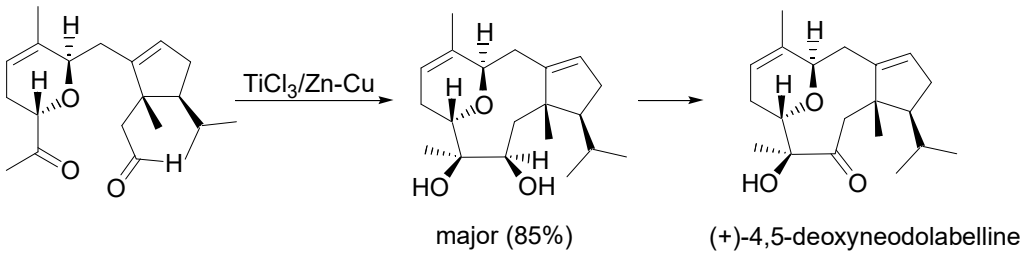
Li et al constructed the 14 membered ring of the macrocyclic diterpene (+)-3,4-epoxycembrene-A using $TiCl_4/Zn$.[169] The final product was obtained as a mixture of four isomers which were separated through HPLC (Scheme 45).

Scheme 45.



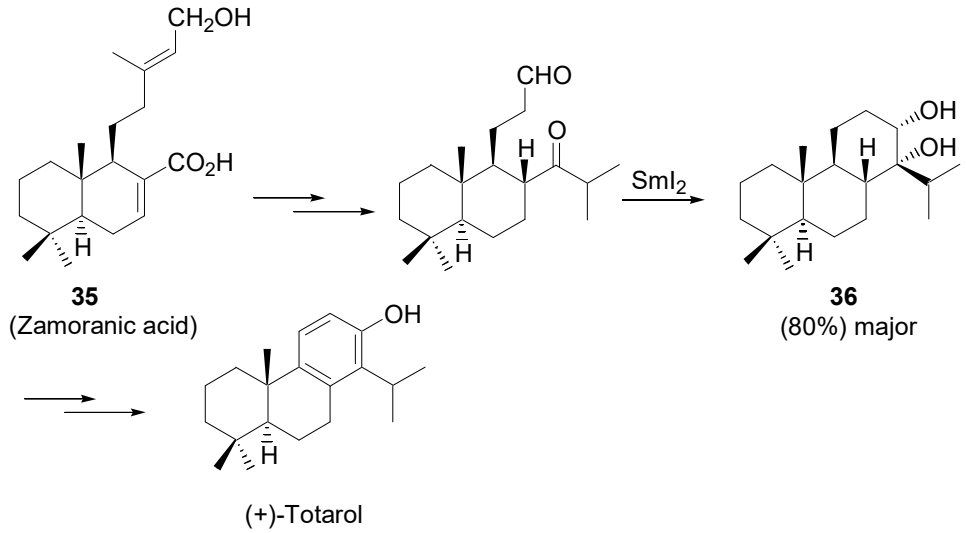
During the synthesis of (+)-4,5-Deoxyneodolabelline, a bicyclic diterpene, Williams et al showed that the low valent titanium produced by $TiCl_3$/Zn-Cu although less selective, is more efficient than the low valent vanadium complex (Scheme 46).[170] The final product was separated after oxidation to get the desired isomer.

Scheme 46.



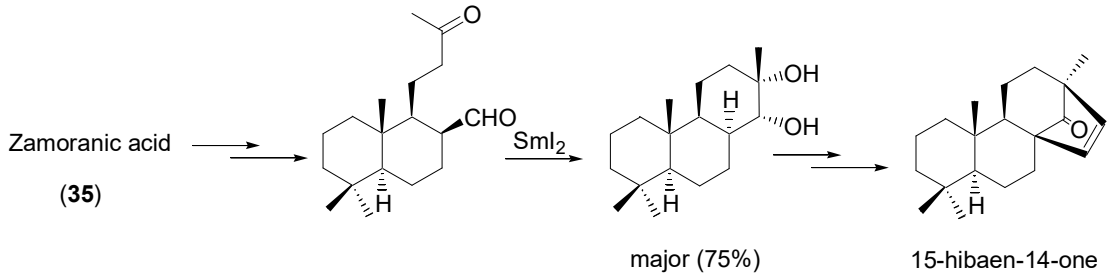
SmI_2 has proved to be equally effective for preparation of various terpenes. Marcos et al synthesized (+)-totarol, a tricyclic diterpene known to have pronounced biological activity from zamoranic acid (**35**) using SmI_2 to form the C ring. The major isomer (**36**) seemed to contain two α-OH groups (80%) (Scheme 47).[171]

Scheme 47.



Following a similar approach, another tetracyclic diterpene was synthesized by the same group (Scheme 48).[172]

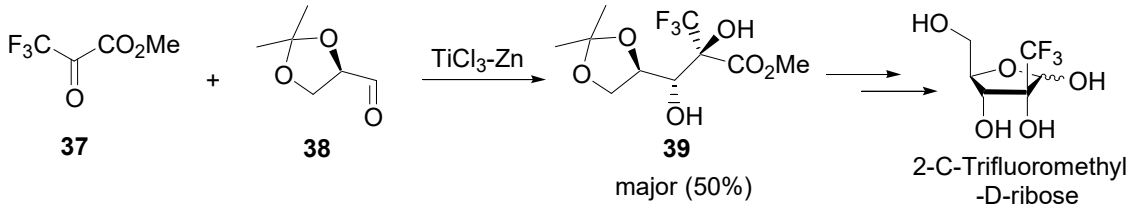
Scheme 48.



Alkaloid: Yoda et al prepared an isoindolobenzazepine alkaloid, chilenine using SmI_2 mediated intramolecular pinacol coupling.[173]

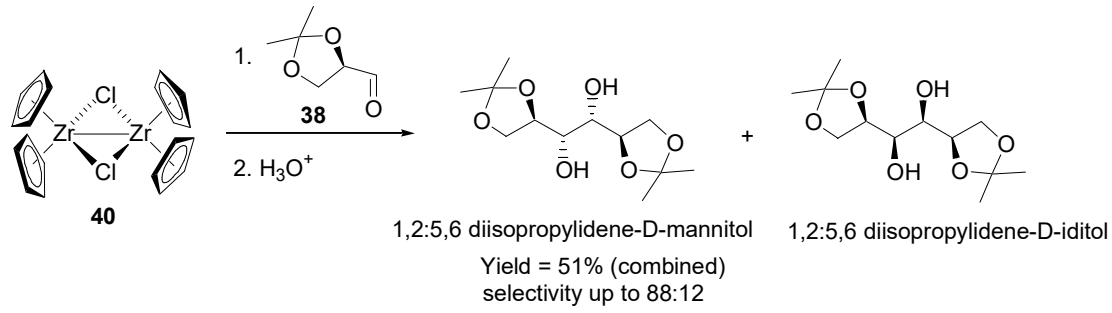
Sugars: The reaction of methyltrifluoropyruvate (**37**) and 2,3-di-*O*-isopropylidene D-glyceraldehyde (**38**) in the presence of $TiCl_3$/Zn proceeded smoothly in moderate yield with a higher ratio of the *trans* isomer (**39**). This coupled product was further manipulated through a series of reaction to prepare D-ribose (Scheme 49).[174]

Scheme 49.



Schwertz et al also prepared mannitol derivative from 2,3-di-*O*-isopropylidene D-glyceraldehyde (**38**) using cyclopentadienyl zirconium complex (**40**) (Scheme 50). Although the yield was moderate, the selectivity went high (mannitol:iditol = 88:12).[175]

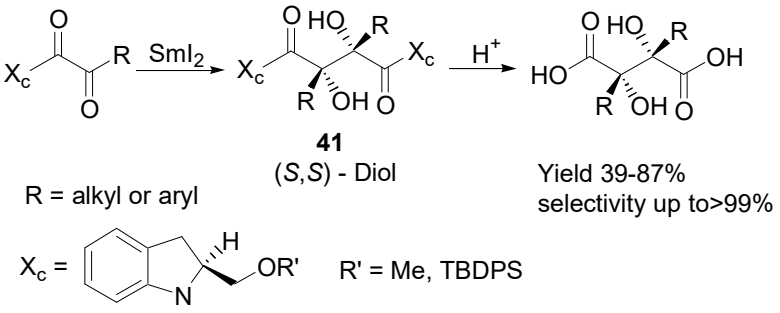
Scheme 50.



Tartaric acid derivatives: Pinacol coupling has also been extended to prepare quaternary tartaric acid in optically pure form. Intramolecular SmI_2 mediated pinacol coupling of two

keto amides provided the quaternary pinacol (**41**) in a very high selectivity (de>98%) (Scheme 51).[176]

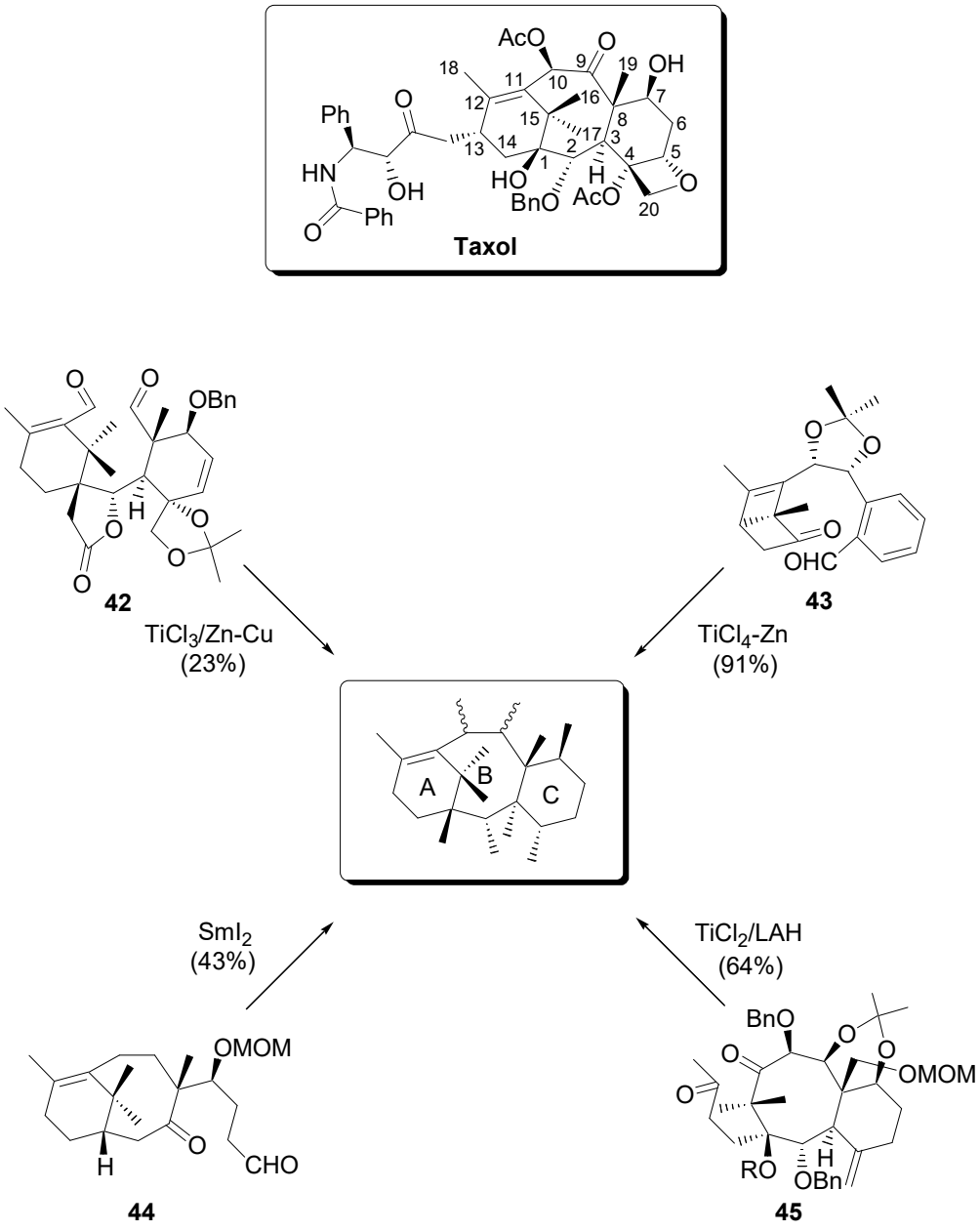
Scheme 51.



Biologically active compounds:

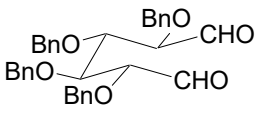
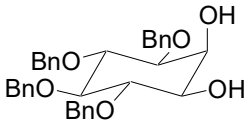
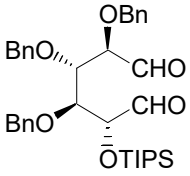
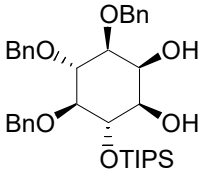
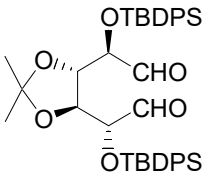
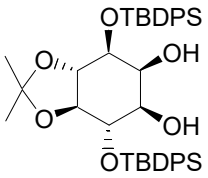
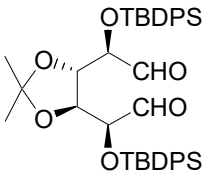
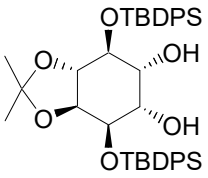
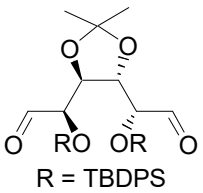
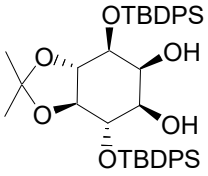
Taxol: Taxol, isolated from *Taxus brevifolia* is a clinically very useful anticancer agent. There are many reports with different approaches for the synthesis of this molecule. In many cases, intramolecular pinacol coupling has been used as the most reliable tool to synthesize this molecule or similar molecular structure (taxane or taxadienes or hydroxytaxols) with the desired stereochemistry. Nicolaou et al has used pinacol coupling as a key step to link the A and C ring by making the C_9-C_{10} bond using $TiCl_3$/Zn-Cu with a predominant *syn* stereochemistry (**42**).[177] In a different approach, Swindell et al constructed the B ring (**43**) by joining C_1-C_2 bond through pinacol coupling using SmI_2 in cases of dimethoxy substituted aromatic rings whereas $TiCl_4$/Zn was found efficient with unsubstituted aromatic rings.[178] SmI_2 has also proved to be an useful reagent for the construction of C ring with *syn* selectivity in a related molecular framework (**44**).[179] The keto-aldehyde coupling proceeded in 43% yield with the formation of C_3-C_4 bond. Recently Mukayama et al have even constructed the A ring of hydroxytaxol (**45**) using $TiCl_2$/LAH combination with a *syn* selectivity (64%) (Scheme 11).[180] Shirahama et al constructed a similar molecular framework using SmI_2 to prepare the B ring.[181] Although the yield was moderate, the selectivity was high.

Figure 11.



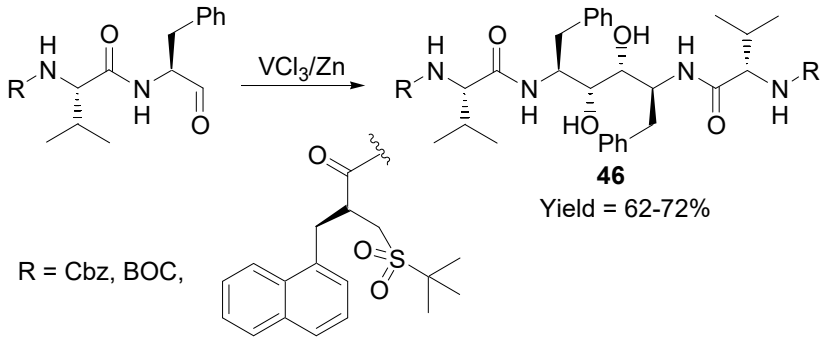
Inositols: Polyphosphoinositides play significant role in the cellular signal transduction system. Among other derivatives, "*myo*" and "*chiro*" inositols have been prepared widely from cheap chiral sources like glucose isomers[182] or natural products like tartaric acid (Table 8).[183] SmI_2 has been used extensively for the intramolecular pinacol coupling, a key step for the preparation of these molecules. In all the cases a very high *syn* selectivity was observed.

Table 8.

No	Starting	Intermediate	Reagent	Product	Yield/ Selectivity (Ref)
1.	L- Iditol		SmI_2, ^{t}BuOH-THF, -78 ^{0}C		56% *myo* *cis* (182a)
2.	D-Xylose		SmI_2, THF, -78 ^{0}C		70% *myo* *cis*:*trans* >20:1 (182c)
3.	D-Mannitol		SmI_2, ^{t}BuOH-THF, -50 ^{0}C		86% *myo* *cis*:*trans* >92:8 (182b)
4.	D-Sorbitol		SmI_2, ^{t}BuOH-THF, -70 ^{0}C		78% *chiro* *cis*:*trans* 94:6 (182d)
5.	2, 3-*O*-iso-Propylidene-D-Tartarate		SmI_2, ^{t}BuOH-THF, -78 ^{0}C		87% *myo* *cis* (183)

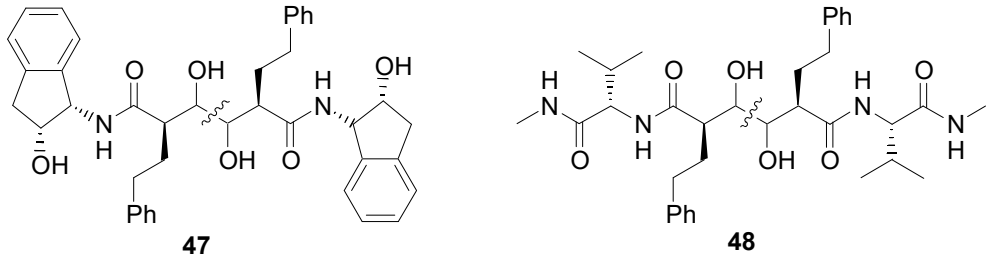
Proteases: C_2-symmetric HIV proteases **46** was prepared using pinacol coupling as the key step. $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ or $NbCl_3$ were proved to be equally effective favouring a high selectivity in the coupled product.[184] However, the yields were high in the former case and this reagent was applicable even in a multigram scale (Scheme 52).

Scheme 52.



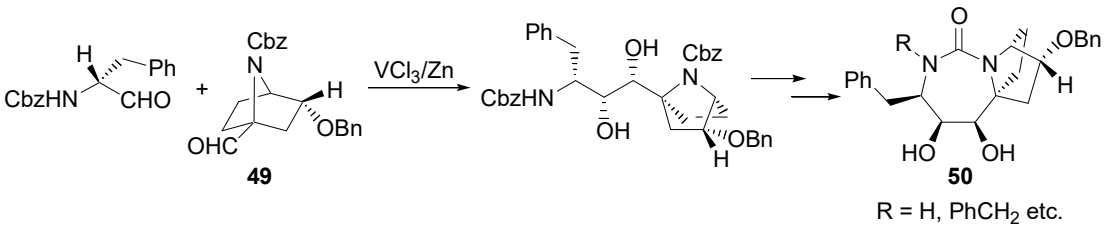
Samuelsson et al prepared similar C_2-symmetric proteases (**47** & **48**) using vanadium to induce pinacol coupling as the key step (Figure 12).[185] The selectivity in this case was not high.

Figure 12.



Han et al prepared a new class of HIV-proteases i.e. a tricyclic urease (**50**) through coupling D-phenylalaninal and a hindered aldehyde (**49)** using VCl_3/Zn.[186] The selectivity of the *cis* isomer was found to be 85%. Further transformation of the diol lead to the final product (Scheme 53).

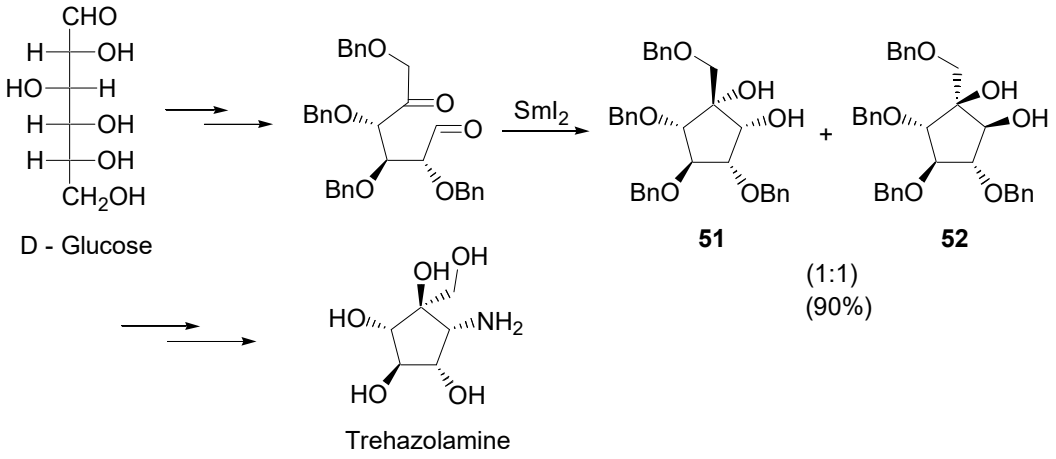
Scheme 53.



Chiara et al prepared the aglycon of the potent trehalase inhibitor of trehazoline, trehazolamine from D glucose using SmI_2 mediated pinacol coupling.[187] Although the

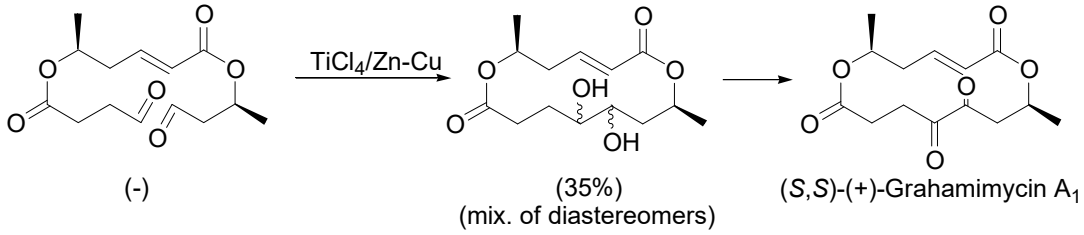
relative stereochemistry of the newly generated stereocenters were *cis*, the two diastereomers (**51** & **52**) were produced in equal amount (Scheme 54). They were separated either through crystallization or through derivatization.

Scheme 54.



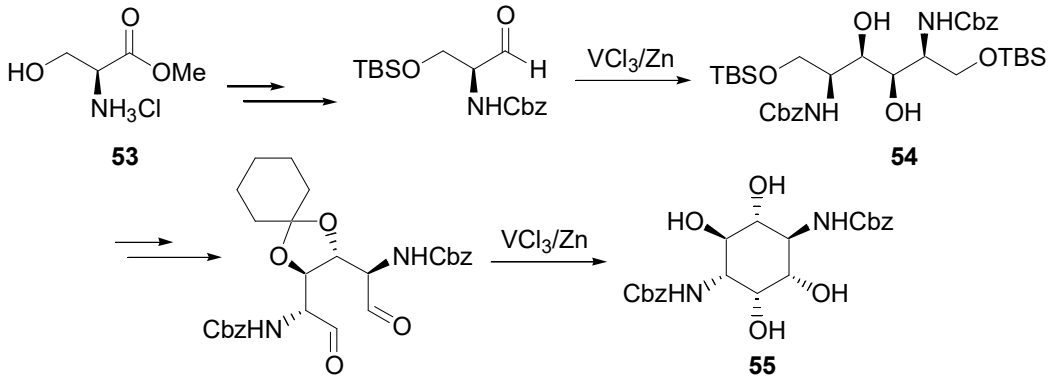
Antibiotics: The 1,2-diketo groups of the antibiotic grahamimycin A_1, a natural macrodiolide, provided a suitable molecular infrastructure for its synthesis through pinacol coupling. Although titanium mediated coupling gave a poor diastereoselectivity, the oxidation of these two hydroxy groups furnished the desired product as a single isomer (Scheme 55).[188]

Scheme 55.



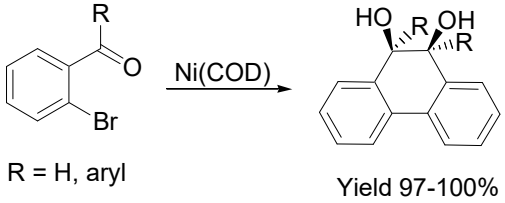
Pederson et al synthesized the broad spectrum antibiotic fortimicin AM and AK via successive inter and intramolecular pinacol coupling.[189] Starting from a N-protected serine derivative (**53**), the first pinacol coupling using VCl_3/Zn determined the *cis* stereochemistry of the two hydroxyl groups in an intermolecular path (**54**). In another step, the intramolecular version with the same reagent provided the cyclic unit (**55**) with the desired orientation of the hydroxyl groups (Scheme 56).

Scheme 56.



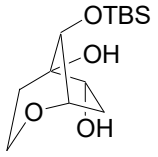
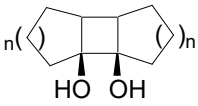
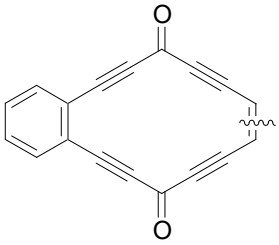
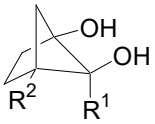
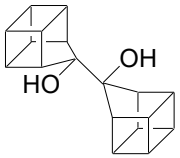
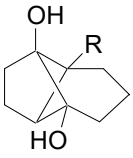
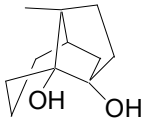
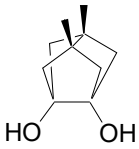
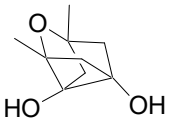
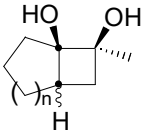
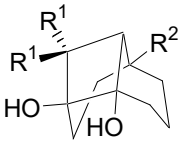
Other Compounds: Besides the above complex molecules, pinacol coupling has been widely used for preparing various class of compounds. Pederson et al prepared chiral [N-(alkoxycarbonyl)amino]-1,2-diols[190] and γ-butyrolactones[191] using low valent vanadium. They also showed that hydroxymethylation of an aldehyde can also be effected via this reagent.[192] In all the cases a high yield and selectivity was observed. Banfi et al prepared lactenediynes in high selectivity using low valent vanadium.[193] 2-Bromobenzaldehyde was transformed to pinacols in one pot using Ni(0) mediated cascade reaction.[194] The pinacol coupling proceeded in excellent yield resulting only *cis* isomer (**56**).

Scheme 57.



Low valent titanium has been used to prepare macrocyclic stilbenediol derivatives from bis carbaldehyde.[195] Contrary to the high yield, the selectivity was moderate. Mataka et al prepared 1,2,9,10-tetrahydroxy-[2.2]-metacyclophanes via aluminium mediated pinacol coupling of 1,3-benzenedicarboxaldehyde.[196] A variety of complex molecular framework has been synthesized via pinacol coupling reaction (Table 9).

Table 9.

Molecule	Reagent	Ref	Molecule	Reagent	Ref
	$TiCl_3$/Zn-Cu	197	 n= 1~4	SmI_2	200
	VCl_3/Zn	198	 R^1= alkyl or aryl R^2= H	SmI_2	201
	$TiCl_4$/Zn	199	 R = H, Me	SmI_2	201
 R^1= R^2 = aliphatic or aromatic	SmI_2	200		SmI_2	201
	SmI_2	202		SmI_2	201
 n = 1, 2, 3	SmI_2	200	 R^1, R^2 = H, Me	SmI_2	201

6. Conclusion:

It is evident from the above account that pinacol coupling, one of the earliest known carbon-carbon bond forming reaction, has evolved as a versatile tool in synthetic organic chemistry. The initial bottleneck for the reaction was to obtain preparatively useful yield. This was followed by efforts to improve the diastereoselectivity and more recently, the enantioselectivity. In these pursuits, a large number of metals from periodic table have been examined. The reaction has been now frequently used during the synthesis of a variety of natural/unnatural products. The most recent success in this area has come as establishment of enantioselective protocols. Almost all kinds of aldehydes can now be coupled with high diastereoselectivity and enantioselectivity. The challenge however remains for the stereoselective coupling of ketones and imines. Equally interesting and useful will be heterocoupling of carbonyl compounds and imines. The daunting task will require deeper insight into the reaction mechanism and fine tuning of metal complexes. The age old reaction thus remains a fertile ground for exciting research in future.

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CHAPTER-2

Designing and Synthesis of Chiral Titanium Complexes

The world is chiral and clinal, enjoy symmetry wherever you find it.

Vladimir Prelog

In organometallic catalysis the most reliable and indispensable tool for the access of an enantiomerically pure compound is a chiral complex. Normally a chiral complex consists of two parts. One is a Lewis acid part which can be a metal atom (in most cases a transitional element) and the other part is a chiral ligand. The latter is of much importance as it can be used to tune parameters like sterics and electronics. In fact they are the only means to transmit chiral information from a chiral source to the prochiral center. Hence a rationale designing of a proper chiral ligand is the key to success for an enantioselective reaction.[1] A good chiral ligand should meet several characteristics.[2]

i) It must be coordinated to the metal during the step in which the chiral center is created on the substrate and not exert merely a chiral medium effect. That means the bond between the coordinating atom with the metal center should not break during the course of the reaction.

ii) The catalytic activity in presence of the chiral ligand should be much better relative to that of the achiral catalyst. In other words, the rate of formation of the desired product should suppress the formation of the undesired compounds.

iii) The structure of the ligand should allow for various chemical modifications to be made in order to permit the synthesis of the variants. In this way optimal ligand substrate matches can be sought.

iv) The synthesis of the ligands must be relatively easy.

v) It is desirable to get both the antipodes of the ligand.

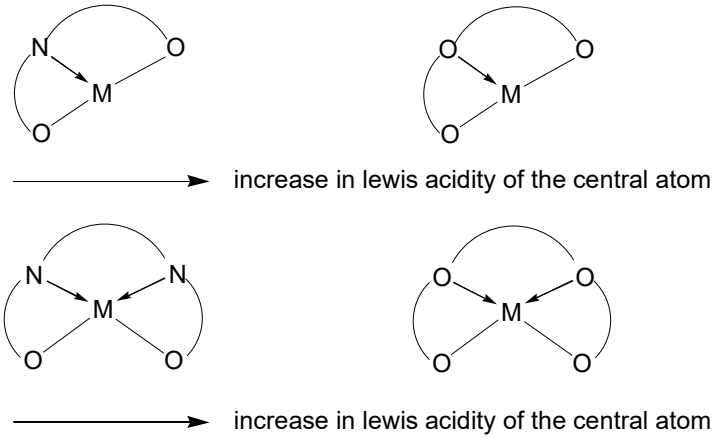
In practice it may not be possible to fulfill all the criteria as stated above, but covering half of them may lead to an efficient catalyst.

Other than these basic requirements, another major aspect to be born in mind while designing a complex, is the stereoelectronic factors. To understand this point, we have to focus on following factors:

i) The role of coordinating atom in forming a good chelate is well understood and does not need any discussion. The other factor to be considered in this context is the variation of the Lewis acidity of the central metal atom with a change in the coordination. For example the shift from TMSCl to TMSOTf or $TMSNTf_2$ gives a

much more reactive catalyst due an increase in the Lewis acidity of the silicon atom. A similar argument can be placed with polydentate ligands (Fig 1).

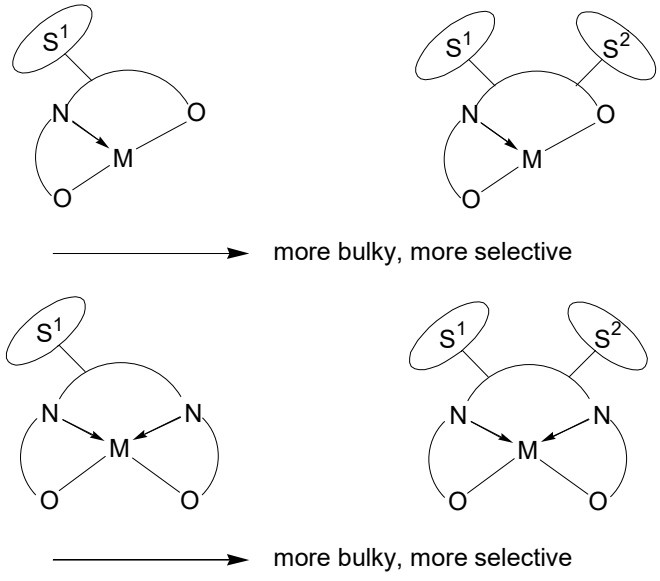
Figure 1.



ii) Steric environment of a chiral ligand is another point to be considered during the synthesis of a chiral catalyst.[3]

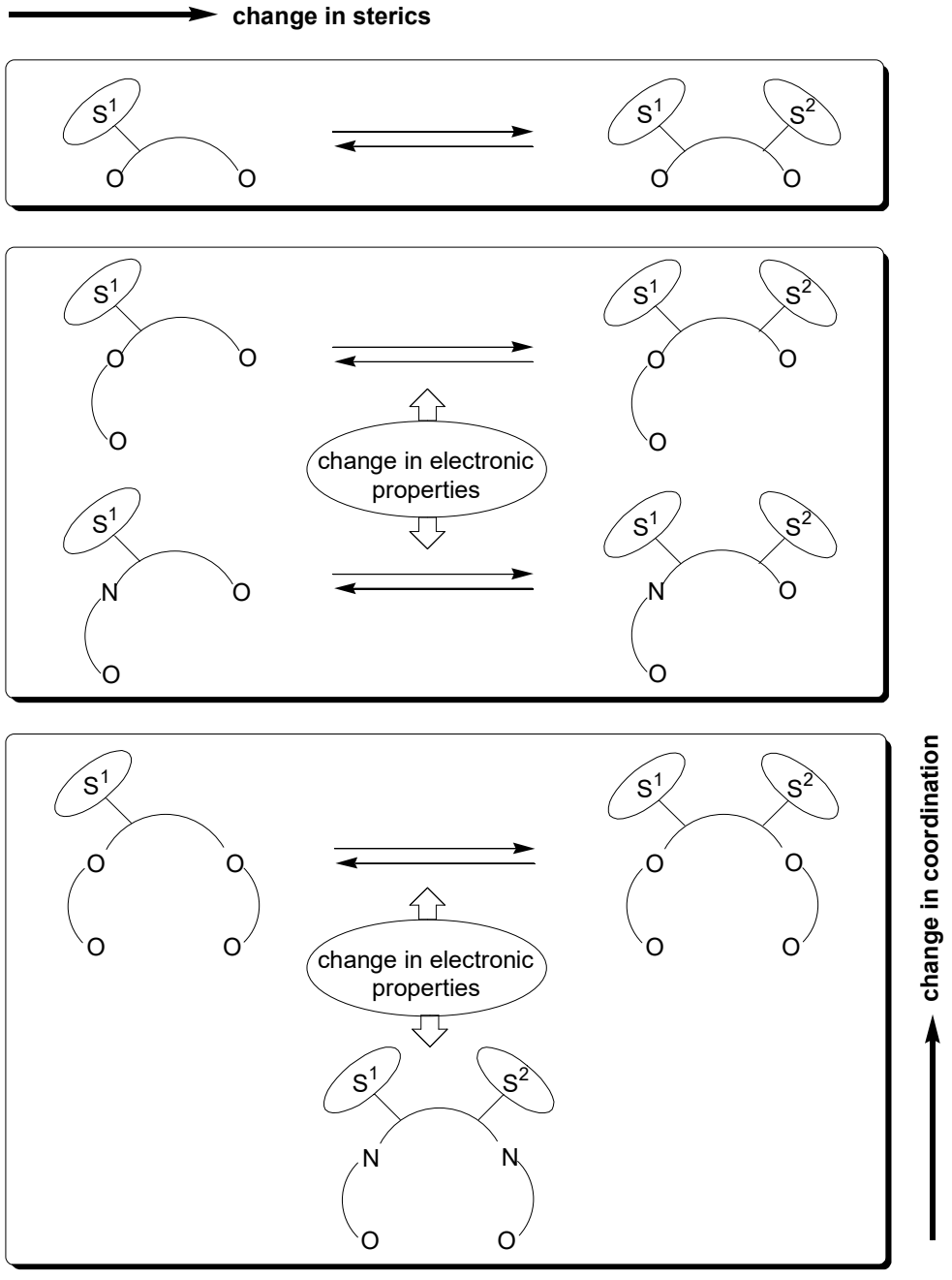
Organometallics in most cases prefer to remain as aggregates. A chelating ligand with a higher sterics inhibits the aggregation and thereby increases the activity of the catalyst. The other advantage of using a bulky substituent in the close vicinity of a coordinating atom, is to fix a particular configuration. A C_2 symmetric ligand is preferred in this context (Fig 2).

Figure 2.



Considering all the above points, we prepared a series of related chiral ligands for titanium complexes based on the scheme shown in figure 3.

Figure 3.

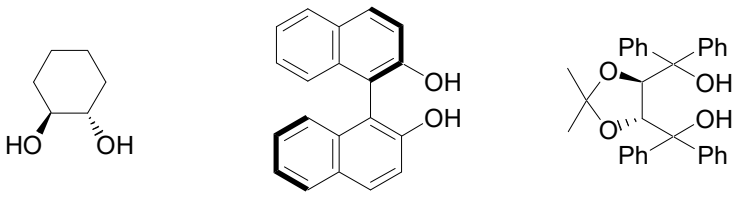


Results and discussion

Bidentate ligands:

As a first step to synthesize the family of ligands, we planed to prepare three bidentate ligands with varying sterics (Fig 4).

Figure 4.



1 **2** **3**

Synthesis:

Ligand **2** and **3** are well known to induce chirality for a variety of reactions. They can be easily prepared from *β*-naphthol[4] and L-tartaric acid[5] respectively following standard literature procedure. There are several reports on the resolution of cyclohexane-1,2-diol (**1**), most of them through chemoenzymatic methods. The exorbitant cost of these enzymes restricted us from using these methods. We set up a target to develop a new route for the "classical resolution" of this diol. To serve this purpose, we synthesized a number of optically active acids and examined them for resolution. Both mono and diesters were prepared. Attempts were made to separate these diastereomers either through crystallization or by chromatography. The details of this study is summarized in Table- 1.

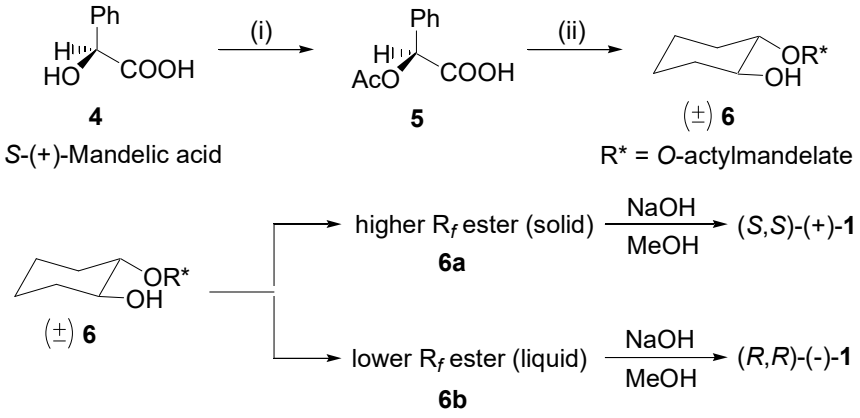
Table 1.

Entry	Acids	Prep. (ref)	Monoester	Diester
1.	Menthoxyacetic acid	6	n.r.	n.r.
2.	*N*-Carbethoxyproline	7	n.r.	n.r.
3.	5-Oxofurancarboxylic acid	8	n.r.	n.r.
4.	ω-Camphanic acid	9	n.r.	n.r.
5.	*N*-Pivaloylproline	a	n.r.	n.r.

a = Prepared by our method; n.r. = not resolved

While our efforts were in progress for developing a suitable resolving agent for (±)-**1**, we realized that *O*-acetyl mandelic acid (**5**), which is an excellent resolving agent in many cases, [10] has not been tried for *vic* diols. We were glad to find this to be an effective resolving acid in the present case (Scheme 1).

Scheme 1.



Reagents: (i) AcCl, reflux, 2 h; (ii) DCC, DMAP, DCM, -10 ^{0}C, 6 h.

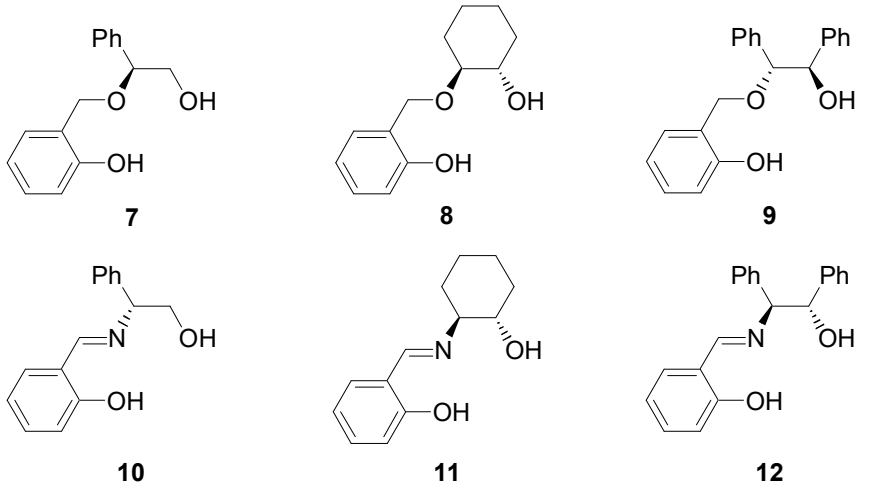
Although these diastereomers were separated through column chromatography, they could also be separated through crystallization for large scale. It could be categorized as a successful resolution as both the enantiomers obtained in more than 80% yield in optically pure form. The only drawback of this protocol is the racemization of the recovered mandelic acid, probably due to the internal racemization in the basic medium during workup.

Tridentate ligands:

After synthesizing the bidentate ligands, we turned our attention towards the tridentate ones (Fig 5).

Even a cursory look at the ligands (**7**-**12**) reveals a well defined stereoelectronic relationship among each other. For example, on going from **7** to **8** to **9**, the steric increases sharply. The same trend can also be noticed with **10** to **11** to **12**. Similarly, a change in coordinating atoms is prominent from **7** to **10**. Changing the oxygen atom of ligand **7** to an imine nitrogen will obviously change the Lewis acidity of the central metal atom of the complex. Thus the effect of electronic tuning can be realized from a comparison of the results afforded by ligand **7** and **10**. A similar effect will be envisioned with **8** and **11** or **9** and **12**.

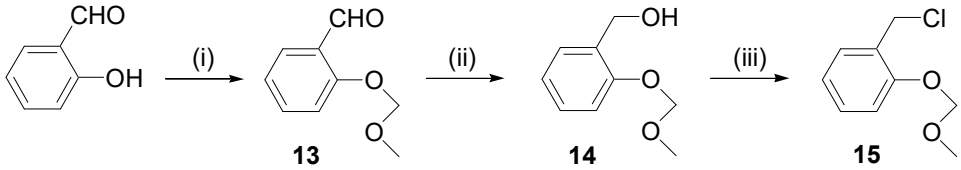
Figure 5.



Synthesis:

Our strategy for the preparation of the first three ligands (**7**, **8** and **9**) was based on the mono alkylation of the respective diols with a protected benzylchloride **15**. Optically pure stilbenediol (**16**)[11] and phenylethyleneglycol (**19**)[12] were prepared according to the literature procedures. The desired benzylchloride **15** was easily obtained form salicylaldehyde (Scheme 2). Considering the requirements for further reaction step, we chose MOM as a protecting group for 2-hydroxybenzylchloride. The reduction of the MOM-protected aldehyde **13** was carried out in situ. The resulting alcohol **14** was used for the next step without any purification. The final product was purified by a kugelrohr distillation.

Scheme 2.

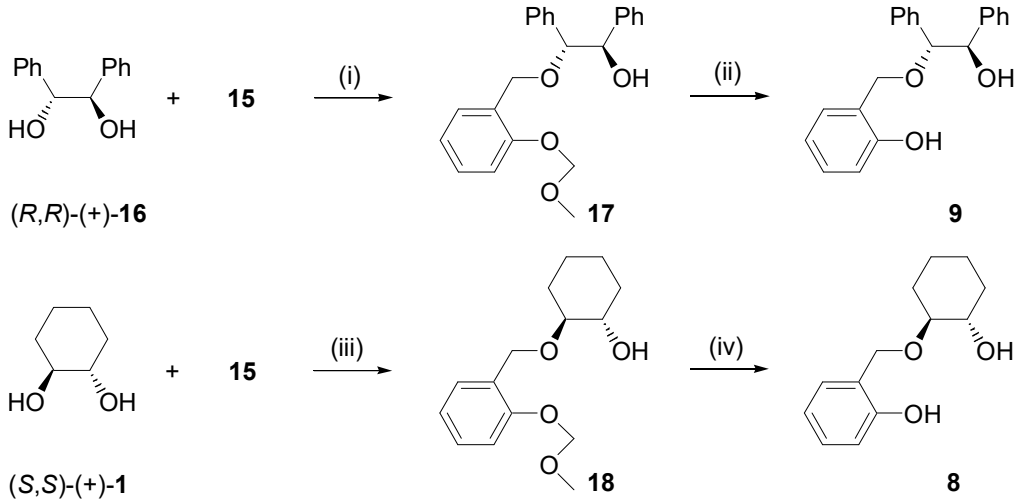


Reagents: (i) NaH, THF/DMF, MOMCl, 0 ^{0}C, 30 min; (ii) H_2O, $NaBH_4$, 0 ^{0}C, 15 min; (iii) PPh_3, CCl_4, Py, rt, 8 h.

The next step for the synthesis of the ligands was the alkylation of one of the two oxygen atoms of the diols. In the case of stilbenediol (**16**) or cyclohexane diol (**1**), two hydroxyl groups were chemically equivalent. In a phase transfer condition, the alkylation

of (+)-**16** gave a good yield of monoester **17**. Owing to a lesser reactivity of the secondary hydroxyl groups, the alkylation of diol (+)-**1** was carried out in THF with NaH and catalytic amount of tetrabutylammoniumiodide. The reaction mixture was passed through a small bed of celite to remove the inorganic impurities and used as such for the next step. The diols after deprotection, were purified using chromatographic separation and further purified by crystallization from a proper solvent (Scheme 3).

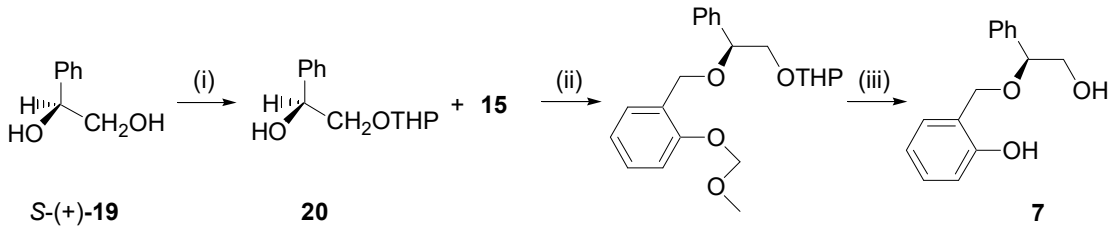
Scheme 3.



Reagents: (i) $NaOH/K_2CO_3$, TBABr (cat.), DCM, rt, 4h; (ii) ^{i}PrOH/THF (1:1), conc. HCl (cat.) rt, 24 h; (iii) NaH, THF, TBAI (cat.) 60 ^{0}C, 8 h; (iv) THF, conc. HCl (cat.), rt, 24 h.

For the preparation of ligand **7**, the primary hydroxyl group of the diol **19** was protected as THP. The mono protected alcohol **20** was alkylated following a similar procedure as described for ligand **8** (Scheme 4).

Scheme 4.

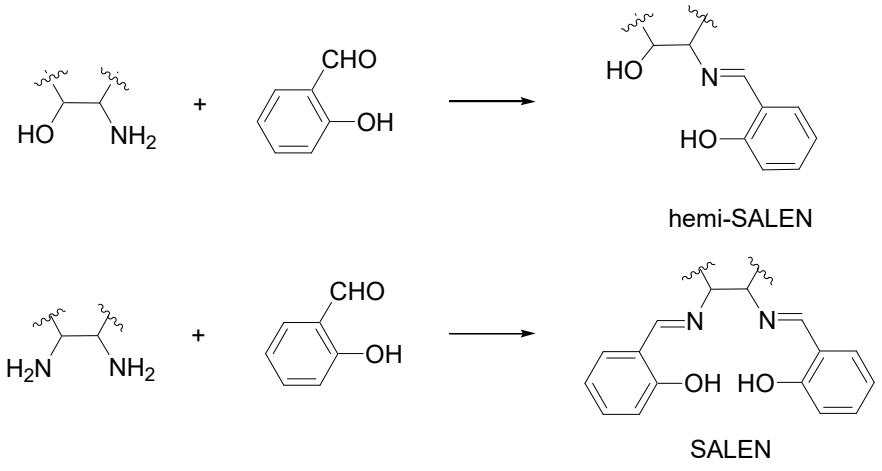


Reagents: (i) DHP, PPTS, DCM, 0 ^{0}C, 12 h; (ii) NaH, TBAI (cat.) THF, reflux, 4 h; (iii) ^{i}PrOH/THF (1:1), conc. HCl (cat.), 24 h.

The chiral ligands **7**, **8** and **9** were prepared in good yield and high optical purity from cheap chiral sources.

The condensation of an amine with an aldehyde was first noticed by Hugo Schiff in 1864[13] and since then this class of compounds are known as Schiff base. Owing to their easy preparation, high yield and the ability to afford high enantioselectivity in a number of cases, they are often called "privileged ligands".[14] The superiority of these ligands lies in the ease of tuning of electronics and sterics. Stereogenic centers or other elements of chirality (chiral plane or chiral axis) can be introduced easily according to the demand of the substrate. A condensation of an amino alcohol with an aldehyde containing another coordinating group results in a quantitative formation of a tridentate ligand involving the imine nitrogen. These class of ligands are normally called "hemi-SALEN" ligands. The condensation is normally carried out in the presence of a dehydrating agent such $MgSO_4$ or molecular sieves or by azeotropic removal of water. Sometimes the reactions are carried out even in boiling ethanol. In the presence of acidic silica or acidic impurities they may decompose. In general, they are stable solids and can be stored for a long time without any precaution. Using a variety of aminoalcohols, a library of hemi-SALEN ligands can be made easily. The chiral part may be present in the aldehyde also. Normally, salicylaldehyde serves the purpose of aldehyde. When two equivalents of salicylaldehyde combines with a diamine, a particular chelating Schiff base is produced. The ligand prepared in this way features two covalent and two coordinating sites situated in a planer array and popularly known as "SALEN" (Fig 6).

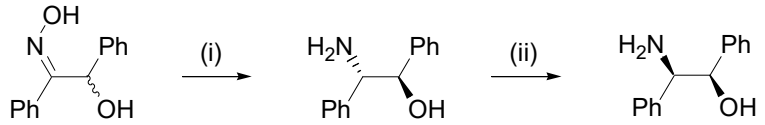
Figure 6.



These C_2 symmetric, sterically well defined ligands are kinetically non-labile and resembles porphyrines. The superiority of these ligands in enantioselective reactions has been attributed to the chiratopic carbons situated in the close vicinity of the metal center, resulting in a better stereochemical communication in the bond forming step.

Ligand **10**, **11** and **12** are a kind of hemi-SALEN ligand. The *rac* aminoalcohol of ligand **12** was prepared according to the literature procedure starting from *α*-benzoinoxime[15] (Scheme 5).

Scheme 5.

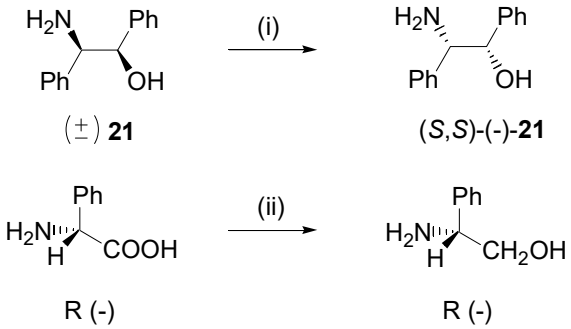


(±) **21**

Reagents: (i) Pd/C, H_2, EtOH, 6 h; (ii) a) EtOH/HCl b) $HCONH_2$, 150 ^{0}C, 15 min c) $SOCl_2$, 5 ^{0}C d) 30 % NaOH solution.

Although a number of classical methods were available for the resolution of *cis* isomer, there were hardly few reports on the resolution of the *trans* isomer. In most cases it was obtained from the optically active *cis* isomer through a similar sequence of reaction as shown in Scheme-5 without any loss of optical purity. However we were able to separate the *trans* racemate **21** using *S*-(-)-pyroglutamic acid. The chiral aminoalcohol of the ligand **10** was prepared by reducing *R*-(-)-phenylglycine with $NaBH_4/I_2$ (Scheme 6)[16].

Scheme 6.



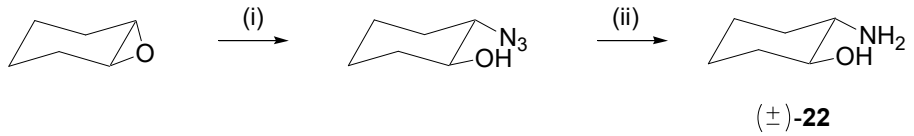
(±) **21** (*S*,*S*)-(-)-**21**

R (-) R (-)

Reagents: (i) a) *S*-(-)-Pyroglutamic acid; b) two crystallizations from EtOH; c) liquor NH_3; (ii) $NaBH_4/I_2$, THF, reflux, 36 h.

The chiral part of ligand **11** was 2-aminocyclohexanol. There was no report of any chemical resolution of this aminoalohol. In one publication, the author accessed the chiral aminoalcohol through stereoselective ring opening of cyclohexeneoxide using a complex of Et_3Al and α-methylbenzylamine.[17] We first prepared the aminoalcohol (±) **22** in an excellent yield (90%) in two steps from cyclohexeneoxide (Scheme 7).

Scheme 7.



(±)-**22**

Reagents: (i) NaN_3/NH_4Cl, EtOH, reflux, 24 h; (ii) Pd/C, H_2, MeOH, rt, 8 h.

We tried a variety of optically active acids for the resolution of the aminoalcohol (±)-**22** (Table-2).

Table 2.

Entry	Optically active acids	Prep. Proced (ref)	Results
1.	Glutamic acid	c/a	n.r.
2.	Pyroglutamic acid	18	n.r.
3.	10-Camphorsulphonic acid	c/a	n.r.
4.	Dibenzoyltartaric acid	c/a	n.r.
5.	BINOL	4	n.r.
6.	BINOL-Phosphoric acid	19	n.r.

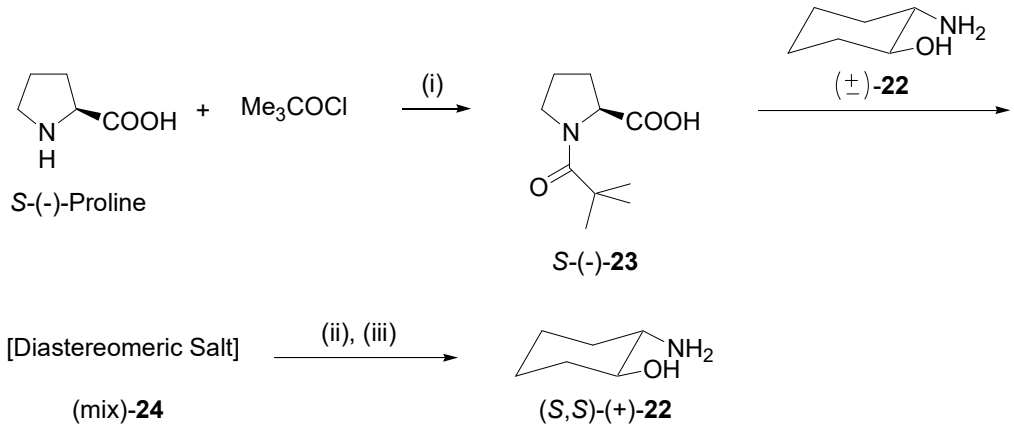
n.r. = Not resolved.; c/a = commercially available

In most cases, one equivalent of acids were employed for the salt formation. No improvement was noticed by reducing the amount of acid to its half. Resolution of (±)-**22** was also tried after making covalent diastereomer of menthylester. Unfortunately no resolution could be achieved.

Finally we succeeded in achieving our goal with a novel proline derivative (**23**). To the best of our knowledge this is the best procedure for a chemical resolution of this aminoalcohol with 68% recovery of the chiral acid **23** with >99% ee and 50% recovery of

one enantiomer of the racemate in optically pure form. The beauty of this resolution is the use of a cheap derivatized proline (**23**) which can be made even in multigram scale. The salt formed by mixing the acid and the base needs three crystallization from a mixture of EtOAc/EtOH to access the pure diastereomer in 60% yield (Scheme 8).

Scheme 8.



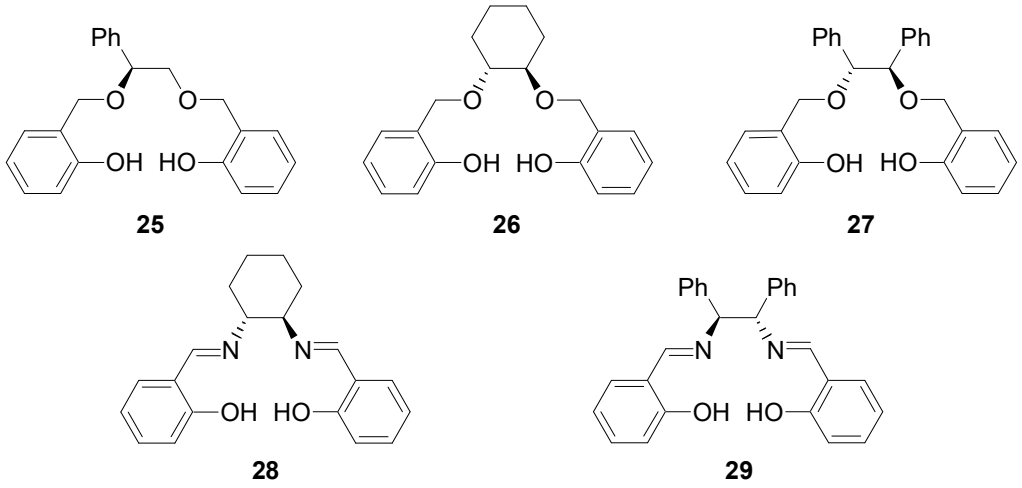
Reagents: (i) NaOH, TBABr (cat.), H_2O-DCM, rt, 4 h; (ii) Three crystallization from EtOAc/EtOH; (iii) Aqueous NaOH solution.

The final part of the prerparation of the ligands was condensation of the aminoalcohol with salicylaldehyde. Except for ligand **12**, the condensation was carried out in DCM in presence of $MgSO_4$. The sparing solubility of 1,2-diphenyl-2-aminoethanol left no choice but to use ethanol as a solvent. All the Schiff bases were purified through crystallization from a proper solvent. Thus the synthesis of ligand **10**, **11** and **12** was accomplished.

Tetradentate ligands:

Our next target was to prepare tetradentate ligands. With this notion, we designed five tetradentate ligands with varying stereobulk and electronic property (Fig 7).

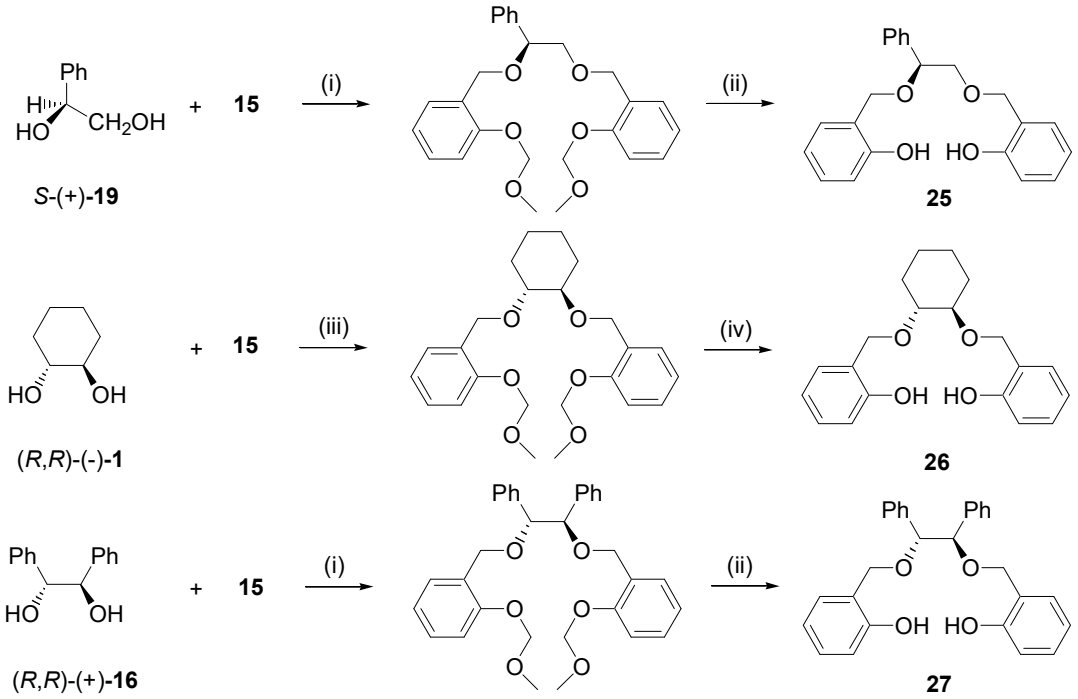
Figure 7.



Synthesis:

The first three ligands (**25**-**27**) were a dialkylated product of the diols. They could be prepared in an analogous way as applied for ligand **7** or **8** but with a little more drastic condition (Scheme 9).

Scheme 9.

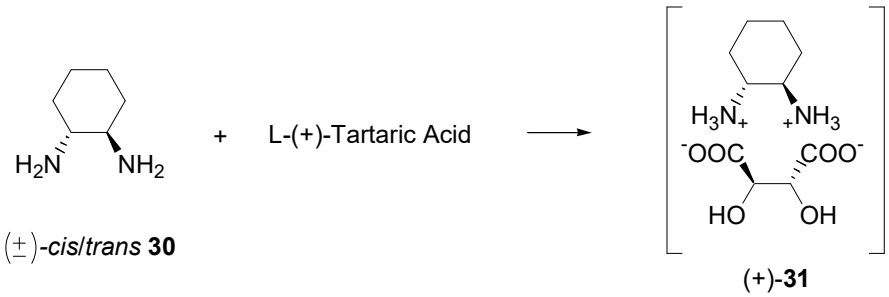


Reagents: (i) NaH, TBAI (cat.), THF, reflux, 4h; (ii) ^{i}PrOH/THF (1:1), conc. HCl (cat.) rt, 24 h; (iii) NaH, TBAI (cat.), THF, reflux, 12 h; (iv) THF, conc. HCl (cat.), rt, 12 h.

We found that the dialkylation in all the cases can be easily carried out in a high yield using NaH and a catalytic amount of TBAI in THF after few hours of reflux (Scheme 9). The alkylation of the benzylic hydroxy groups was over in 4 h whereas the rate was much slower in case of cyclohexanediol (**1**). The MOM protected diols were purified by passing through a bed of celite to remove inorganic impurities. Similar to the previous ligands, the deprotection of the MOM group was achieved using catalytic amount of concentrated HCl in a mixed solvent of ^{i}PrOH/THF or in THF (Scheme 9).

The chiral diamine of ligand **28** was obtained by resolving a mixture of *cis*/*trans*-1,2-diaminocyclohexane (**30**) with L-(+)-tartaric acid (Scheme 10).[20]

Scheme 10.

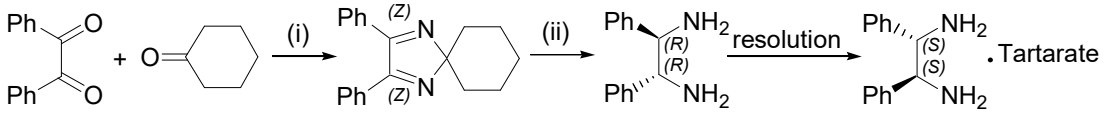


(±)-*cis*/*trans* **30**

(+)-**31**

The chiral amine for ligand **29** was obtained using Corey's method (Scheme 11).[21]

Scheme 11.

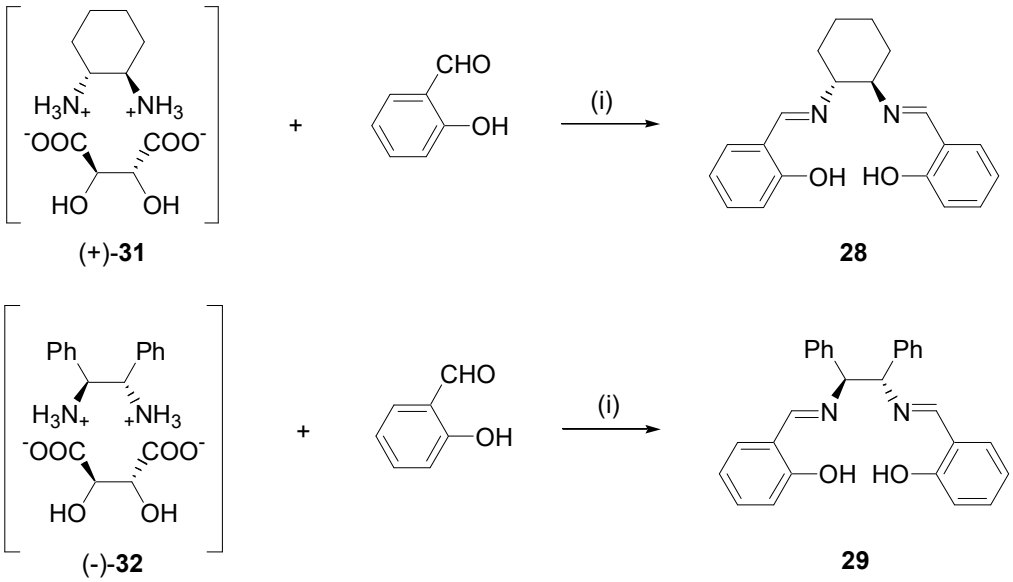


(±) (-)-**32**

Reagents: (i) NH_4OAc, AcOH (glacial), reflux, 2 h; (ii) a) Li, THF, NH_3, 0.5 h; b) NH_4Cl; c) 2 N NaOH solution (aq).

The SALEN ligands **28** and **29** were prepared by in situ basification of the salt **31** and **32** respectively followed by subsequent Schiff base formation in a biphasic mixture of DCM-H_2O in presence of salicylaldehyde (Scheme 12).

Scheme 12.

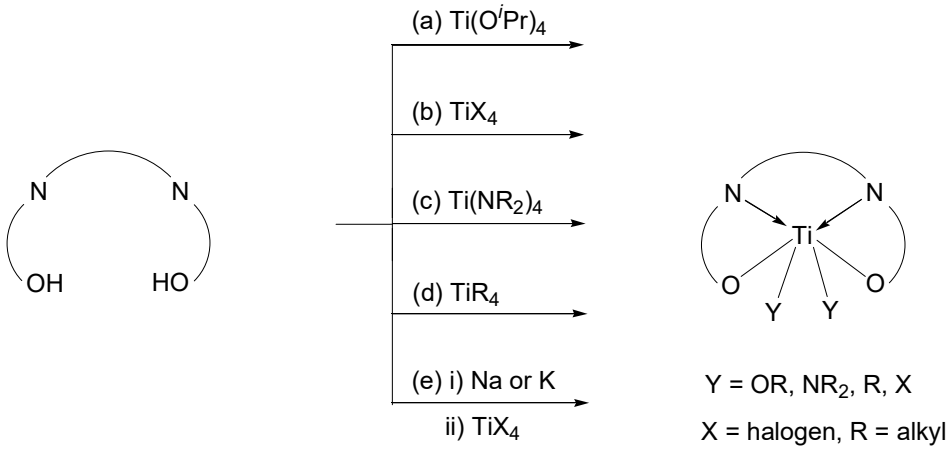


Reagents: (i) $NaHCO_3$, H_2O/DCM.

Preparation of Ti-catalysts:

In asymmetric synthesis, in most cases, the complexes are prepared in situ and the reactions are carried out without any characterization of the catalyst. This practice is encouraged due to two reasons. Firstly, the inconvenience of isolating the catalyst in very small quantity when the reactions are carried out in milligram scale. Secondly, many catalysts are unstable to air and moisture. However, a preformed robust catalyst is always desirable and a better way of performing organometallic catalysis. There are several methods available in literature for the preparation of titanium complexes[22] (Fig. 8).

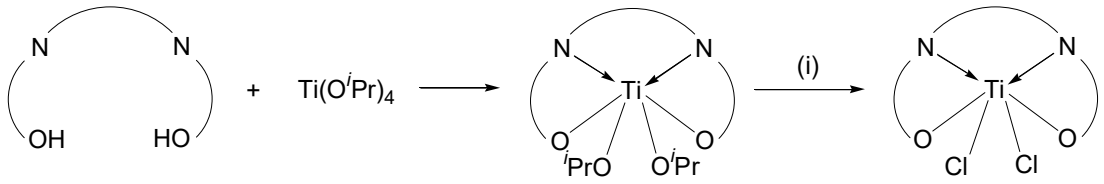
Figure 8.



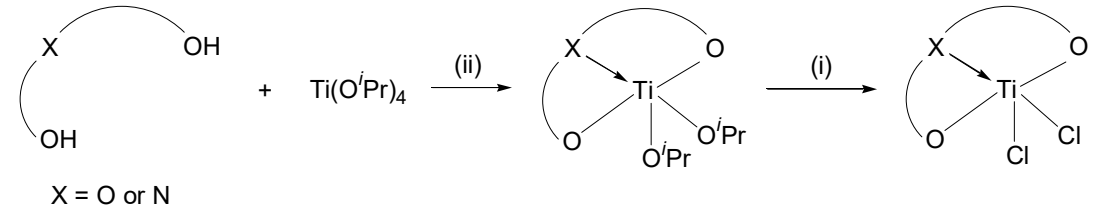
The use of titanium alkoxides and halides are advantageous than other precursors due to their wide availability and ease of handling. The deprotonation of the acidic hydrogen using metal causes a concomitant generation of metal halides. These metal salts become impossible to separate and the purification of the catalyst gets inhibited. Use of titanium halide causes a simultaneous stoichiometric generation of HCl which may prove fatal to the imine nitrogen. Using an organic base such as triethylamine or pyridine again generates a quaternary salt which remained as a side product in the reaction medium. Finally we sought the first procedure i.e. to use titanium alkoxide to prepare the dialkoxy complex. The procedure seemed to work well with [O,N,N,O] tetradentate SALEN type ligands (method **A**). But for those with [O,O,O] or [O,N,O] coordination, we modified the procedure slightly (method **B**). In those cases, the dialkoxy complex formation was ensured by azeotropic removal of ^{i}PrOH using ethylenedichloride as a solvent. The same procedure was adopted for [O,O,O,O]-SALEN mimics. The second step was normally carried out by exchanging the isopropoxy group with chloride using trimethylsilylchloride in toluene. Complexes having a poor solubility precipitated out of the reaction medium as a red solid. But for complexes having higher solubility, the solvent was pumped off in vacuum at room temperature. The halide exchange in all the cases could be visualized by the sharp change in colour. The catalysts were triturated in most cases with dry ether to remove soluble impurities.

Scheme 13.

Method A:



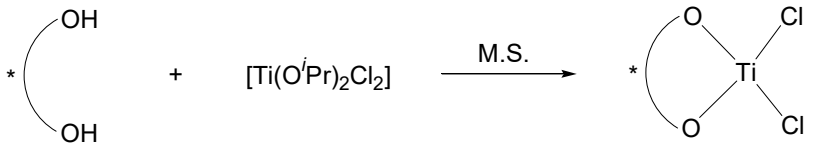
Method B:



Reagents: (i) TMSCl, rt; (ii) Azeotropic distillation.

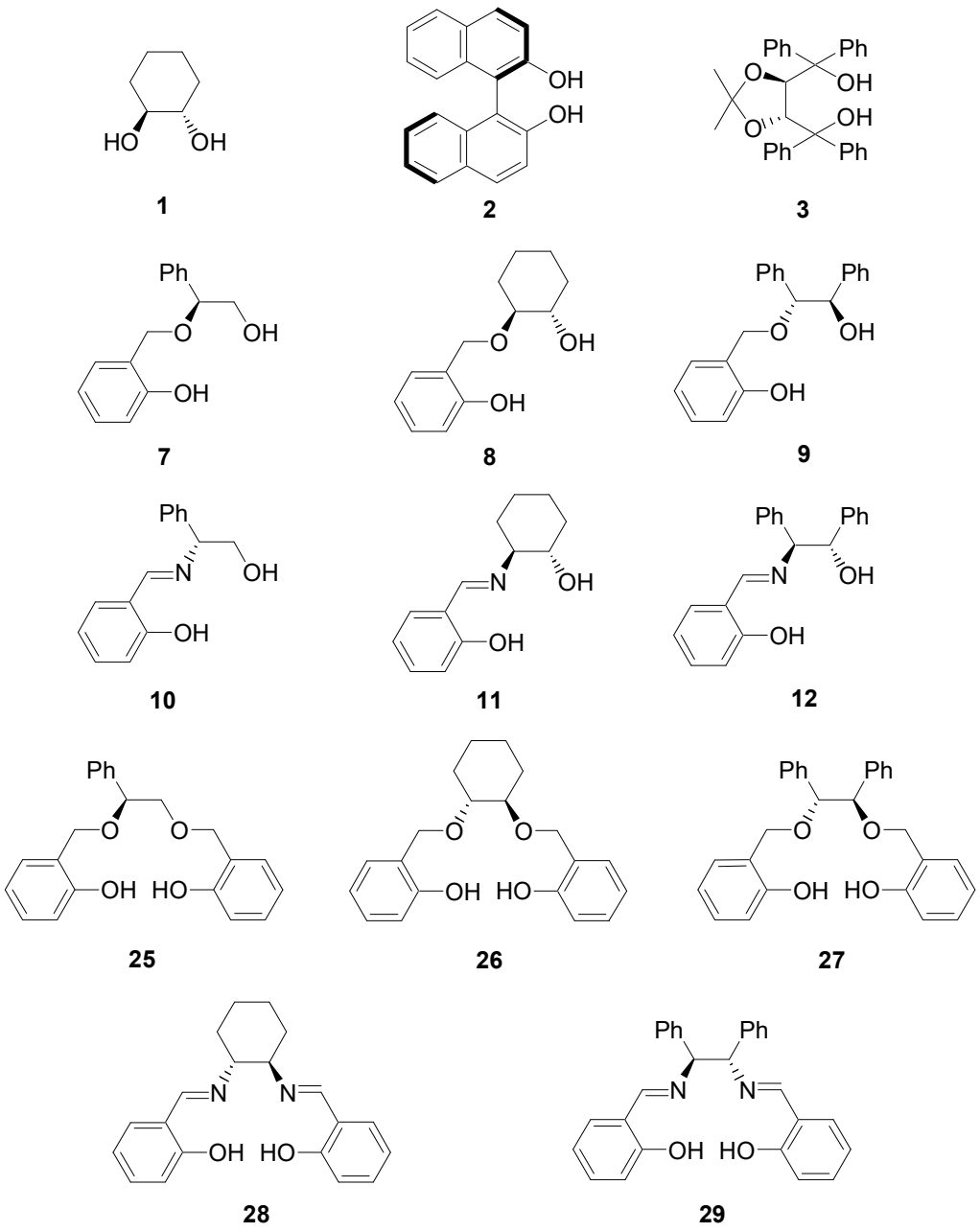
The bidentate Ti-complexes were prepared in situ according to the literature procedure by mixing $Ti[(O^iPr)_2Cl_2]$ and the diol in equal amount in presence of molecular sieves[23].

Scheme 14.



The family of ligand synthesized is shown in figure 9.

Figure 9.



Data for the titanium complexes prepared are summarized in Table 3.

Table 3.

Entry	Ti-Complex	Prep. Proced.	Yield	m.p.	$[\alpha]_D$
1.	Ti-**7**	Method **B**	quantitative	200-240 ^{0}C (decomp.)	- 33.33 (*c* 0.2, $CHCl_3$)
2.	Ti-**8**	Method **B**	quantitative	>300 ^{0}C (decomp.)	+ 7.5 (*c* 0.15, $CHCl_3$)
3.	Ti-**9**	Method **B**	quantitative	220-280 ^{0}C (decomp.)	+ 142.9 (*c* 0.21, $CHCl_3$)
4.	Ti-**10**	Method **B**	quantitative	235-238 ^{0}C	+ 228.5 (*c* 0.07, $CHCl_3$)
5.	Ti-**11**	Method **B**	quantitative	230-235 ^{0}C*	+ 168.75 (*c* 0.16, $CHCl_3$)
6.	Ti-**12**	Method **B**	quantitative	225-230 ^{0}C	- 159 (*c* 0.2, $CHCl_3$)
7.	Ti-**25**	Method **B**	quantitative	(a)	(b)
8.	Ti-**26**	Method **B**	quantitative	(c)	(c)
9.	Ti-**27**	Method **B**	quantitative	200-220 ^{0}C (decomp.)	+ 90 (*c* 0.2, $CHCl_3$)
10.	Ti-**28**	Method **A**	quantitative	330-350 ^{0}C (decomp.)	+ 514.3 (*c* 0.014, $CHCl_3$)
11.	Ti-**29**	Method **A**	75%	>300 ^{0}C**	- 303 (*c* 0.017, $CHCl_3$)

(a) didn't melt but decomposes at 280 ^{0}C. (b) very low. (c) highly hygroscopic. * Colour changes at 190 ^{0}C. ** colour changes at 285 ^{0}C.

Conclusion:

i) The resolution of (±)-1,2-cyclohexanediol has been achieved in good yield using *O*-actylmandelic acid. Both the enantiomers were obtained in >80% yield in optically pure form.

ii) (±)-*trans*-2-amino-1,2-diphenylethanol has been resolved in moderate yield using *S*-(-)-pyroglutamic acid.

iii) The resolution of (±)-2-aminocyclohexanol has also been achieved using a cheap derivative of proline where one of the enantiomers has been separated in 50% yield. To the best of our knowledge, this is the best method for chemical resolution of this aminoalcohol.

iv) Starting from cheap sources, a series of bidentate, tridentate and tetradentate ligands have been prepared in moderate to high yield and high optical purity.

v) For the preparation of Ti-SALEN complexes, a simple methodology has been developed which can be operated in multigram scale.

vi) Finally, we were able to synthesize a variety of tetra, penta and hexacoordinated titanium complexes of varying steric and electronic properties. In most of the cases, these complexes were separated and characterized by m.p. and rotation.

Experimental

(±)-Cyclohexane-1,2-diol (1):

A 500 mL three necked round bottom flask equipped with a stirring bar, a thermometer and a dropping funnel was charged with 88-90% formic acid (150 mL, 300 mmol) and 30% hydrogen peroxide (35 mL, 310 mmol). To this vigorously stirred solution, freshly distilled cyclohexene (25.5 mL, 250 mmol) was added over a period of 20 min. maintaining the internal temperature between 40-45 ^{0}C (controlling the temperature by ice-bath). After the addition was over, the reaction mixture was further stirred for an hour at 40 ^{0}C (keeping a water bath) and then left for overnight stirring at room temperature. The aqueous solution was reduced to ~70 mL by evaporation on a rotavapor to remove most of the volatile substrate, basified to pH ~10 by careful addition of NaOH solution. The extraction was carried out with EtOAc (80 mL) by a vigorous stirring at 45 ^{0}C. The solution was transferred to a pre heated separating funnel and the organic layer was separated. This procedure was repeated five more times. The combined organic layer was reduced to a volume when solid material started precipitating (~40 mL). It was then kept on an ice-bath and filtered. The mother liquor was further reduced (~20mL) and the second crop of crystals were collected. The combined solid was distilled under reduced pressure (120 ^{0}C at 10 mm of Hg) in a kugelrohr apparatus.

	White solid	
Yield:	18 g (62%)	
m.p.	104-105 ^{0}C	[lit[24] 103-104 ^{0}C]

Resolution of (±)-cyclohexane-1,2-diol (1)

A. Preparation of (*S*)-*O*-acetylmandelic acid (5):

A flame dried 100 mL two necked round bottom flask equipped with a stirring bar and a dropping funnel was attached to a bubler. *S*-(+)-Mandelic acid (**4**) (15.2 g, 100 mmol) was placed inside the flask and acetylchloride (35.5 mL, 500 mmol) was added slowly with vigorous stirring. The stirring was continued initially at room temperature and then under reflux for 2 h. Excess acetylchloride was removed in a rotary evaporator and the semisolid mass was suspended in minimum volume of water. The acid was extracted with DCM (3 x 40 mL) and the combined organic layer was washed with brine (2 x 20 mL). It was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The sticky mass obtained after keeping in high vacuum for 2 h at 50 ^{0}C solidified slowly in refrigerator (2 days). The

solid was crystallized from a combination of petroleum ether and diethyl ether to give white crystals of (*S*)-(+)-*O*-acetylmandelic acid (**5**).

	White solid	
Yield:	12.27 g (63%)	
m.p.	103-105 ^{0}C	[lit.[25] 95-97.5 ^{0}C]
$[\alpha]_D$	+ 152 (*c* 1, acetone)	[lit.[25] + 148 (*c* 1.87, acetone)]

B. Preparation of monoester 6a and 6b:

A flame dried two necked round bottom flask was charged with DCC (9.06 g, 44 mmol), (±)-1,2-cyclohexanediol (**1**) (4.65 g, 40 mmol) and DMAP (0.48 g, 4 mmol) under argon atmosphere. Freshly distilled DCM (80 mL) was introduced into the flask and the solution was kept at -10 ^{0}C. (*S*)-(+)-*O*-acetylmandelic acid (**5**) (7.76 g, 40 mmol) was added slowly as a solution in DCM (20 mL). Stirring was continued for 6 h till the completion of the reaction (TLC). The reaction mixture was filtered to remove the urea derivative and the filtrate was evaporated to obtained a pasty mass, which was chromatographed using 230-400 mesh silicagel and 10% EtOAc/petroleum ether as eluent. The solid monoester (**6a**) was crystallized from a combination of petroleum ether and ethylacetate.

[TLC data: Solvent = petroleum ether : Ethylacetate (4:1) (two runs), R_f (**6a**) = 0.4; R_f (**6b**) = 0.28]

Monoester 6a:

	White solid
Yield	4.1 g (35% overall)
m.p.	101-103 ^{0}C
$[\alpha]_D$	+ 78.3 (*c* 1.2, acetone)
IR ($CHCl_3$) cm^{-1}	3544, 2943, 1741
^{1}H NMR ($CDCl_3$)	δ 1.17-1.39 (m, 4H, C*H*$_2$), 1.66-1.74 (m, 3H, C*H*$_2$, O*H*), 1.90-2.08 (m, 2H, C*H*$_2$), 2.21 (s, 3H, C*H*$_3$), 3.39-3.50 (m, 1H, C*H*), 4.58-4.64 (m, 1H, C*H*), 5.91 (s, 1H, C*H*Ph), 7.37-7.50 (m, 5H, H_{Ar})
^{13}C NMR ($CDCl_3$)	δ 20.3, 23.1, 23.3, 29.2, 32.0, 71.6, 74.6, 79.0, 127.3, 128.5, 128.9, 133.8, 168.2, 170.3

Analysis for	$C_{16}H_{20}O_5$
Calculated (%)	C, 65.75; H, 6.91
Found (%)	C, 65.40; H, 6.94

Monoester 6b:

	Liquid
Yield	4.65 g (40 %)
$[\alpha]_D$	+ 40.8 (*c* 1.2, acetone)
IR ($CHCl_3$) (cm^{-1})	3523, 2943, 1741.
^1H NMR ($CDCl_3$)	δ 1.14-1.39 (m, 4H, C*H*$_2$), 1.60-1.73 (m, 2H, C*H*$_2$), 1.77-1.85 (m, 2H, C*H*$_2$, O*H)*, 2.0-2.10 (m, 1H, CH_2), 2.20 (s, 3H, C*H*$_3$), 3.57-3.64 (m, 1H, C*H*), 4.66-4.74 (m, 1H, C*H*), 5.85 (s, 1H, C*H*Ph), 7.36-7.52 (m, 5H, H_{Ar})
^{13}C NMR ($CDCl_3$)	δ 20.3, 23.2, 23.3, 28.9, 32.1, 71.6, 74.6, 78.9, 127.3, 128.4, 128.9, 133.5, 168.5, 170.4
Analysis for	$C_{16}H_{20}O_5$
Calculated (%)	C, 65.75; H, 6.91
Found (%)	C, 65.12; H, 7.01

C. Preparation of (*S*,*S*)-(+)-1,2-cyclohexanediol (1):

The solid monoester (**6a**) (4.1 g) was stirred in 1 N NaOH solution in MeOH (36 mL) at room temperature for 4 h. When the TLC showed the disappearance of the ester, MeOH was evaporated and the diol was extracted with DCM (4 x 20 mL) from a saturated aqueous solution of K_2CO_3. The crude product was purified through kugelrohr distillation (120 ^{0}C at 4 mm Hg) to obtain (*S*,*S*)-(+)-**1** in 97% optical purity.

	White solid	
Yield	1.5 g (92%)	
m.p.	115-116 ^{0}C	[lit.[26] 107.5-108.5]
$[\alpha]_D$	+ 40 (*c* 1.6, H_2O) (97% ee)	
		[lit.[27] - 36.9 (*c* 1.4, H_2O) for 89% ee]

Preparation of (*R*,*R*)-(-)-1,2-cyclohexanediol (1):

(*R*,*R*)-(-)-**1** was obtained in a similar way from liquid monoester (**6b**). The diol was recrystallized from ethylacetate (96% optical purity).

	White solid	
Yield	1.5 g (81%)	
m.p.	110-112 ^{0}C	[lit.[26] 107.5-108.5]
$[\alpha]_D$	- 39.4 (*c* 1.6, H_2O) (96% ee)	
		[lit.[27] - 36.9 (*c* 1.4, H_2O) for 89% ee]

Preparation of (2-Methoxymethoxy-phenyl)-methanol (14):

To a suspension of NaH (4.8 g, 110 mmol) in a mixture of THF/DMF (50 mL each) under argon atmosphere was added salicylaldehyde (10.6 mL, 100 mmol) dropwise at 0 ^{0}C. Immediately a vigorous reaction started and the evolution of the H_2 gas was monitored through a bubbler. When the rate slowed down, the reaction mixture was brought to room temperature and stirred for half an hour. Methoxymethylenechloride (8.3 mL, 110 mmol) was added to it dropwise at 0 ^{0}C. The reaction mixture was stirred at room temperature for another half an hour till the completion of the reaction (TLC). Water (10 mL) was added to the reaction mixture cautiously, keeping the heterogeneous reaction mixture in an ice-bath. $NaBH_4$ (4.8 g, 120 mmol) was added portionwise while the colour of the reaction mixture changed from yellow to white. After 15 min when the TLC showed the disappearance of the aldehyde, water (~200 mL) was added to the reaction mixture cautiously and the compound was extracted with ether (3 x 50 mL). The combined organic layer was washed with brine (1 x 20 mL) and kept over anhydrous Na_2SO_4. On evaporation of the solvent a colourless liquid was obtained.

	Colourless liquid
Yield	17.5 g (quantitative)
IR (neat) (cm^{-1})	3407, 1458
^{1}H NMR ($CDCl_3$)	δ 3.48 (s, 3H, OCH_3), 4.70 (s, 2H, CH_2Ph), 5.23 (s, 2H, CH_2), 6.98-7.11 (m, 2H, H_{Ar}), 7.22-7.32 (m, 2H, H_{Ar})

Preparation of 1-chloromethyl-2-methoxymethoxy-benzene (15):

Benzylalcohol (**14**) (3.36 g, 20 mmol) was placed in a single necked round bottom flask. Freshly distilled dry CCl_4 was introduced. PPh_3 (5.7 g, 22 mmol) was added at once and the reaction mixture was stirred at rt. After dissolution of the solid material dry pyridine (2 mL, 25 mmol) was added to the reaction mixture and stirring was continued for 8 h at room temperature. When the starting vanished (TLC), petroleum ether (100 mL) was added and the solid material was triturated. After allowing the solid to settle down, the supernant solvent was decanted off slowly. This procedure was repeated three more times. The combined organic layer was evaporated on a rotary evaporator. The resulting liquid (some solid may appear) was distilled in a kugelrohr to obtain a colourless liquid. This liquid was further purified by chromatography using 100-200 mesh neutral silicagel and petroleum ether as an eluent.

	Colourless liquid
Yield	2.52 g (68%)
b.p.	160 ^{0}C at 4 mm of Hg
IR (neat) (cm^{-1})	2956, 2850, 1492
^{1}H NMR ($CDCl_3$)	δ 3.49 (s, 3H, OC*H*$_3$), 4.66 (s, 2H, C*H*$_2$Ph), 5.23 (s, 2H, C*H*$_2$), 6.96-7.11 (m, 2H, H_{Ar}), 7.25-7.33 (m, 2H, H_{Ar})
^{13}C NMR ($CDCl_3$)	δ 41.6, 56.1, 94.0, 114.1, 121.7, 126.4, 129.9, 130.5, 154.8
Analysis for	$C_9H_{11}O_2Cl$
Calculated (%)	C, 57.91; H, 5.95
Found (%)	C, 58.24; H, 5.85

Preparation of (*S*)-2-(2-Hydroxy-1-phenylethoxymethyl)phenol (7)

A. Preparation of Phenylethane-1,2-diol (19):

S-(+)-Mandelic acid (**4**) (3.04 g, 20 mmol) dissolved in 100 mL of diethyl ether was added dropwise to a suspension of LAH (1.7 g, 50 mmol) in ether (100 mL) at a rate sufficient to maintain a gentle reflux. After the addition was complete, the reaction mixture was refluxed for 30 min, cooled and treated cautiously with EtOAc (5 mL) to destroy the excess LAH. The resulting mixture was hydrolyzed by the addition of 5 mL of 15% aqueous NaOH solution. The solid material was filtered and washed with diethyl ether

(100mL). The ethereal layer was dried over anhydrous Na_2SO_4 and then concentrated at reduced pressure. The crude diol (**19**) thus obtained was purified through kugelrohr distillation (190 ^{0}C at 4 mm of Hg).

	White solid	
Yield	2.19 g (79%)	
m.p.	65-67 ^{0}C	[lit.[12] 66-67 ^{0}C]
$[\alpha]_D$	+ 39 (*c* 3, EtOH)	
		[lit.[12] + 39.3 (*c* 3.13, EtOH)]
IR ($CHCl_3$) (cm^{-1})	3373, 1452	

B. Mono THP diol (20):

To a solution of (*S*)-(+)-(**19**) (2.76 g, 20 mmol) and PPTS (0.5 g, 2 mmol) in freshly distilled dry DCM was added DHP (2.0 mL, 22 mmol) at 0 ^{0}C. Stirring was continued at that temperature for 6 h and then at room temperature overnight. The reaction mixture was diluted with DCM and washed with bicarbonate solution (2 x 20 mL). It was further washed with brine (1 x 10 mL) and kept over anhydrous Na_2SO_4. Finally the monoprotected alcohol (**20**) was purified through column chromatography over 100-200 mesh neutral silica gel using 15% EtOAc/petroleum ether as eluent.

	Viscous liquid
Yield	2.85 g (64%)
$[\alpha]_D$	+ 123.18 (*c* 4.4, $CHCl_3$)
IR ($CHCl_3$) (cm^{-1})	3434, 2941, 1452
^{1}H NMR ($CDCl_3$)	δ 1.36-1.99 (m, 6H, C*H*$_2$), 3.38-4.08 (m, 4H, C*H*$_2$), 4.43-4.66 (m, 1H, C*H*Ph), 4.72-4.98 (m, 1H, C*H*), 7.20-7.44 (m, 5H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 20.1, 25.1, 30.8, 63.6, 73.2, 75.8, 100.4, 126.2, 127.7, 128.3, 140.3

C. Alkylation of 20:

To a suspension of NaH (0.68 g, 14.1 mmol) in 30 mL THF was added the mono protected diol (**20**) (2.85 g, 12.8 mmol) dissolved in 5 mL THF under argon atmosphere. After the rate of hydrogen evolution slowed down, benzylchloride (**15**) (2.62 g, 14.1 mmol)

dissolved in 5 mL THF was added to the reaction mixture. TBAI (0.46 g, 1.2 mmol) was introduced directly into the reaction mixture. The reaction vessel was purged thoroughly with argon and then refluxed for 4 h till the starting alcohol vanished (TLC). Most of the THF was evaporated on a rotavapor, 50 mL of water was added carefully into the reaction mixture and the desired product was extracted with diethyl ether (3 x 30 mL). The combined ethereal layer was washed with brine (1 x 20 ml) kept over anhydrous Na_2SO_4. On evaporation a sticky mass was obtained which was purified by passing through a small bed of celite to remove inorganic impurities. The sticky liquid obtained was used as such for the next step.

D. Deprotection of the MOM group:

The above product (3.6 g) was dissolved in a mixed solvent of ^{i}PrOH/THF (20 mL, 1:1) and few drops of concentrated HCl was added to it. After 48 h when the reaction went to completion (TLC), the reaction mixture was worked up in the usual way. The diol (**7**) was isolated through flash chromatography using 15% EtOAc/petroleum ether as eluent. Finally the diol (**7**) was crystallized from a mixture of petroleum ether/ethylacetate.

	White needles
Yield	1.3 g (26% overall)
m.p.	98-100 ^{0}C
$[\alpha]_D$	+ 102 (*c* 1, EtOH)
IR ($CHCl_3$) (cm^{-1})	3384, 2918, 1585
^{1}H NMR ($CDCl_3$)	δ 2.61 (bs, 1H, O*H*), 3.66-3.87 (m, 2H, CH_2), 4.47-4.79 (m, 3H, C*H*Ph), 6.78-7.02 (m, 3H, H_{Ar}), 7.17-7.48 (m, 6H, H_{Ar}) 7.61 (bs, 1H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 66.9, 70.2, 82.9, 116.7, 120.0, 122.7, 127.0, 128.6, 128.8, 129.7, 137.4, 156.0
Analysis for	$C_{15}H_{16}O_3$
Calculated (%)	C, 73.74; H, 6.61
Found (%)	C, 73.51; H, 6.58

Preparation of ligand (*S*,*S*)-2-(2-Hydroxy-cyclohexylmethyl)-phenol (8)

A. Alkylation of (*S*,*S*)-(+)-1,2-cyclohexanediol (1):

Applying a similar alkylation procedure as described for ligand (**7**) (*S*,*S*)-(+)-1,2-cyclohexanediol (**1**) (1.16g, 10 mmol) was alkylated with benzylchloride (**15**) (2.04 g, 11 mmol) at 60 ^{0}C for 8 h.

B. Deprotection of the MOM-ether (18):

The resulting product (**18**) following the removal of inorganic impurities was dissolved in THF (14 mL) and few drops of concentrated HCl was added to it. The homogeneous solution was stirred at room temperature for 24 h till the starting disappeared (TLC). Usual workup followed by flash chromatography using 230-400 mesh silica gel and 10% EtOAc/ petroleum ether as eluent afforded the diol (**8**) which was further purified through crystallization from a mixture of petroleum ether/ethylacetate.

	White solid
Yield	0.96 g (64%)
m.p.	130-132 ^{0}C
$[\alpha]_D$	+ 40.5 (*c* 1.21, $CHCl_3$)
IR ($CHCl_3$) (cm^{-1})	3380, 3018, 2937, 1490
^{1}H NMR ($CDCl_3$)	δ 1.11-1.43 (m, 4H, C*H*$_2$), 1.59-1.81 (m, 2H, C*H*$_2$), 1.93-2.23 (m, 2H, C*H*$_2$), 2.96 (bs, 1H, O*H*), 3.17-3.36 (m, 1H, C*H*), 3.44-3.60 (m, 1H. C*H*), 4.68 (d, *J* = 11.2 Hz, 1H, C*H*$_2$Ph), 4.80 (d, *J* = 11.2 Hz, 1H, C*H*$_2$Ph), 6.77-6.95 (m, 2H, H_{Ar}), 7.01-7.28 (m, 2H, H_{Ar}), 7.96 (bs, 1H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 23.9, 24.1, 29.7, 33.0, 70.7, 74.0, 84.0, 116.5, 119.8, 123.4, 129.0, 129.5, 156.0
Analysis for	$C_{13}H_{18}O_3$
Calculated (%)	C, 70.23; H, 8.18
Found (%)	C, 69.82; H, 8.21

Preparation of ligand (*R*,*R*)-2-(2-Hydroxy-1,2-diphenyl-ethoxymethyl)-phenol (9)

A. Alkylation of (*R*,*R*)-(+)-1,2-diphenylethane-1,2-diol (16):

A mixture of (*R*,*R*)-(+)-stilbene diol (**16**) (1.07 g, 5 mmol), NaOH (1 g, 25 mmol), K_2CO_3 (13.8 g, 100 mmol) and TBABr (0.34 g, 1 mmol) was crushed finely in a motar

pastle. The fine powder was placed in a 50 mL round bottom flask and 25 mL DCM was added to it. Benzylchloride (**15**) (1.3 g, 7 mmol) was added to the vigorously stirred solution and stirring was continued till the diol vanished in TLC (4 h). Water (20 mL) was added cautiously to the reaction vessel and the DCM layer was separated. The organic layer was given a brine wash (1 x 10 mL) and then kept over anhydrous Na_2SO_4. On evaporation a pasty mass was obtained which was passed through a small bed of celite to remove inorganic impurities. The sticky liquid (**17**) obtained was used as such for the next step.

B. Deprotection of the MOM-ether (17):

The above material (**17**) (1.6 g) was dissolved in a mixed solvent of THF/^{i}PrOH (10 mL, 1:1) and few drops of concentrated HCl was added to it. After 48 h of stirring when the starting vanished (TLC), most of the solvent was evaporated under reduced pressure at room temperature. Water (20 mL) was added to it and the diol was extracted with EtOAc (3 x 20 mL). The combined organic layer was gven a brine wash, kept over anhydrous Na_2SO_4 and then evaporated to obtain a pasty mass which was purified through column chromatography using 230-400 mesh silicagel and 20% EtOAc/petroleum ether as eluent. The viscous liquid obtained solidified after keeping in the vacuum for a long time. The diol (**9**) was further purified through crystallization from a mixture of petroleum ether/ EtOAc.

	White solid
Yield	1.15 g (72% overall)
m.p.	121-123 ^{0}C
$[\alpha]_D$	- 22.4 (*c* 2, EtOH)
IR ($CHCl_3$) (cm^{-1})	3390, 1454, 1066
^{1}H NMR ($CDCl_3$)	δ 3.1 (bs, 1H, O*H*), 4.47 (d, *J* = 8.1 Hz, 1H, C*H*Ph), 4.55 (d, *J* = 11.5 Hz, 1H, CH_2), 4.62 (d, *J* = 11.5 Hz, 1H, CH_2) 4.82 (d, *J* = 8.1 Hz, 1H, C*H*Ph), 6.81-6.96 (m, 3H, H_{Ar}), 7.03-7.09 (m, 4H, H_{Ar}), 7.16-7.26 (m, 7H, H_{Ar}), 7.55 (bs, 1H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 70.6, 78.5, 87.6, 116.7, 119.9, 122.9, 127.2, 127.7, 128.0, 128.1, 128.2, 128.9, 129.7, 136.9, 139.3, 156.1
Analysis for	$C_{21}H_{20}O_3$
Calculated (%)	C, 78.71; H, 6.30
Found (%)	C, 78.19; H, 6.35

Preparation of (*R*)-(+)-2-[(2-Hydroxy-1-phenyl-ethylimino)-methyl]phenol (10):

To a solution of (*R*)-(-)-phenyl glycinol[16] (0.68 g 5 mmol) in DCM (5 mL) was added salicylaldehyde (0.53 mL, 5 mmol) and $MgSO_4$ (1 g) at room temperature. The solution immediately turned yellow and the stirring was continued for 8 h till the completion of the reaction (TLC). The reaction mixture was diluted with 10 mL of DCM and filtered. On evaporation of the DCM layer a yellowish solid (**10**) was obtained which was crystallized from a mixture of petroleum ether/ethylacetate.

	Yellow solid
Yield	1.0 g (83%)
m.p.	91-93 ^{0}C
$[\alpha]_D$	+ 109.24 (*c* 1.1, EtOH)
IR ($CHCl_3$) (cm^{-1})	3421, 3016, 1629
^{1}H NMR ($CDCl_3$)	δ 1.62 (bs, 1H, O*H*), 3.90-3.96 (m, 2H, CH_2), 4.48 (t, *J* = 6.56 Hz, 1H, C*H*Ph) 6.88-6.92 (m, 1H, H_{Ar}), 6.97-6.99 (m, 1H, H_{Ar}), 7.24-7.42 (m, 7H, H_{Ar}), 8.49 (s, 1H, C*H*), 13.28 (s, 1H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 67.5, 75.6, 117.0, 118.7, 118.8, 127.1, 127.8, 128.8, 131.7, 132.6, 139.3, 161.0, 166.2
Analysis for	$C_{15}H_{15}NO_2$
Calculated (%)	C, 74.65; H, 6.28; N, 5.81
Found (%)	C, 75.01; H, 6.24; N, 5.76

Preparation of (*S*,*S*)-(+)-2-[(2-Hydroxycyclohexylimino)-methyl]-phenol (11)

A. Preparation of (±) *trans*-2-azidocyclohexanol:

To a solution of cyclohexeneoxide (22 mL, 200 mmol) in EtOH (300 mL) was added NaN_3 (26 g, 400 mmol) and NH_4Cl (21.2 g, 400 mmol). The heterogeneous mixture was refluxed for 24 h. All the EtOH was evaporated on a rotavapor and the solid was triturated with THF and finally filtered. After evaporating the solvent, the crude azidoalcohol was obtained which was purified through kugelrohr distillation.

	Colourless liquid at room temperature
Yield	26.33 g (93%)
b.p.	90 ^{0}C at 4 mm of Hg [lit.[28] 70-71 ^{0}C at 1.5 mm of Hg]

B. Preparation of (±)-*trans*-2-aminocyclohexanol (22):

(±)-*trans*-2-azidocyclohexanol (14 g, 100 mmol) was reduced using 5% Pd/C (1 g) in MeOH (100 mL). The solution was shaken on 50 psi of hydrogen for 8 h in a Parr apparatus. The reaction mixture was filtered through a short bed of celite and MeOH was evaporated on a rotary evaporator. The crude compound was distilled in a kugelrohr to obtain the aminoalcohol (±)-**22** as a white hygroscopic solid.

	White solid (hygroscopic)
Yield	10.35 g (90%)
m.p.	60 ^{0}C [lit.[29] 65 ^{0}C]
b.p.	120 ^{0}C at 10 mm of Hg [lit.[28] 70 ^{0}C at 2 mm of Hg]
IR ($CHCl_3$) (cm^{-1})	3359, 2860, 2931

C. Resolution of aminoalcohol (±)-*trans*-2-aminocyclohexanol (22)

a) Preparation of *N*-pivaloyl proline (23):

To a solution of L-proline (25.3 g, 220 mmol) in water (100 mL) was added NaOH solution (17.6 g dissolved in 50 mL of H_2O) slowly at 0 ^{0}C. TBABr (3.5 g, 11 mmol) was added to the solution and the stirring was continued for an hour. Pivaloylchloride (24.6 mL, 200 mmol) dissolved in 70 mL DCM was added slowly to the vigorously stirred reaction mixture in such a rate so that the addition completed in 1 h. At the end of the addition the reaction became vigorous and the temperature was maintained at 0 ^{0}C for 1 h. It was further stirred for 4 h at room temperature. In work up, the aqueous layer was separated and washed with DCM (1 x 30 mL) to remove neutral impurities. It was then acidified to pH~3 with concentrated HCl and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (1 x 30 mL) and kept over anhydrous Na_2SO_4. The pasty mass obtained after evaporating the solvent solidified partly on keeping under vacuum for a long time. However the material was kept in refrigerator for 24 h after adding 10 mL petroleum ether where it solidified completely. It was crystallized twice from EtOAc to get a white solid of *N*-pivaloyl proline (**23**).

	White solid
Yield	28.6 g (72%)
m.p.	130-135 ^{0}C

$[\alpha]_D$	- 73 (*c* 1, EtOH)
IR ($CHCl_3$) (cm^{-1})	3294, 2981, 1749
^1H NMR ($CDCl_3$)	δ 1.28 (s, 9H, C*H*$_3$), 1.90-2.22 (m, 4H, C*H*$_2$), 3.66-3.83 (m, 2H, C*H*$_2$), 4.51-4.63 (m, 1H, C*H*), 10.01 (bs, 1H, COO*H*)
^{13}CNMR ($CDCl_3$)	δ 25.5, 26.7, 27.0, 38.4, 47.9, 60.8, 175.8, 177.4
Analysis for	$C_{10}H_{17}NO_3$
Calculated (%)	C, 60.26; H, 8.62; N, 7.03
Found (%)	C, 60.01; H, 8.69; N, 7.09

b) Preparation of the diastereomeric salt 24:

To a solution of (±)-(**22**) (8.06 g, 70 mmol) in MeOH (25 mL) was added slowly a solution of (*S*)-(-)-*N*-pivaloyl proline (**23**) (13.9 g, 70 mmol) in MeOH (25 mL). After few minutes of stirring, the solvent was evaporated on a rotavapor and the salt (**24**) was recrystallized from a mixture of EtOAc/EtOH (three times).

	White solid
Yield	7.15 g (32.5% overall)
m.p.	188-194 ^{0}C
$[\alpha]_D$	- 30.4 (*c* 1, H_2O)

c) Hydrolysis of the salt:

To the aqueous solution of the salt (obtained after three crystallization) (7.15 g in 5 mL of H_2O) was added a NaOH solution (1.6 g in 10 mL of H_2O) slowly at 0 ^{0}C. The aminoalcohol was extracted with a solvent mixture of THF/diethylether (1:4, 4 x 20 mL). The combined organic layer was washed with brine (1 x 10 mL) and then kept over anhydrous K_2CO_3. On evaporating the solvent a viscous liquid was obtained which was distilled in kugelrohr at 140 ^{0}C at 4 mm of Hg. After cooling, the aminoalcohol (*S*,*S*)-(+)-**22** solidified as hygroscopic mass.

	White solid (highly hygroscopic)	
Yield	2.1 g (80%)	
m.p.	92-94 ^{0}C	[lit.[17] 88-89 ^{0}C]
$[\alpha]_D$	+ 49.01 (*c* 1, MeOH) (98% ee)	
		[lit.[17] + 48.2 (*c* 1, MeOH) for 96% ee]

d) Recovery of *N*-pivaloylproline (23):

The aqueous layers from the previous reaction and those obtained after the hydrolysis of the mother liquors of 1st, 2nd and 3rd crystallizations were combined together and acidified to pH~3 with concentrated HCl. The aqueous layer was saturated with NaCl and extracted with DCM (3 x 50 mL). The combined organic layer was washed with brine (1 x 20 mL) and kept over anhydrous Na_2SO_4. The crude acid was obtained by the evaporation of the solvent under reduced pressure. A single crystallization from ethylacetate afforded *N*-pivaloylproline (**23**) in optically pure form.

Yield	9.45 g (68%)
m.p.	130-135 ^{0}C
$[\alpha]_D$	- 73 (*c* 1, EtOH)

D. Preparation of the Schiff base (11):

Following a similar procedure as described for ligand (**10**), (*S*,*S*)-(+) (**22**) (0.58 g, 5 mmol) and salicylaldehyde (0.53 mL, 5 mmol) after 6 h afforded 0.95 g (87%) of ligand (**11**) as a yellow solid after crystallization from petroleum ether.

	Yellow solid
Yield	0.95 g (87%)
m.p.	101-102 ^{0}C
$[\alpha]_D$	+ 115.83 (*c* 1.2, MeOH)
IR ($CHCl_3$) (cm^{-1})	3415, 2935, 1631
^{1}H NMR ($CDCl_3$)	δ 1.23-1.52 (m, 3H, C*H*$_2$), 1.55-1.93 (m, 4H, C*H*$_2$), 1.99-2.16 (m, 2H, C*H*$_2$, O*H*), 2.90-3.08 (m, 1H, C*H*), 3.55-3.74 (m, 1H, C*H*) 6.81-7.01 (m, 2H, H_{Ar}), 7.19-7.38 (m, 2H, H_{Ar}), 8.42 (s, 1H, C*H*), 13.30 (bs, 1H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 24.0, 24.2, 32.6, 32.7, 73.1, 74.9, 116.9, 118.4, 118.5, 131.3, 132.2, 161.3, 165.0
Analysis for	$C_{13}H_{17}NO_2$
Calculated (%)	C, 71.19; H, 7.83; N, 6.39
Found (%)	C, 70.82; H, 7.88; N, 6.32

Preparation of (*S*,*S*)-(-)-2-[(2-Hydroxy-1,2-diphenylethylimino)-methyl]-phenol (12)

A. Preparation of the (±)-*trans*-2-amino-1,2-diphenylethanol (21):

The aminoalcohol (±)-**21** was prepared according to literature procedure[15].

B. Resolution of (±)-*trans*-2-amino-1,2-diphenylethanol (21)

a) Preparation of the diastereomeric salt:

To a solution of (*S*)-(-)-Pyroglutamic acid (4.8 g, 37.2 mmol) in ethanol (30 ml) was added (±)-*trans*-2-amino-1,2-diphenylethanol (**21**) (7.3 g, 34 mmol) in batches and the reaction mixture was heated to reflux for half an hour. After cooling the crystallization commenced immediately and was left overnight at room temperature. The white crystals were collected by filtration and washed with cold EtOH (5 mL). The solid was dried in vacuum and again recrystallized from same amount of solvent.

	White solid
Yield	3.56 g (31% overall)
m.p.	198-201 ^{0}C
$[\alpha]_D$	- 71.26 (*c* 2, H_2O)

b) Hydrolysis of the salt:

The solid (3.56 g) was dissolved in minimum amount of water and basified with liquor NH_3 keeping in an ice-bath. It was further stirred for half an hour before filtration. The solid was washed with minimum amount of cold water and then dried. Thus (*S*,*S*)-(-) aminoalcohol (**21**) was obtained in good yield.

	White solid	
Yield	2.1 g (94% recovery, 29% overall)	
m.p.	114-115 ^{0}C	[lit.[15] 116.5-117 ^{0}C]
$[\alpha]_D$	- 124.2 (*c* 1.2, EtOH)	[lit.[15] - 124 (*c* 1.18, EtOH)]

C. Preparation of the Schiff base (12):

The aminoalcohol (*S*,*S*)-(-)-*trans*-2-amino-1,2-diphenylethanol (**21**) (1.07 g, 5 mmol) was heated gently in 15 mL of EtOH. After the reaction mixture cooled to room temperature, salicylaldehyde (0.53 mL, 5 mmol) was added to it followed by anhydrous $MgSO_4$ (1 g). On completion of the reaction (TLC), the reaction mixture was diluted with

15 mL of acetone and was filtered. On evaporation of the mother liquor in reduced pressure, a yellowish solid was obtained which was crystallized from petroleum ether/ethylacetate.

	Yellow solid
Yield	1.3 g (82%)
m.p.	138-139 ^{0}C
$[\alpha]_D$	- 98.18 (*c* 1.1, EtOH)
IR ($CHCl_3$) (cm^{-1})	3421, 1629
^{1}H NMR ($CDCl_3$)	δ 2.43 (bs, 1H, O*H*), 4.42 (d, *J* = 7.4 Hz, 1H, C*H*Ph), 5.01 (d, *J* = 7.4 Hz, 1H, C*H*Ph), 6.82-7.04 (m, 2H, H_{Ar}), 7.08-7.4 (m, 12H, H_{Ar}), 8.42 (s, 1H, C*H*), 13.30 (bs, 1H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 78.4, 81.1, 117.0, 118.7, 118.8, 127.0, 127.6, 127.8, 128.0, 128.3, 131.8, 132.7, 139.2, 140.0, 161.0, 166.7
Analysis for	$C_{21}H_{19}NO_2$
Calculated (%)	C, 79.46; H, 6.05; N, 4.41
Found (%)	C, 79.60; H, 6.07; N, 4.49

Preparation of *O,O'*bis(2-hydroxyphenylmethyl)-phenylethane diol (25)

A. Alkylation of (S)-(+)- 1-phenyl-1,2-ethanediol (19):

To a suspension of NaH (0.58 g, 12 mmol) in THF (10 mL) was added (*S*)-(+)-1-phenyl-1,2-ethanediol (**19**) (1.07 g, 5 mmol) dissolved in 10 mL THF dropwise under argon atmosphere. The reaction was left to stir for an hour. When the evolution of H_2 almost ceased, benzylchloride (**15**) (2.23 g, 12 mmol) was introduced inside the flask followed by TBAI (0.18 g, 0.5 mmol). The reaction vessel was purged thoroughly with argon and the reflux was continued till the alcohol disappeared (TLC, 4 h). After cooling the reaction mixture, most of the THF was evaporated in vacuum and 20 ml of water was added cautiously. The desired compound was extracted with ether (3 x 30 mL). The combined organic layer was given a brine wash (1 x 20 ml) and then kept over anhydrous Na_2SO_4. After evaporating the organic solvent, a viscous liquid was obtained which was passed through a short pad of celite to remove inorganic impurities and the viscous liquid obtained was used as such for the next step.

B. Deprotection of MOM-ether:

The crude product obtained from the previous step (2.17 g, 99%) was dissolved in a mixed solvent of THF/^{i}PrOH (1:1, 20 mL). A few drops of concentrated HCl was added and the reaction mixture was stirred at room temperature till the starting disappeared (TLC, 24 h). After completion of the reaction, most of the solvent was evaporated in vacuum at room temperature, water was added and the compound was extracted with EtOAc (3 x 20 mL). The combined organic layer was washed with brine (1 x 20 mL) and then kept over anhydrous Na_2SO_4. After evaporating the solvent, the diol (**25**) was obtained through flash chromatography using 10% EtOAc/petroleum ether as eluent.

	Colourless liquid
Yield	1.35 g (77% overall)
$[\alpha]_D$	+ 53.3 (*c* 2.2, $CHCl_3$)
IR ($CHCl_3$) (cm^{-1})	3382, 1490
^{1}H NMR ($CDCl_3$)	δ 3.60-3.64 (m, 1H, C*H*$_2$), 3.69-3.75 (m, 1H, C*H*$_2$), 4.50-4.83 (m, 5H, C*H*Ph), 6.78-7.04 (m, 6H, H_{Ar}), 7.11 (bs, 1H, O*H*), 7.18-7.41 (m, 7H, H_{Ar}), 7.59 (bs, 1H, -O*H*)
^{13}CNMR ($CDCl_3$)	δ 70.1, 72.2, 74.0, 80.3, 116.7, 117.0, 120.0, 120.1, 122.1, 122.3, 127.0, 128.6, 128.8, 129.7, 129.8, 136.9, 155.9, 156.1
Analysis for	$C_{22}H_{22}O_4$
Calculated (%)	C, 75.40; H, 6.34
Found (%)	C, 74.89; H, 6.42

Preparation of ligand (26):

According to the general procedure as described for ligand (**25**), (*R*,*R*)-(-)-1,2-cyclohexane diol (**1**) (0.81 g, 7 mmol) and benzylchloride (**15**) (3.2 g, 17 mmol) after 12 h of reflux followed by the deprotection in THF afforded ligand (**26**). The ligand was further purified by crystallization from a mixture of petroleum ether/diethyl ether.

	White solid
Yield	1.5 g (65% overall)
m.p.	74-76 ^{0}C
$[\alpha]_D$	- 7.01 (*c* 1.14, $CHCl_3$)
IR ($CHCl_3$) (cm^{-1})	3353, 2933, 1492

^{1}H NMR ($CDCl_3$)	δ 1.10-1.45 (m, 4H, C*H*$_2$) 1.61-1.74 (m, 2H, C*H*$_2$), 2.04-2.17 (m, 2H, C*H*$_2$), 3.35-3.47 (m, 2H, C*H*), 4.77 (s, 4H, C*H*$_2$Ph), 6.77-7.27 (m, 8H, H_{Ar}), 7.63 (s, 2H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 23.5, 29.7, 70.5, 81.6, 116.7, 119.9, 122.9, 128.4, 129.5, 156.0
Analysis for	$C_{20}H_{24}O_4$
Calculated (%)	C, 73.13; H, 7.38
Found (%)	C, 73.30; H, 7.32

Preparation of *O*,*O'*bis(2-hydroxyphenylmethyl)-1,2-1,2-diphenylethanediol (27):

According to the general procedure as described for ligand (**25**), (*R*,*R*)-(+)-stilbene diol (**16**) (1.07 g, 5 mmol) and benzylchloride (**15**) (2.6 g, 14 mmol) after 4 h of reflux followed by the deprotection in a mixed solvent of THF/^{i}PrOH afforded ligand (**27**). The ligand was further purified by crystallization from a mixture of petroleum ether/ethylacetate.

	White solid
Yield	1.6 g (75% overall)
m.p.	111-113 ^{0}C
$[\alpha]_D$	- 40.0 (*c* 2, EtOH)
IR ($CHCl_3$) (cm^{-1})	3388, 1454
^{1}H NMR ($CDCl_3$)	δ 4.52-4.67 (m, 6H, C*H*Ph), 6.79-6.88 (m, 4H, H_{Ar}), 6.94-7.03 (m, 6H, H_{Ar}), 7.16-7.24 (m, 8H, H_{Ar}), 7.64 (bs, 2H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 69.7, 85.6, 117.3, 120.1, 122.6, 127.8, 128.3, 128.4, 129.1, 129.8, 136.3, 156.0
Analysis for	$C_{28}H_{26}O_4$
Calculated (%)	C, 78.84; H, 6.16
Found (%)	C, 78.72; H, 6.14

Preparation of (*R*,*R*)-*N*,*N'*bis(2'-hydroxylphenylmethene)-1,2-cyclohexanediimine (28):

A. Resolution of *cis*/*trans*-1,2 diaminocyclohexane[20]:

To a solution of L tartaric acid (30 g, 200 mmol) in distilled water (80 mL) was added (±) *cis*/*trans* 1,2 diaminocyclohexane (48 mL, 0.38 mmol) in a rate sufficient to

maintain the temperature below 70 ^{0}C. This was followed by addition of glacial acetic acid (20 mL) maintaining the reaction temperature below 90 ^{0}C. The reaction mixture was stirred at room temperature for 2 h and then cooled to 5 ^{0}C and kept for 2 h. The reaction mixture was filtered, the solid residue was washed with cold water (1 x 20 mL) followed by MeOH (2 x 10 mL) and then dried under reduced pressure to obtain the desired (1*R*,2*R*)-(+)-1,2-diammoniumcyclohexane-L-tartarate (**31**) as a white solid. This solid was crystallizes form boiling water (~1/10 w/v).

Yield	25.6 g (80%)	
$[\alpha]_D$	+ 14.5 (*c* 4, H_2O)	[lit.[30] + 12.5 (*c* 4, H_2O)]

B. Preparation of the Schiff base (28):

To a solution of (1*R*,2*R*)-(+)-1,2-diammoniumcyclohexane-L-tartarate (**31**) (2.65 g, 10 mmol) in water (20 mL) was added $NaHCO_3$ (1.68 g, 20 mmol) in portions. When the effervescence ceased, salicylaldehyde (2.1 mL, 20 mmol) dissolved in 10 mL DCM was added to the reaction mixture. The vigorous stirring was continued for 6 h (TLC). The DCM layer was separated and given a brine wash (1 x 10 mL). It was dried over anhydrous Na_2SO_4 and on evaporation of the organic solvent a yellow viscous liquid was obtained which was dissolved in hexane and cooled to -10 ^{0}C to obtain (*R*,*R*)-*N*,*N'*-bis(2'-hydroxylphenylmethene)-1,2-cyclohexanediimine (**28**) as a yellow solid.

	Yellow solid	
Yield	5.15 g (80% overall)	
m.p.	64-66 ^{0}C	[lit.[30] 64-66 ^{0}C]
$[\alpha]_D$	- 650 (*c* 1, MeOH)	[lit.[30] - 650 (*c* 1, MeOH)]

Preparation of (1*S*,2*S*)-*N*,*N'*bis(2'-hydroxylphenylmethene)-1,2-diphenylethylenedimine (29)

A. Preparation of (±)-stilbene diamine:

The preparation and the resolution of the (±) stilbeneamine was achieved according to Corey's method[21]. The diastereomerically pure salt (-)-**32** after third crystallization was directly used for SALEN preparation instead of the free amine.

B. Preparation of Schiff base (29):

Following a similar procedure as described for ligand (**28**), Tartarate salt (obtained after three crystallization as described above) (**32**) (4.5 g, 12.4 mmol) and salicylaldehyde (2.6 mL, 24.8 mmol) after 8 h afforded ligand (**29**) as a yellow solid which was recrystallized from ethanol.

	Yellow solid	
Yield	4 g (74% overall)	
m.p.	160-162 ^{0}C	[lit.[31] 157-159 ^{0}C]
$[\alpha]_D$	-8.8 (*c* 1, $CHCl_3$)	[lit.[31] - 17.1 (*c* 1, $CHCl_3$)]
IR ($CHCl_3$) (cm^{-1})	3421, 1629	
^{1}H NMR ($CDCl_3$)	δ 4.73 (s, 2H, C*H*Ph), 6.75-7.32 (m, 18H, H_{Ar}), 8.30 (s, 2H, C*H*), 13.31 (s, 2H, O*H*)	
^{13}CNMR ($CDCl_3$)	δ 80.2, 116.9, 118.6, 118.8, 127.6, 127.8, 128.4, 131.8, 132.6, 139.4, 160.9, 166.2	

General procedure for the preparation of titanium complexes

Method A:

To a solution of titanium tetraisopropoxide (5 mL of 1 M solution in toluene, 5 mmol) was added SALEN (2mL of 2.5 M solution in toluene, 5 mmol) under argon atmosphere. The resulting homogeneous solution was stirred at room temperature until the starting disappeared on TLC. The reaction mixture was diluted with 40 mL of toluene and treated dropwise with TMSCl (1.26 mL, 10 mmol). The reaction mixture was stirred for 4 h. In those cases (Ti-**28** & Ti-**29**) where the complex precipitated out, it was collected through filtration. But for the soluble complexes, the solvent was evaporated under reduced pressure and the solid was triturated with ether and filtered. The complexes were kept at 50^0 C for 2 h under high vacuum.

Method B:

To a solution of titanium tetraisopropoxide (1 mL of 1 M solution in toluene, 1 mmol) in EDC (8 mL) was added ligand (2 mL of 0.5 M solution in EDC, 1 mmol) under argon atmosphere. The resulting homogeneous solution was stirred for an hour and then most of the solvent was distilled out. The concentrated solution was treated dropwise with TMSCl (0.26 mL, 2 mmol) at room temperature. The reaction mixture turned red and

stirring was continued for 4 h. All the solvent was evaporated in vacuum and the solid material obtained was triturated with ether (in cases where the complexes were not soluble). The ethereal layer decanted off. The complexes were kept at 50 ^{0}C for 2 h under high vacuum.

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CHAPTER-3

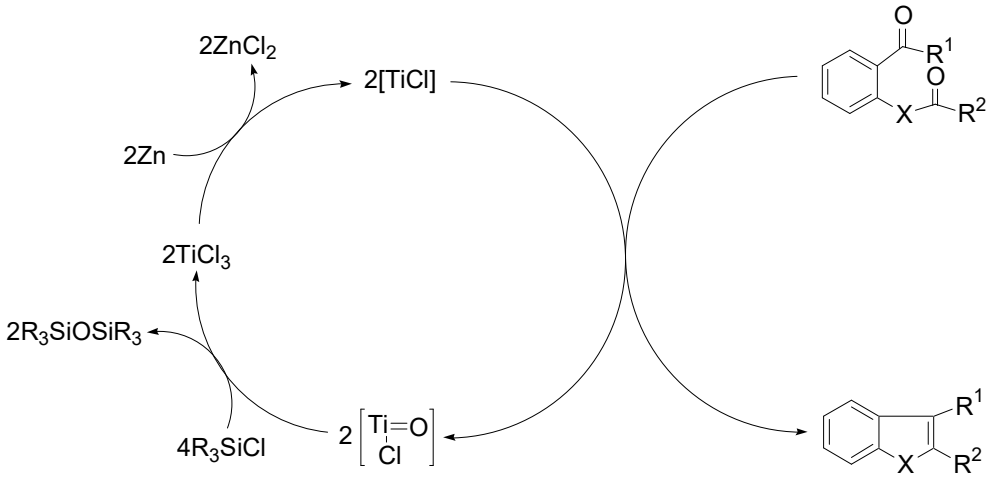
Application of Chiral Ti(III) Complexes for Pinacol Coupling and Related Reactions

Introduction:

The high reducing ability together with a pronounced oxophilicity of titanium culminated in an excellent efficacy to be used as a precursor for the coupling of carbonyl compounds. Although initially more attention was put for the coupling of carbonyl compounds to alkenes, commonly known as McMurry coupling, later it appeared to be an alternative path to obtain diols by maintaining a milder condition. In fact McMurry et al proposed the diol to be an "intermediate" during the alkene formation.[1] The volumous literature on titanium for promoting McMurry coupling slowly started attracting the organic chemists to tune the low valent titanium reagents for the generation of the diols. In the early nineties, a number of reports appeared where a high diastereoselectivity had been achieved. However these methods required stoichiometric amount of titanium.

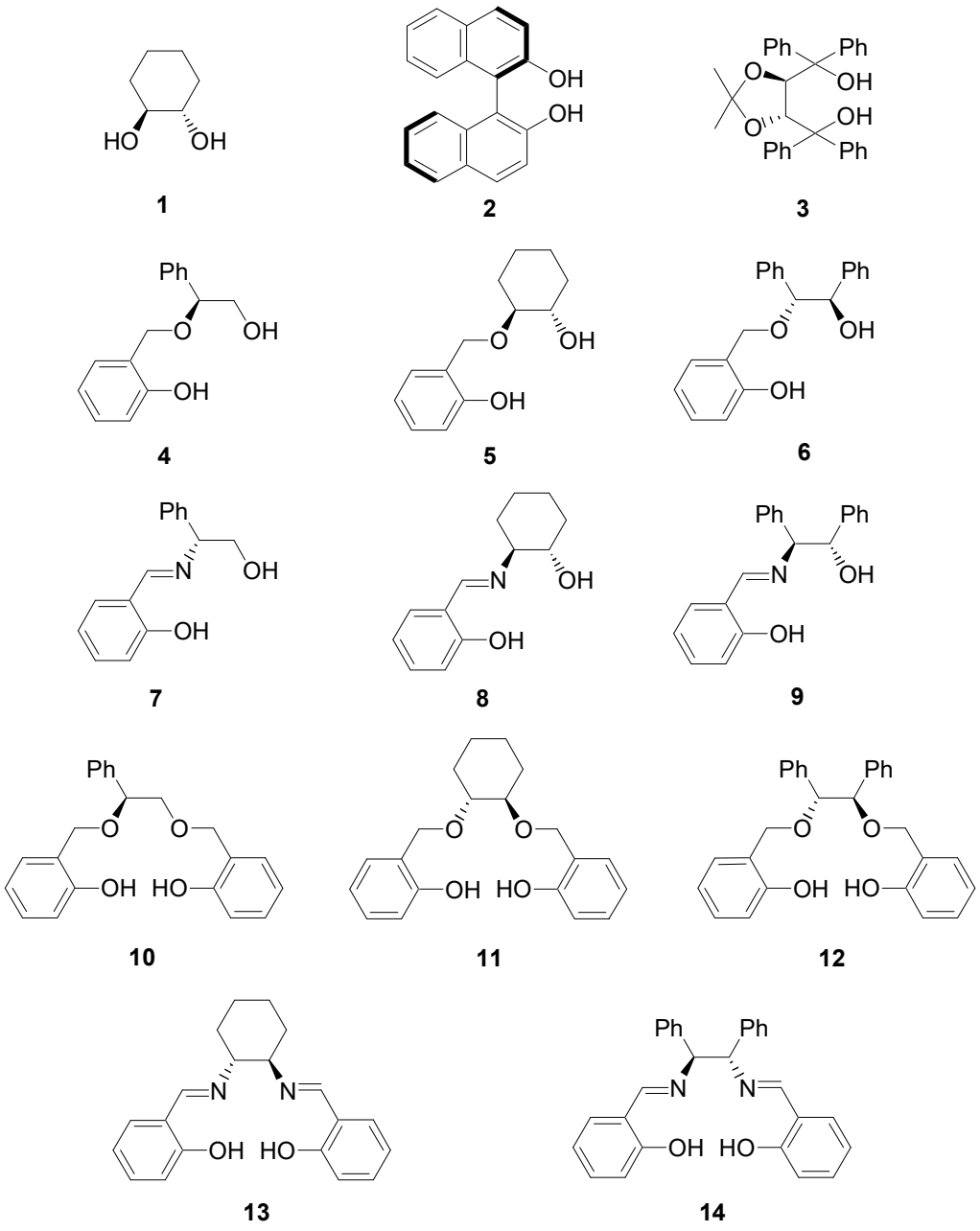
In 1995, Fürstner et al discovered a catalytic cycle of titanium using TMSCl as the additive for the reductive coupling of carbonyls to alkene.[2] TMSCl cleaved the titanium-oxygen bond in the intermediate regenerating titaniumchloride which immediately slipped into another "instant" coupling event as the former one. Thus a catalytic cycle continued generating disiloxane as the final oxygen trap (Fig 1).

Figure 1.



Applying Fürstner's protocol a variety of titanium complexes were designed and in many cases a good diastereoselectivity has been reported. However, a high enantioselectivity in pinacol coupling reaction remained a challenge. With a goal to develop a chiral catalyst for the enantioselective pinacol coupling reaction, we started examining systematically a series of chiral titanium complexes (Fig 2) starting from bidentate to tridentate to tetradentate one.

Figure 2.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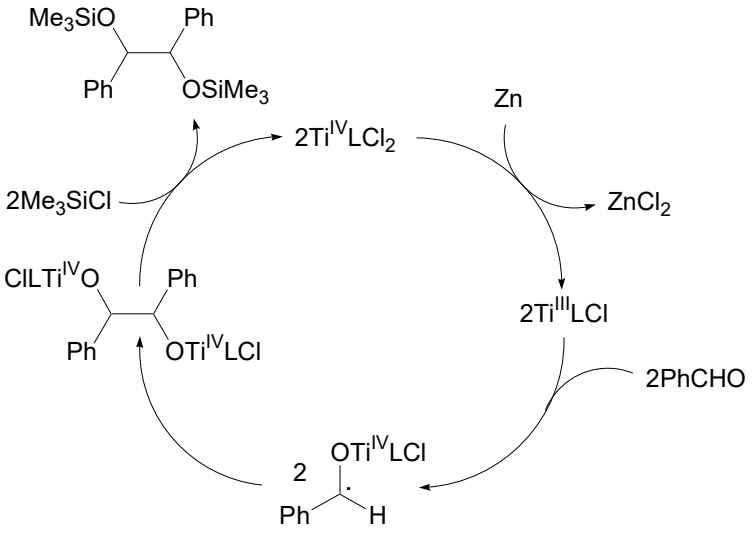
Results and discussion:

At the very outset, we chose zinc as the stoichiometric reductant and trimethylsilyl chloride as the catalyst regenerator. As for the model substrate, we were interested in a reactive aldehyde with a known rotation value of the pinacol. Benzaldehyde was found to be a good choice in this context. The catalyst was loaded in 10 mol% concentration and acetonitrile was used as a solvent at room temperature (Fig 3). Diastereomeric ratios were determined from ^{1}H NMR spectrum (the α-proton to the hydroxyl group in the *dl* isomer appears ca. 0.1-0.2 ppm up field than that of the *meso* isomer). The yields were reported for the column purified products. Ee's were determined by rotation and only for those reactions showing a de of more than 80%.

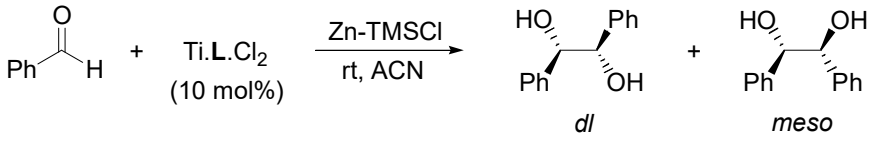
Figure 3.



The tetracoordinated catalysts were prepared in situ. Unlike the penta or hexacoordinated complexes, these complexes were light yellow in colour. On mixing these catalysts with Zn dust in degassed acetonitrile, no colouration could be observed. However a little darkening of the colour of the reaction medium was noticed after the addition of TMSCl. The yields were quite high in cases of Ti-**1** or Ti-**3** (Table 1). Ti-BINOL complex gave a moderate yield. But in all the cases the stereoselectivities were quite low. With an increase in the ligand bulk, a fall in the *dl* selectivity was observed (Table 1).

From these results, we wondered whether these complexes were stable in the presence of TMSCl. After performing a control reaction, we could not detect any silylated ligand. Hence the question of dissociation of the titanium complex was ruled out.

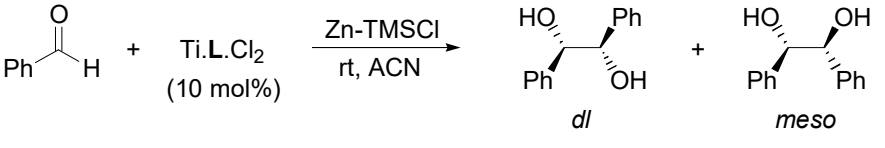
Table 1



Entry	Ti.**L**.Cl_2	Yield	*dl*:*meso*	ee
1.	Ti.**1**.Cl_2	83%	50:50	-
2.	Ti.**2**.Cl_2	52%	67:33	-
3.	Ti.**3**.Cl_2	79%	40:60	-

All the pentacoordinated titanium complexes were red in colour in degassed acetonitrile and turned green to blue after reduction by zinc. In these cases there was no observable colour change after the addition of TMSCl. In most cases the selectivity was poor and the *dl* selectivity even went lower with the less bulky ligands (Ti-**4** & Ti-**7**, Table 2). The electronic changes were found to have no effect on the yield as well as selectivity (Ti-**6** *vs* Ti-**9** and Ti-**4** *vs* Ti-**7**, Table 2). However a drastic change in the selectivity was noticed in case of Ti-**8**. The [O,N,O] donor with a cyclohexyl backbone proved to be better than the homologous [O,O,O] coordination.

Table 2.



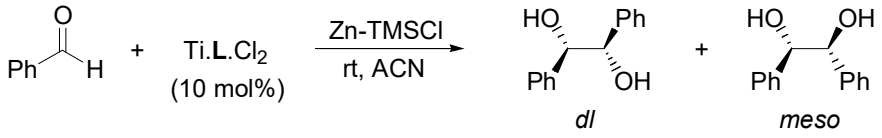
Entry	Ti.**L**.Cl_2	Yield	*dl*:*meso*	ee
1.	Ti.**4**.Cl_2	65%	44:56	-
2.	Ti.**5**.Cl_2	94%	52:48	-
3.	Ti.**6**.Cl_2	76%	60:40	-
4.	Ti.**7**.Cl_2	65%	46:54	-
5.	Ti.**8**.Cl_2	86%	91:9	0
6.	Ti.**9**.Cl_2	76%	50:50	-

The reason for this superiority is not clear to us, the hypothesis that can be made at this stage is that the less bulky nature of the ligand structure allows two such species to dimerize to form a dinuclear complex as described by Inanaga.[3] Thus two titanium complexes form a tightly bound dimeric structure resulting in better stereocontroll in the

final product. This kind of dimerization is inhibited in other complexes. Probably an increase in the Lewis acidity of the central metal atom on changing the coordination from nitrogen to oxygen encourages an aggregation of the active species (Ti-**5**). As a result, the dimerization is inhibited and the selectivity is reduced by uncatalyzed pathways. The backbone rigidity of the Schiff base should be considered in this regard.

Similar to the pentacoordinated complexes, hexacoordinated complexes are brick red in colour and unstable to air and moisture with exception of the Ti-SALEN complexes (Ti-**13** & Ti-**14**). The colour of the solution became bluish green to blue when the complexes were stirred with Zn dust in degassed acetonitrile. The SALEN mimics (Ti-**11**, Ti-**12**) although provided good to excellent yields, the stereoselectivity was poor in all the cases (Table 3). Ti-SALEN complex (Ti-**14**) containing two phenyl groups in the imine bridge was also equally poor in inducing selectivity. Gratifyingly, Ti-SALEN complex, derived from 1,2-cyclohexanediamine provided excellent results (Ti-**13**, Table 3**)**.

Table 3.

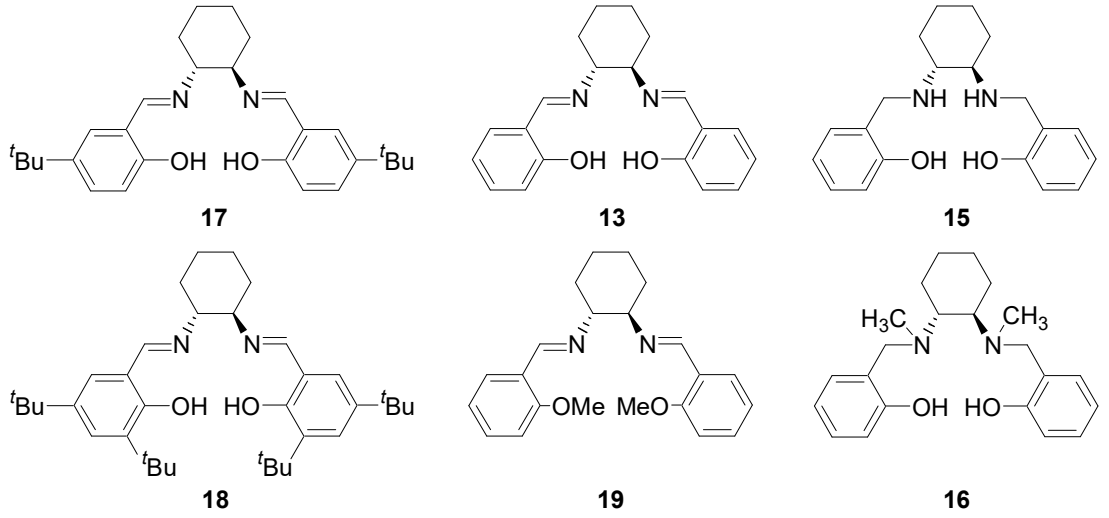


Entry	Ti.**L**.Cl_2	Yield	*dl*:*meso*	ee
1.	Ti.**10**.Cl_2	76%	50:50	-
2.	Ti.**11**.Cl_2	91%	53:47	-
3.	Ti.**12**.Cl_2	71%	50:50	-
4.	Ti.**13.**Cl_2	88%	95:5	68%
5.	Ti.**14**.Cl_2	62%	41:59	-

With these results in hand, we became curious to see the effect of tuning ligand architecture of SALEN-**13**. A variation of sterics at 3,3' or 5,5' position of the aromatic ring was examined (Ti-**17**, Ti-**18**). We also considered the change of basicity of the nitrogen atom by changing the imine to an amine (Ti-**16**). We wondered the need for an -OH group and hence eliminated them in one example (Ti-**19**). To examine all the all above parameters, ligands **15**-**19** were synthesized (Fig 4).

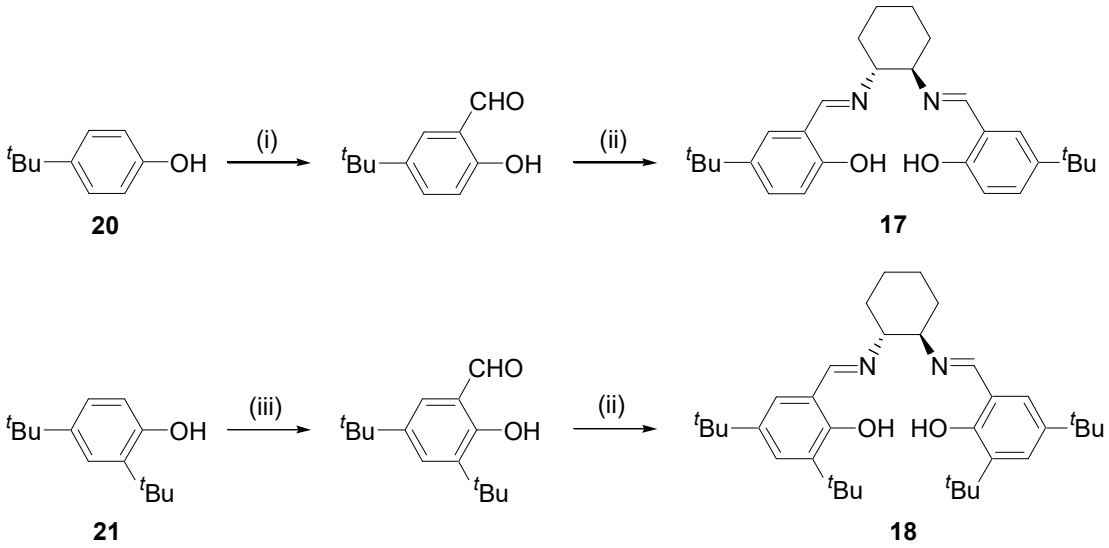
Ligand **15** was prepared by reducing the imine **13** with $NaBH_4$ in EtOH. The alkylation of the amine **15** was carried out using paraformaldehyde and $NaBH_4$ in presence of TFA.[4]

Figure 4.



The aldehyde part of the ligand **17** and **18** were prepared by formylation of the appropriate derivative. The formylation of 4-*tert* butyl phenol (**20**) was carried out using Mg and paraformaldehyde.[5] 2,4-di-*tert*-butylphenol (**21**) was formylated using HMT according to literature procedure[6] (Scheme 1). Ligand **19** was prepared by condensing cyclohexanediamine with *o*-anisaldehyde.

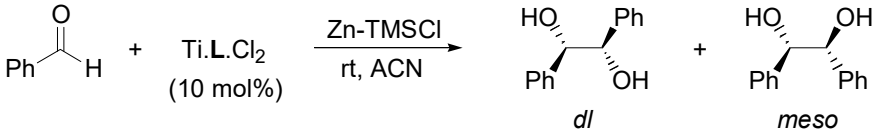
Scheme 1.



Reagents: (i) a) $Mg(OMe)_2/(HCHO)_n$, reflux, 2 h; b) H_3O^+; (ii) (*R*,*R*)-1,2-diammoniumcyclohexane mono-(+)-L-tartrate, K_2CO_3, EtOH-H_2O, reflux, 3 h; (iii) a) HMT, AcOH, reflux, 4 h; b) H_3O^+.

The titanium complexes of these ligands were prepared in a similar way as described for the parent SALEN **13**. Unfortunately, all the titanium complexes furnished poor selectivity. A decrease in the selectivity was also noticed with an increase in the bulk (Table 4). But this effect was much prominent when the crowding resided in the nitrogen atom instead of the aromatic ring (Ti-**16** *vs* Ti-**18**). Also the two -OH groups were found to be indispensable for a stable ligand (Table 4).

Table 4.



Entry	Ti.**L**.Cl_2	Yield	*dl*:*meso*	ee
1.	Ti.**16**.Cl_2	66%	50:50	n.d.
2.	Ti.**17**.Cl_2	79%	71:19	n.d
3.	Ti.**18**.Cl_2	40%	79:21	n.d
4.	Ti.**19**.Cl_2	76%	50:50	n.d

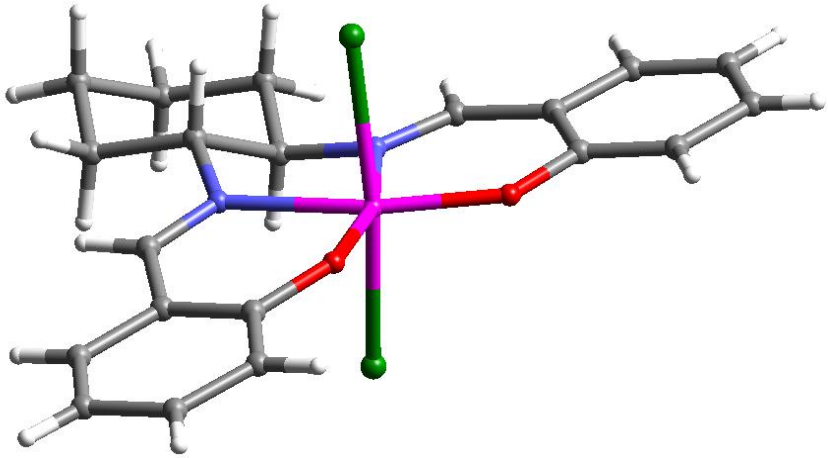
n.d = not determined

The conclusion that can be drawn from the above sets of experiments is that the parent ligand **13** is the best for the optimum selectivity and yield.

Characterization of Ti-13:

Literature search revealed that although Ti-**13** has been used for many reactions to obtain good selectivity, it has never been characterized fully.[7] Probably the poor solubility of the complex became a barrier to apply the analytical techniques. We for the first time characterized the complex through all probable techniques including NMR, microanalysis, X-ray etc. The single crystal diffraction X-ray crystallography showed that the two chlorine atoms takes the two apex of a regular octahedron. The nitrogen and the oxygen atom reside in the equatorial plane (Fig. 5).

Figure 5.

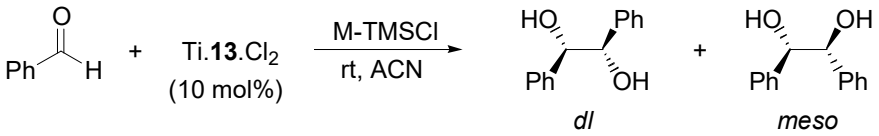


Optimization of the reaction parameters:

After optimizing the ligand framework and analyzing the ligand structure, our next goal was to standardize all the reaction parameters for a better enantioselectivity.

To begin with, we screened a variety of reducing metals as an alternative to the zinc dust. Fe, Al or Mg failed to reduce the Ti(IV) complex. Mn did work but provided poor yield. The colour of the reaction turned green instead of dark blue pointing towards an insufficient generation of Ti(III) species (Table 5).

Table 5.



Entry	Variant (M)	Yield[b]	*dl*:*meso*	ee[a]
1.	Zn	88%	95:5	68%
2.	Mn	28%	81:9	-
3.	Fe	n.r.	-	-
4.	Al	n.r	-	-
5.	Mg turning	n.r	-	-

a. ee's were determined only where dr >90%. *b*. Isolated and purified yield.
n.r. = no reaction

The next parameter examined was the solvent. We observed a sharp decrease in selectivity in ether solvents. No reaction was observed in DCM whereas in a very high polar solvent like DMF, the yield and selectivity were quite low. Next we turned our attention towards mixed solvents like ether/ACN or toluene/ACN (Table 6). Since none of these solvents were able to provide better result as compared to ACN, we decided to pursue further study using ACN.

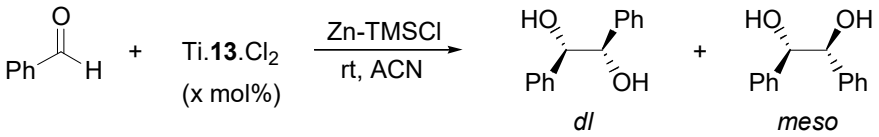
Table 6.

Entry	Variant (Solvent)	Yield[b]	*dl*:*meso*	ee[a]
1.	ACN	88%	95:5	68%
2.	THF	70%	58:42	-
3.	DME	89%	84:16	-
4.	DMF	30%	46:54	-
5.	Ether/ACN (2:1)	86%	82:18	-
6.	Toluene/ACN (5:3)	50%	82:18	-

a. ee's were determined only where dr >90%. *b*. Isolated and purified yield.

Catalyst loading was the next parameter to be standardized. We were interested to see whether it is possible to reduce the catalyst loading beyond 10 mol% or to get a better selectivity with a higher loading.

Table 7.



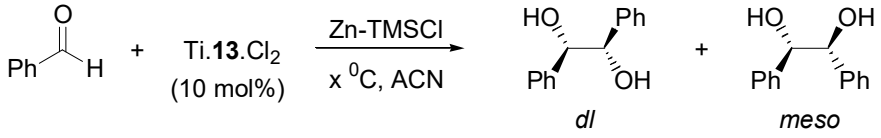
Entry	Variant (x mol%)	Yield[b]	*dl*:*meso*	ee[a]
1.	5	70%	82:18	-
2.	10	88%	95:5	68%
3.	20	82%	96:4	72%

a. ee's were determined only where dr >90%. *b*. Isolated and purified yield.

On increasing the loading to 20 mol% no better diastereoselectivity could be observed but the enantioselectivity increased by 4%. So it was clear to us that an increased catalyst loading had no beneficial effect. A decrease in loading to 5 mol% resulted in a sharp fall in the yield as well as selectivity of the reaction. Hence we decided to use 10 mol% of the catalyst (Table 7).

Decrease of the reaction temperature from 25 ^{0}C to 0 ^{0}C had favourable effect on enantioselectivity. Further lowering of temperature to -10 ^{0}C increased both the de and ee more than 95%. Interestingly, when the reaction was carried out at -40 ^{0}C, a decrease in ee was observed. This could be attributed to the inefficiency of the catalytic cycle at that temperature. As a result of which, uncatalyzed paths started operating causing a decrease in the overall ee (Table 8).

Table 8.



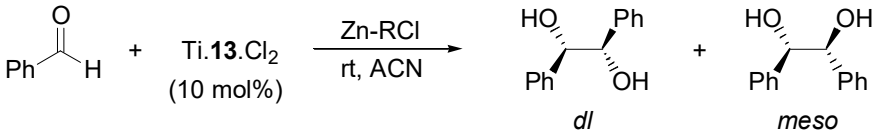
Entry	Variant (x ^{0}C)	Yield[a]	*dl*:*meso*	ee
1.	r.t.	88%	95:5	68%
2.	0 ^{0}C	90%	96:4	84%
3.	-10 ^{0}C	94%	98:2	95%
4.	-40 ^{0}C	92%	93:7	64%

a. Isolated and purified yield.

The effect of chlorosilanes in the pinacol coupling reaction is well known in literature. It is the slowest and hence rate determining step of the reaction.[8] The use of TMSCl is encouraged mainly due to two reasons. Firstly, this is the cheapest chlorosilane and generates hexamethyldisiloxane as the final oxygen trap. As both the compounds are volatile, the workup procedure becomes simple. Secondly, it is of lowest sterics among common silylating agents like ^{t}BuMe$_2$SiCl, Ph$_3$SiCl etc. It is to be borne in mind that an increased steric bulk of the chlorosilane hampers the oxygen transfer from titanium to silicon and hence the overall conversion. On the other hand a reactive chlorosilane such as Me$_2$SiCl$_2$ or SiCl$_4$ can lead to a better turnover number. However it is still difficult to predict the exact silylating agent that can afford the best selectivity and yield. We tried a

number of silylating agent from a very reactive to a bulky one. Surprisingly no better result could be obtained as compared to TMSCl (Table 9). As an alternate to silylating agent for the breaking of the Ti-oxygen bond, we tried acetic anhydride, acetylchloride, benzoyl chloride etc. None of them were able to recycle the catalyst. Use of amine hydrochlorides for the same purpose was our last try. For this purpose we prepared a variety of salts of different pKa values. It was disappointing that none of them were successful in our case and we finally chose TMSCl as the most suitable silylating agent (Table 9).

Table 9.



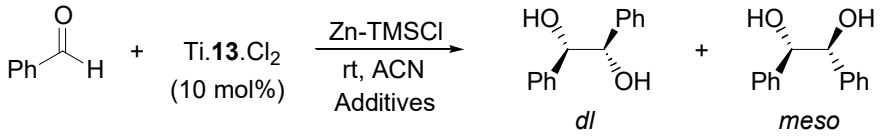
Entry	Variant (RCl)	Yield[b]	*dl*:*meso*	ee[a]
1.	TMSCl	88%	95:5	68%
2.	TBDMSCl	35%	81:9	-
3.	$SiCl_4$	58%	84:16	-
4.	Ac_2O	36%	71:29	-
5.	AcCl	n.r	-	-
6	$Q_3NH^+Cl^-$ Q = Py, collidine	n.r.	-	-

a. ee's were determined only where dr >90%. *b*. Isolated and purified yield.

After optimizing all the parameters, we decided to check the effect of additives in the stereochemical outcome. It was shown by Gansäuer et al that the addition of one equivalent of $MgBr_2$ resulted in a better selectivity for the pinacols.[8] The logic provided was the formation of a tighter trimeric species replacing $ZnCl_2$ from its center. When we added one equivalent of $MgBr_2$ in our system, we ended up with a racemic product with equal proportion of *dl* and *meso* isomer (Table 10). Although this result was not much exciting in true sense, it led us to think of a different reaction path unlike that of Gansäuer's protocol. Addition of highly chelating agent e.g. TMEDA completely arrested the reaction which could be visualized from a colour change of deep blue to green. A weakly coordinating agent such as dioxane didn't afford any observable change in the reaction.

Similarly, a strong Lewis acid such as $ZnBr_2$ changed the enantioselectivity to a negligible extent (Table 10).

Table 10.



Entry	Additives	Yield[a]	*dl*:*meso*	ee
1.	$MgBr_2$	70%	95:5	68%
2.	TMEDA	n.r.	-	-
3.	Dioxane	84%	93:7	95%
4.	$ZnBr_2$	88%	98:2	64%

n.r. = no reaction. *a.* Isolated and purified yield.

The optimization of parameters led us to choose ACN as a solvent, zinc dust as a coreductant, TMSCl as the catalyst generator, 10 mol% catalyst loading at -10 ^{0}C as the best condition to pursue pinacol coupling with our protocol. Applying these conditions, benzaldehyde was coupled in almost quantitative yield with de of 96% and ee 95%. A single crystallization afforded the optically active diol in a high yield. Thus a new methodology for the catalytic enantioselective pinacol coupling was established. It is to be mentioned here that it was the "first" protocol to provide enantiomerically pure hydrobenzoin through catalytic pinacol coupling reaction.

Our next goal was to examine the versatility of our catalyst. We investigated the coupling of a number of aromatic aldehydes with different substituent. We observed that most of them provided a very high diastereoselectivity. In fact the de was found to be insensitive to the nature of the functional group. Even for an aldehyde containing a hetero atom or ortho/para substituent, it remained high throughout. The ee was found to be much sensitive to the sterics as well as electronics. An electron donating substituent at the para position favoured a higher ee whereas an electron withdrawing one at the same position caused a noticeable decrease. In case of *p*-tolaldehyde the ee was 96% whereas it became 68% with *p*-fluorobenzaldehyde (entry 2 *vs* entry 6, Table 11). A similar decrease was noticed in case of ortho substituted or bulky aldehydes. To circumvent this problem a higher catalyst loading was used (entry 3 & 7, Table 11). When *o*-tolaldehyde was coupled

with 20 mol% catalyst loading, the selectivities again went high. A highly chelating group such as NMe_2 at the para position was not compatible with our catalyst. *p*-Nitrobenzaldehyde could not be coupled under this condition. Furfuraldehyde although afforded a high diastereoselectivity, the enantioselectivity was low (50%) (entry 9, Table 11).

Table 11.

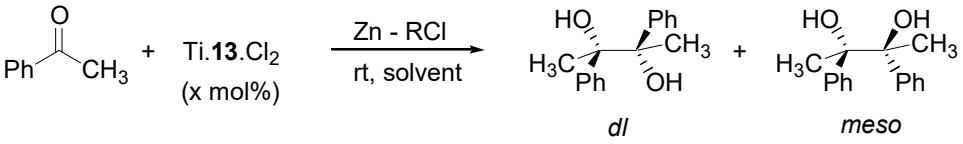
Entry	Ar	Time	Yield[a]	*dl*:*meso*[b]	ee[c]
1.	Ph	4h	94%	98:2	95%
2.	*p*-MePh	4h	84%	91:9	96%
3.	*o*-MePh	4h	75%	96:4[d]	82%
4.	*p*-MeOPh	3h	72%	100:0	78%
5.	*p*-ClPh	4h	79%	89:11	68%
6.	*p*-FPh	5h	65%	90:10	68%
7.	1-Naphthyl	5h	88%	91:9[d]	86%
8.	2-Naphthyl	4h	82%	94:6	91%
9.	Furfuryl	3h	86%	93:7	50%

a. Isolated and purified yield. *b.* Determined by ^{1}H NMR spectroscopy. *c*. Determined by rotation. *d*. 20 mol% catalyst was used.

After succeeding to establish a true catalytic cycle using a Ti-SALEN complex (Ti-**13**) and verifying its versatility, we tried to extend its applicability for related coupling reactions. Although the enantioselective coupling of aromatic aldehydes met with good success, aliphatic aldehydes and ketones are still difficult substrates. To date there is no report of catalytic, enantioselective pinacol coupling of aromatic ketones. Very recently, Yamamoto et al has achieved for the first time an enantioselective pinacol coupling of aliphatic aldehyde using a chromium based catalyst.[9] We tried to apply our protocol to an *α*,*β* unsaturated aldehyde (**22**). Noticing no product formation, we turned our attention toward the aromatic ketone. As a model substrate we chose acetophenone. Unfortunately, our protocol didn't prove suitable for this substrate. A change in the other parameters such

as a more reactive silylating agent like TMSBr or an increase in catalyst loading didn't lead to a better selectivity. Variation of the solvent polarity also failed to bring about any significant change and the racemic product with a poor to moderate yield was isolated (Table 12).

Table 12.

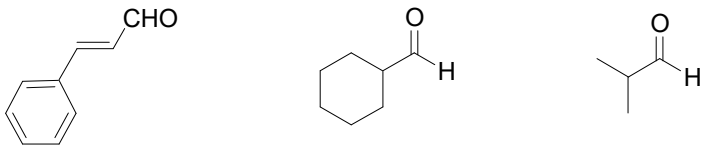


Entry	Cat loading	RCl	Solvent	Yield[b]	*dl*:*meso*[c]	ee[a]
1.	10 mol%	TMSCl	ACN	34%	72:28	-
2.	10 mol%	TMSBr	ACN	50%	55:45	-
3.	10 mol%	$SiCl_4$	ACN	41%	70:30	-
4.	10 mol%	TMSCl	Toluene	42%	83:17	-
5.	10 mol%	TMSCl	DME	63%	72:28	-
6.	20 mol%	TMSCl	ACN	46%	75:25	-

a. ee was not determined as the d.r was low. *b.* Isolated and purified yield. *c*. Determined by ^{1}H NMR spectroscopy (reference 10).

The results obtained in cases of aliphatic aldehydes were disappointing. When cyclohexanecarboxaldehyde (**23**) was subjected to coupling with our protocol, no product formation was observed. Acyclic aldehydes such as isobutyraldehyde (**24**) also didn't afford any coupled product. Finally we examined imine coupling.

Figure 6.

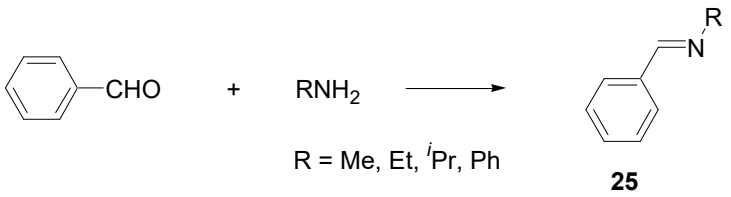


22 **23** **24**

The major problem associated with imine coupling is the inertness of the imine bond as compared to the carbonyl. Therefore a probable solution could be the use of an activating group. However, the formation of bibenzyl or amine is a serious problem.[11] To

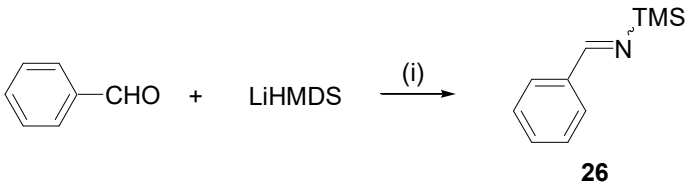
cope up with the above inconveniences, we prepared few protected imines through Schiff base formation and tried them for coupling. (Scheme 2)[12].

Scheme 2.



Realizing the harsh condition needed to remove the protecting group to obtain a free amine, we shifted our attention towards easily removable protecting groups. Amidst the very narrow choice, we decided to use TMS for this purpose. This amine derivative was prepared from benzaldehyde using LiHMDS[13] (Scheme 3).

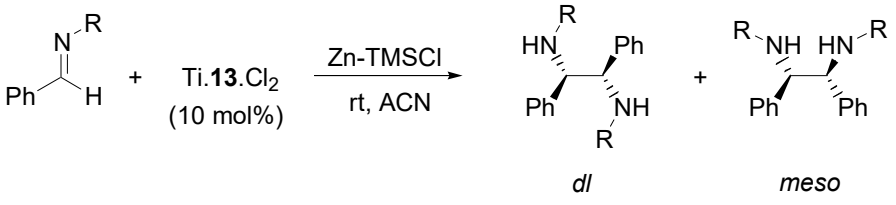
Scheme 3.



Reagents: (i) a) 0 ^{0}C, 30 min; b) TMSCl, rt, 30 min.

N-alkylated (**25**) and *N*-silylated (**26**) imines were found inert to our protocol. But *N*-phenyl imine was coupled in moderate yield and selectivity.

Table 13.



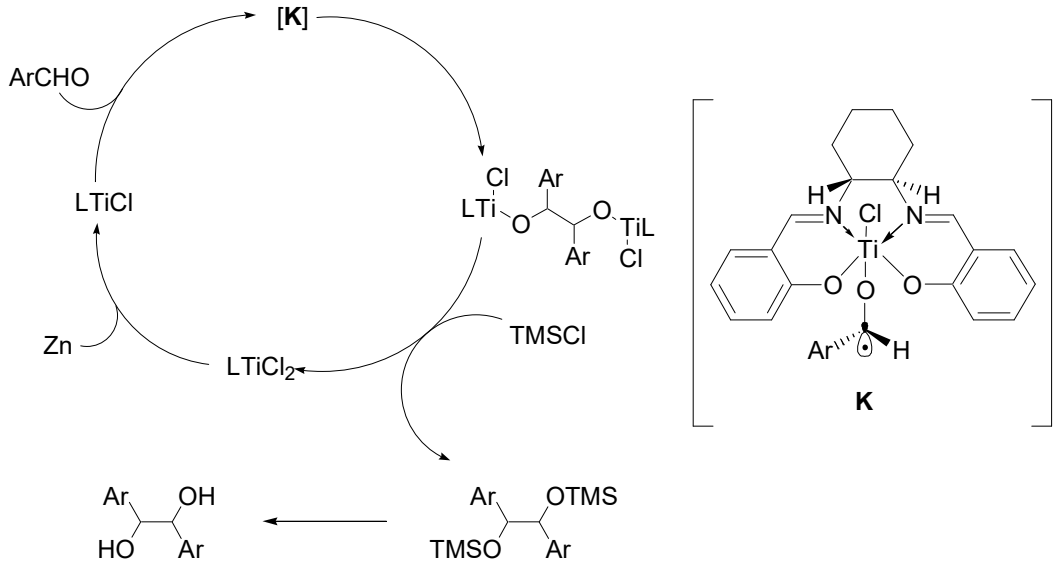
Entry	R	Yield[a]	*dl*:*meso*[b]	ee
1.	Alkyl (Me, Et, ^{i}Pr)	-	-	-
2.	TMS	-	-	-
3.	Ph	55%	37:63	-

a. Isolated and purified yield. *b*. Determined by ^{1}H NMR spectroscopy (ref 14).

Reaction mechanism:

With the experiments of the present study, it is not possible to derive the precise mechanism of the reaction. We nevertheless proposed a cooperative, intramolecular catalysis involving two metal centers to rationalize the observed selectivity of the final product. Considering a number of probable approaches, we predicted the dimerization of the aldehyde radicals generated by SET process as the most plausible path. Reduction of Ti(IV) complex with Zn generates a Ti(III) species with two oxygen, two nitrogen and a chlorine atom at the five corners of a twisted square pyramid (based on modeling studies). The aldehyde immediately forms a bond with the metal atom where a significant unpaired electron density resides at the carbon center generating a carbon radical. While coupling with another radical, the two aryl groups orient *trans* to each other favoring a *dl* stereochemistry in the product. The α-H atom of the C-N bond of the cyclohexane ring plays a key role in enantioselection as shown in figure 7. We believe that the steric interaction between aryl group of aldehyde and the α-H atom of ligand favour the transition state shown as **K** (simplified assembly), which then explains the stereochemical outcome of the reaction. This mechanism also explains our observation that increasing the steric bulk on the phenyl ring of SALEN provides poor selectivity.

Figure 7.



Conclusion:

1. Effect of various bidentate, tridentate and tetradentate ligands in the pinacol coupling reaction of aromatic aldehydes was studied systematically.
2. Hexacoordinated complexes containing [O,N,N,O] atoms are most stable as compared to other ligands.
3. We have developed a novel catalytic system for a true enantioselective pinacol coupling reaction of aromatic aldehydes using a readily accessible ligand.
4. We have also proved that the present catalyst structure is “optimum” and any change in sterics or electronics is detrimental to the stereochemical outcome of the reaction.
5. A plausible mechanism for the observed stereochemical outcome was also proposed. Although the model is based on chemical intuition, studies are under way to establish the true path of the reaction.
6. The present catalyst system appeared to be unsuitable for related reactions e.g. ketone coupling, imine coupling etc.

Experimental:

Preparation of (1*R*,2*R*)-*N*,*N'*-dimethyl-*N*,*N'*-bis(2-hydroxybenzyl)-1,2-cyclohexanediamine (16):

A. Preparation of (1*R*,2*R*)-*N*,*N'*-bis(2-hydroxybenzyl)-1,2-cyclohexanediamine (15):

To a solution of SALEN **13** (3.2 g, 10 mmol) in EtOH (20 mL) was added $NaBH_4$ (0.95 g, 25 mmol) in batches maintaining the temperature with a water bath. The yellow coloured solution immediately changed white. After the completion of the reaction (15 min, TLC) most of the solvent was removed in a rotary evaporator at room temperature and water (10 mL) was added to it carefully. The solution was acidified (pH~6) with 2 N HCl and washed with ether (1 x 10 mL) to remove any neutral impurity. The reaction mixture was then basified with $NaHCO_3$ and extracted with DCM (3 x 25 mL). The combined organic layer washed with brine (1 x 20 mL) and kept over anhydrous Na_2SO_4. The white solid obtained after evaporation of the solvent in vacuum, was recrystallized from MeOH to obtain pure **15.**

	White solid
Yield	2.54 g (78%)
m.p.	127-130 ^{0}C
$[\alpha]_D$	- 45.24 (*c* 1, MeOH)
IR ($CHCl_3$) (cm^{-1})	3313, 3292, 2935, 1589
^{1}H NMR ($CDCl_3$)	δ 1.03-1.35 (m, 4H, C*H*$_2$), 1.57-1.84 (m, 2H, C*H*$_2$), 2.05-2.25 (m, 2H, C*H*$_2$), 2.35-2.57 (m, 2H, C*H*$_2$), 3.85-4.11 (m, 4H, C*H*$_2$Ph), 5.63 (bs, 4H, N*H*, O*H*), 6.62-7.24 (m, 8H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 24.1, 30.3, 49.6, 59.7, 116.4, 119.2, 122.9, 128.2, 128.8, 157.9

B. Alkylation of 15:

A 100 mL two necked round bottom flask equipped with a stirring bar and an addition funnel was charged with paraformaldehyde (1.5 g, 50 mmol), $NaBH_4$ (1.14 g, 30 mmol) and **15** (1.63 g, 5 mmol) under argon atmosphere. Freshly distilled dry THF (30 mL) was introduced into the flask and the reaction mixture was kept at 0 ^{0}C. TFA (25 mL) was added dropwise over a period of 20 min. The reaction mixture was then warmed to room temperature. Stirring was continued for 24 h at that temperature. Most of the volatile materials were evaporated under reduced pressure on a rotary evaporator at room

temperature. Aqueous 2N HCl solution (10 mL) was added to the pasty mass. The neutral impurities were removed through an ether wash (1 x 20 mL). The acidic solution was neutralized with $NaHCO_3$ and the compound was extracted with DCM (3 x 20 mL). The combined organic layer washed with brine (1 x 20 mL) and kept over anhydrous Na_2SO_4. The white solid obtained after evaporation of DCM layer in vacuum, was recrystallized from MeOH to obtain pure **16.**

	White solid
Yield	1.5 g (84%)
m.p.	142-144 ^{0}C
$[\alpha]_D$	+ 33.33 (*c* 2.4, MeOH)
IR ($CHCl_3$) (cm^{-1})	3350, 3015, 2937, 1487
^{1}H NMR ($CDCl_3$)	δ 1.05-1.35 (m, 4H, C*H*$_2$), 1.75-1.87 (m, 2H, C*H*$_2$), 1.95-2.09 (m, 2H, C*H*$_2$), 2.23 (s, 6H, NC*H*$_3$), 2.66-2.76 (m, 2H, C*H*$_2$), 3.56-3.92 (m, 4H, C*H*$_2$Ph), 6.72-7.23 (m, 8H, H_{Ar}), 10.1 (bs, 2H, O*H*)
^{13}CNMR ($CDCl_3$)	δ 22.2, 25.2, 35.5, 56.8, 61.9, 116.4, 119.0, 122.3, 129.0, 129.1, 157.8
Analysis for	$C_{22}H_{30}N_2O_2$
Calculated (%)	C, 74.52; H, 8.55; N 7.90
Found (%)	C, 74.92; H, 8.60; N, 7.98

Preparattion of (1*R*,2*R*)-*N*,*N*'-bis(5-*tert*-butyl-salicylidene)-1,2-cyclohexanediamine (17):

A. Preparation of 2-hydroxy-5-*tert*-butylbenzaldehyde:

A 100 mL three necked round bottom flask equipped with a magnetic bar and a reflux condenser was charged with activated Mg turnings (1.44 g, 60 mmol) and few crystals of iodine. The reaction vessel was flushed thoroughly with argon and freshly distilled anhydrous MeOH (28 mL) was introduced into it. The mixture was heated to 50 ^{0}C to initiate the reaction. When the vigorous reaction subsided, it was further refluxed for one hour to form the white cake completely (no Mg turning left). After cooling the reaction mixture, phenol (15 g, 100 mmol) was added in one lot under a gentle stream of argon and half of the MeOH was distilled out slowly. When the reaction mixture became solid, some toluene was added to make it stirrable. Distillation was continued and toluene was added

in intervals (total 16 mL) to maintain the stirring. When the temperature rose to 95 ^{0}C, solid paraformaldehyde (9 g, 300 mmol) was added in portions (1 h). The reaction mixture was further refluxed for 2 h and then left for overnight stirring at room temperature. 10 % H_2SO_4 solution (90 mL) was added and the reaction mixture was kept at 50 ^{0}C for 2 h by which time two clean layers appeared. The organic layer was separated and the aqueous layer was washed with toluene (2 x 30 mL). The combined organic layer was washed with water (2 x 30 mL) and then with brine (1 x 20 mL). It was kept over anhydrous Na_2SO_4 and the solvent was removed at reduced pressure in a rotary evaporator. The aldehyde was obtained through a careful fractional distillation (106-108 ^{0}C at 4 mm of Hg). The G.C. showed the presence of 20 % phenol. This compound was used as such without further purification.

Yield	16.24 g (73%)

B. Schiff base formation:

The (1*R*,2*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt[6] (2.64 g, 10 mmol) was dissolved in 25 mL of water in presence of K_2CO_3 (3.5 g, 26 mmol). After the dissolution, 100 mL of EtOH was added to the reaction mixture and the homogeneous solution was heated to reflux. 2-Hydroxy-5-*tert*-butylbenzaldehyde (4.45 g, 25 mmol, considering the purity 80 %) was added slowly (in 20 mL EtOH) to the reaction mixture at that temperature. The homogeneous mixture was further refluxed for 3 h till the completion of the reaction (TLC). After cooling to room temperature, 25 mL of water was added to it. Some solid started appearing. It was further stirred for an hour and then kept at 0 ^{0}C for 2 h before filtration. The solid obtained after filtration was dissolved in DCM (100 mL). It was washed with water (2 x 25 mL), brine (1 x 25 mL) and then dried over anhydrous Na_2SO_4. The solid material obtained after evaporating the organic layer under reduced pressure was recrystallized from petroleum ether to give pure **17**.

	Yellow solid	
Yield	3.7 g (85%)	
m.p.	163-164 ^{0}C	[lit.[15] 116-118 ^{0}C]
$[\alpha]_D$	- 201.37 (*c* 1, CH_2Cl_2)	[lit.[15] - 179 (*c* 1, CH_2Cl_2)]
IR ($CHCl_3$) (cm^{-1})	3433, 3018, 1631	

^{1}H NMR ($CDCl_3$)	δ 1.23 (s, 18H, CH_3), 1.42-1.95 (m, 8H, CH_2), 3.29-3.33 (m, 2H, CH), 6.81-6.86 (m, 2H, H_{Ar}), 7.11-7.31 (m, 4H, H_{Ar}), 8.26 (s, 2H, CH) 13.15 (s, 2H, OH)
^{13}CNMR ($CDCl_3$)	δ 24.1, 31.3, 33.1, 33.8, 72.7, 116.1, 117.9, 127.8, 129.4, 141.1, 158.5, 164.9

Preparation of (1*R*,2*R*)-*N*,*N*'-bis(2-methoxy-salicylidene)-1,2-cyclohexanediamine (19):

The (1*R*,2*R*)-1,2-diammoniumcyclohexane mono-(+)-tartrate salt[6] (2.64 g, 10 mmol) was dissolved in 20 mL of water in presence of K_2CO_3 (2.9 g, 22 mmol). *o*-Anisaldehyde (2.4 mL, 20 mmol) dissolved in EtOH (5 mL) was added slowly to the homogeneous reaction mixture. Almost immediately some solid started appearing. 10 mL of DCM was added to it and the homogeneous reaction mixture was stirred till the completion of the reaction (6 h, TLC). The reaction mixture was diluted with DCM (10 mL) and the organic layer was separated. After the brine wash (1 x 10 mL) it was kept over anhydrous Na_2SO_4 and then concentrated in vacuum to obtain a white solid which was further purified through crystallization from petroleum ether.

	White solid	
Yield	2.78 g (79%)	
m.p.	104-106 ^{0}C	[lit.[16] 105-106 ^{0}C]
$[\alpha]_D$	- 67.6 (*c* 1, MeOH)	[lit.[16] - 69.2 (*c* 1, MeOH)]
IR ($CHCl_3$) (cm^{-1})	2931, 2853, 1637, 1487.	
^{1}H NMR ($CDCl_3$)	δ 1.38-1.58 (m, 2H, CH_2), 1.71-1.95 (m, 6H, CH_2), 3.35-3.49 (m, 2H, CH), 3.71 (s, 6H, OCH_3), 6.74-6.93 (m, 4H, H_{Ar}), 7.21-7.33 (m, 2H, H_{Ar}), 7.77-7.86 (m, 2H, H_{Ar}) 8.62 (s, 2H, CH)	
^{13}CNMR ($CDCl_3$)	δ 24.5, 33.0, 55.2, 73.9, 110.6, 120.3, 125.1, 127.3, 131.1, 157.2, 158.5	

[(1*R*,2*R*)-*N*,*N'*-bis-salicylidene-1,2-cyclohexanediaminato(2-)]titanium(IV)dichloride (Ti-13):

According to the general protocol as discussed in Chapter **2**, (method **A**) SALEN (**13**) (1.61g, 5 mmol), Ti(O^iPr)$_4$ (5mL, 1M in toluene, 5 mmol) and TMSCl (1.3 mL, 10 mmol) afforded Ti-**13** within 8 h at room temperature (The spectra has been paged up to make the compound peaks prominent).

	Brick red solid
Yield	2.2 g (quantitative)
m.p.	330-350 ^{0}C (decomposed)
$[\alpha]_D$	+ 514.3 (*c* 0.014, $CHCl_3$)
^{1}H NMR ($CDCl_3$)	δ 1.42-1.48 (m, 2H, C*H*$_2$), 1.61-1.67 (m, 2H, C*H*$_2$), 2.10-2.18 (m, 2H, C*H*$_2$), 2.58-2.61 (m, 2H, C*H*$_2$), 4.06-4.08 (m, 2H, C*H*$_2$), 6.9 (d, *J* = 8.2 Hz, 2H. H_{Ar}), 7.12-7.17 (m, 2H, H_{Ar}), 7.56-7.62 (m, 4H, H_{Ar}), 8.42 (s, 2H, C*H*)
^{13}CNMR ($CDCl_3$)	δ 24.1, 28.7, 67.7, 116.4, 122.7, 125.4, 135.0, 136.4, 159.6, 162.5
Analysis for	$C_{20}H_{20}N_2O_2Cl_2Ti$
Calculated (%)	C, 54.72; H 4.60; N, 6.38
Found (%)	C, 54.84; H, 4.61; N, 6.40

General Procedure for Pinacol Coupling:

A round bottom flask equipped with a magnetic stir-bar, was charged with catalyst Ti-**13** (0.18 g, 0.4 mmol) and Zn dust (0.52 g, 8 mmol). The system was thoroughly flushed with argon. Anhydrous and degassed acetonitrile (4 mL) was added and the resulting blue mixture was stirred for 0.5 hours at room temperature. It was then cooled to the desired temperature, aldehyde (4 mmol) was added in one lot followed by a dropwise addition of TMSCl (0.76 mL, 6 mmol) diluted with acetonitrile (1 mL). Stirring was continued till the time indicated in Table **11**, and the progress of the reaction was monitored through GC. The reaction was quenched with MeOH (0.1 mL), filtered and most of the solvent was evaporated under reduced pressure. The resulting residue was stirred for 10 minutes with TBAF (1 M in THF; 5 mL, 5mmol). The reaction mixture was diluted with EtOAc (20 mL), washed with brine (1 x 10 mL) and dried over anhydrous Na_2SO_4. The product was

isolated as usual and purified by flash chromatography on silica gel using petroleum ether/EtOAc as the eluent.

(*R,R*)-(+)-1,2-diphenylethane-1,2-diol:

According to the general protocol, benzaldehyde (0.42 mL, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol) and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-diphenylethane-1,2-diol within 4 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of 98:2.

	White solid	
Yield	0.4g (94%)	
m.p.	148-150 ^{0}C	[lit.[17] 148-150 ^{0}C]
$[\alpha]_D$	+ 89.4 (*c* 1, EtOH)	[lit.[17] - 94.5 (*c* 1, EtOH) for 100% ee)]

(*R,R*)-(+)-1,2-di(*p*-methylphenyl)ethane-1,2-diol:

According to the general protocol, *p*-methylbenzaldehyde (0.48 mL, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol) and TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*p*-methylphenyl)ethane-1,2-diol within 4 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of 91:9.

	White solid	
Yield	0.41g (84%)	
m.p.	105-107 ^{0}C	[lit.[17] 105-107 ^{0}C]
$[\alpha]_D$	+ 98.4 (*c* 1, EtOH)	[lit.[17] - 102.5 (*c* 1, EtOH) for 100% ee]
IR ($CHCl_3$) (cm^{-1})	3365, 1650, 1515	
^{1}H NMR ($CDCl_3$)	δ 2.29 (s, 6H, C*H*$_3$), 2.90 (bs, 2H, O*H*), 4.65 (s, 1.82H, C*H*Ph), 4.73 (s, 0.18H, C*H*Ph), 7.02 (bs, 8H, H_{Ar})	
^{13}CNMR ($CDCl_3$)	δ 21.1, 78.7, 126.9, 128.8, 137.0, 137.4	

(*R,R*)-(+)-1,2-di(*o*-methylphenyl)ethane-1,2-diol:

According to the general protocol, *o*-methylbenzaldehyde (0.46 mL, 4 mmol), Ti-**13** (0.36g, 0.8 mmol), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*o*-methylphenyl)ethane-1,2-diol within 4 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of 96:4.

	White solid
Yield	0.42 g (84%)
m.p.	108-110 ^{0}C [lit.[18] 109-110 ^{0}C]
$[\alpha]_D$	+ 53.3 (*c* 1, EtOH) [lit.[18] - 64.8 (*c* 0.83, EtOH) for 100% ee]
IR ($CHCl_3$) (cm^{-1})	3402, 1488
^{1}H NMR ($CDCl_3$)	δ 1.66 (s, 6H, C*H*$_3$), 3.30 (bs, 2H, O*H*), 4.98 (s, 1.92H, C*H*Ph), 5.20 (s, 0.08H, C*H*Ph), 6.88-6.92 (m, 2H, H_{Ar}), 7.07-7.23 (m, 4H, H_{Ar}), 7.57-7.61 (m, 2H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 18.7, 74.6, 125.9, 127.2, 127.7, 130.1, 135.9, 138.0

(*R,R*)-(+)-1,2-di(*p*-methoxylphenyl)ethane-1,2-diol:

According to the general protocol, *p*-methoxybenzaldehyde (0.48 mL, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-bis(paramethoxyphenyl)ethane-1,2-diol within 3 h at -10 ^{0}C. NMR shows only *dl* isomer.

	White solid
Yield	0.4 g (72%)
m.p.	132-134 ^{0}C [lit.[17] 132-134 ^{0}C]
$[\alpha]_D$	+ 92.3 (*c* 1, EtOH) [lit[17] - 118.3 (*c* 1, EtOH) for 100% ee]
IR ($CHCl_3$) (cm^{-1})	3380, 1612, 1514
^{1}H NMR ($CDCl_3$)	δ 2.94 (bs, 2H, O*H*), 3.76 (s, 6H, OC*H*$_3$), 4.63 (s, 2H, -C*H*Ph), 6.73-6.78 (m, 4H, H_{Ar}), 7.01-7.06 (m, 4H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 55.2, 78.7, 113.5, 128.1, 132.0, 159.1

(*R,R*)-(+)-1,2-di(*p*-chlorophenyl)ethane-1,2-diol:

According to the general protocol, *p*-chlorobenzaldehyde (0.56g, 4 mmol), Ti-**13** (0.18g, 0.4 mmol, 10 mol%), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*p*-chlorophenyl)ethane-1,2-diol within 4 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of 89:11.

	White solid	
Yield	0.45 g (79%)	
m.p.	130 ^{0}C	[lit.[19] 127 ^{0}C]
$[\alpha]_D$	+ 63.3 (*c* 1, EtOH).	
		[lit.[19] + 93 (*c* 1, EtOH) for 100% ee]
IR ($CHCl_3$) (cm^{-1})	3338, 1490	
^{1}H NMR ($CDCl_3$)	δ 2.51 (bs, 2H, O*H*), 4.61 (s, 1.78H, C*H*Ph), 4.83 (s, 0.22H, C*H*Ph), 6.98-7.12 (m, 4H, H_{Ar}), 7.18-7.28 (m, 4H, H_{Ar})	
^{13}CNMR ($CDCl_3$)	δ 78.5, 128.3, 133.8, 137.9	

(*R,R*)-(+)-1,2-di(*p*-fluorophenyl)ethane-1,2-diol:

According to the general protocol, *p*-fluorobenzaldehyde (0.43 mL, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(*p*-fluorophenyl)ethane-1,2-diol within 5 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of 90:10.

	White solid	
Yield	0.32 g (65%)	
m.p.	134-135 ^{0}C	[lit.[10] 108-110 ^{0}C]
$[\alpha]_D$	+ 36.0 (*c* 1, EtOH)	
		[lit.[20] + 53 (*c* 1.10, EtOH) for 100% ee]
IR ($CHCl_3$) (cm^{-1})	3315, 1514	
^{1}H NMR ($CDCl_3$)	δ 2.39 (bs, 2H, O*H*), 4.61 (s, 1.8H, C*H*Ph), 4.83 (s, 0.2H, C*H*Ph), 6.87-7.18 (m, 8H, H_{Ar})	
^{13}CNMR ($CDCl_3$)	δ 78.6, 114.7, 115.1, 128.5, 128.6, 135.3, 159.9, 164.8	

(*R,R*)-(+)-1,2-di(1'-naphthyl)ethane-1,2-diol:

According to the general protocol, 1-naphthaldehyde (0.54 mL, 4 mmol), Ti-**13** (0.36g, 0.8 mmol), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(1'-naphthyl)ethane-1,2-diol within 5 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of 91:9.

	White solid
Yield	0.47 g (75%)
m.p.	174-175 ^{0}C
$[\alpha]_D$	+ 58.5 (*c* 1, THF) [lit.[21] + 68 (*c* 0.86, THF) for 100% ee]
IR (nujol) (cm^{-1})	3339
^{1}H NMR ($CDCl_3$)	δ 2.60 (bs, 2H, O*H*), 5.73 (s, 1.82H, C*H*), 5.92 (s, 0.18H, C*H*), 7.21-7.83 (m, 14H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 74.5, 123.0, 124.9, 125.1, 125.3, 125.7, 128.6, 128.7, 131.0, 133.7, 136.1
Analysis for	$C_{22}H_{18}0_2$
Calculated (%)	C, 84.04; H, 5.78
Found (%)	C, 84.10; H, 5.76

(*R,R*)-(+)-1,2-di(2'-naphthyl)ethane-1,2-diol:

According to the general protocol, 2-naphthyldehyde (0.63g, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(2'-naphthyl)ethane-1,2-diol within 4 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of 94:6.

	White solid
Yield	0.51 g (82%)
m.p.	243 ^{0}C [lit.[21] 242-244 ^{0}C]
$[\alpha]_D$	+ 203.8 (*c* 1, THF) [lit.[21] + 224 (*c* 1, THF) for 100% ee]
IR (nujol) (cm^{-1})	3413
^{1}H NMR (DMSO)	δ 3.45 (bs, 2H, O*H*), 4.84 (s, 0.12H, C*H*), 4.90 (s, 1.88H, C*H*), 7.29-7.47 (m, 6H, H_{Ar}), 7.66-7.81 (m, 8H, H_{Ar})
^{13}CNMR (DMSO)	δ 75.6, 123.5, 123.8, 124.7, 125.4, 125.7, 130.3, 130.6, 138.2.

(*R,R*)-(+)-1,2-di(2'-furyl)ethane-1,2-diol:

According to the general protocol, *2*-furaldehyde (0.33 mL, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded 1,2-di(2'-furyl)ethane-1,2-diol within 3 h at -10 ^{0}C. NMR shows a *dl*:*meso* ratio of

93:7. The compound is a viscous liquid and deteriorates rapidly at ambient temperature. Therefore it was difficult to crystallize.

	Colourless liquid
Yield	0.33 g (86%)
$[\alpha]_D$	+ 15.5 (*c* 1, EtOH) [lit.[17] - 31.0 (*c* 1, EtOH) for 100% ee]
^{1}H NMR ($CDCl_3$)	δ 3.48 (bs, 2H, O*H*), 4.96 (s, 1.86H, C*H*), 4.99 (s, 0.14H, C*H*), 6.20-6.27 (m, 4H, H_{Ar}), 7.32-7.33 (m, 2H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 69.9, 107.8, 110.2, 142.2, 152.8

2,3-Diphenyl-butane-2,3-diol:

According to the general protocol, Acetophenone (0.47 mL, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol), TMSCl (0.76 mL, 6 mmol), followed by desilylation, afforded (±)-2,3-diphenyl-butane-2,3-diol within 8 h at room temperature. NMR shows a *dl*:*meso* ratio of 72:28.

	White solid
Yield	0.16 g (34%)
m.p.	118 ^{0}C [lit.[10] 120-123 ^{0}C]
IR ($CHCl_3$) (cm^{-1})	3442, 3018
^{1}H NMR ($CDCl_3$)	δ 1.49 (s, 4.32H, CH_3), 1.58 (s, 1.68H, CH_3), 2.36 (bs, 2H, O*H*), 7.13-7.31 (m, 10H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 24.8, 25.0, 78.6, 78.8, 126.8, 126.9, 127.0, 127.1, 127.2, 127.3, 143.4, 143.7

1,2-*N*,*N*'-Tetraphenyl-ethane-1,2-diamine:

The reaction was carried out in a similar way as described in the general procedure with the only difference that the desilylation was carried out using saturated NH_4Cl solution. Benzylidene-phenyl-amine (0.72 g, 4 mmol), Ti-**13** (0.18g, 0.4 mmol), Zn (0.52 g, 8 mmol), followed by desilylation, afforded (±)-1,2-*N*,*N*'-tetraphenyl-ethane-1,2-diamine within 3 h at room temperature. NMR shows a *dl*:*meso* ratio of 37:63.

	Yellowish solid
Yield	0.4 g (55%)

m.p.	139-141 ^{0}C
IR ($CHCl_3$) (cm^{-1})	3407
^{1}H NMR ($CDCl_3$)	δ 4.54 (s, 0.74H, C*H*), 4.96 (s, 1.26H, C*H*), 6.48-7.29 (m, 20H, H_{Ar})
^{13}CNMR ($CDCl_3$)	δ 62.1, 64.0, 113.8, 114.1, 117.8, 118.1, 127.4, 127.5, 128.2, 128.3, 129.1, 129.2, 138.3, 139.9, 146.5, 147.1

Crystal data of Ti-13:

Empirical formula	$C_{20}H_{20}C_{l2}N_2O_2Ti$
Formula weight	439.18
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system, space group	?, ?
Unit cell dimensions	a = 11.226(6) A alpha = 90 deg. b = 12.837(6) A beta = 90 deg. c = 13.783(7) A gamma = 90 deg.
Volume	1986.1(17) A^3
Z, Calculated density	4, 1.469 Mg/m^3
Absorption coefficient	0.718 mm^-1
F(000)	904
Crystal size	? x ? x ? mm
Theta range for data collection	2.17 to 25.00 deg.
Limiting indices	-13<=h<=13, -15<=k<=15, -16<=l<=16
Reflections collected / unique	23160 / 3491 [R(int) = 0.1646]
Completeness to theta = 25.00	99.6 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3491 / 0 / 245
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R1 = 0.0758, wR2 = 0.1602
R indices (all data)	R1 = 0.1060, wR2 = 0.1819
Absolute structure parameter	-0.02(7)
Extinction coefficient	0.0106(17)
Largest diff. peak and hole	1.031 and -0.765 e.A^-3

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