

**Enantioselective Hydroamination By Ti-  
based ligand and  
Synthesizing Challenging compounds by  
a Tripodal Scorpionate ligand.**

C500 Project Report

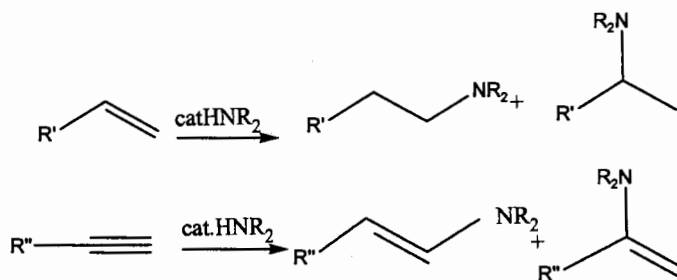
By

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## Background

The catalytic formation of carbon-nitrogen bonds is a rapidly developing field of interest due to the ubiquity of these bonds in natural products, pharmacological agents and fine chemicals. Direct amination of common feed stocks such as olefins and alkynes (Scheme 1) are the focus of attention of various groups.<sup>1</sup> A reaction used commercially for the generation of some amines (e.g. tert-butyl amine) is the hydroamination of an olefin. The reaction merges perfect atom economy with thermodynamic feasibility. However, the kinetic barrier for the reaction is too large and catalysts are necessary in order to facilitate it.

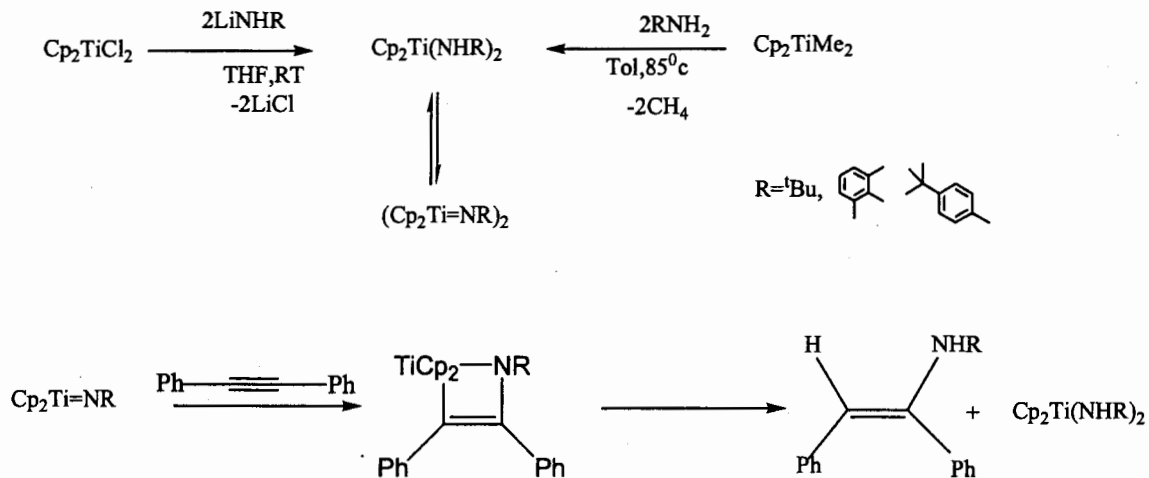
## Scheme1



Currently catalysts effective for the hydroamination of activated olefins and alkynes where some electron withdrawing group is attached have been developed. Metals of certain designs from across the periodic table may catalyze this type of reaction. Many transition metal complexes have been shown to be active hydroamination catalyst precursors. Among these are the class of bis(cyclopentadienyl)zirconium and titanium imido complexes. Alkyne hydroamination catalysts have been studied by Bergman<sup>2</sup>

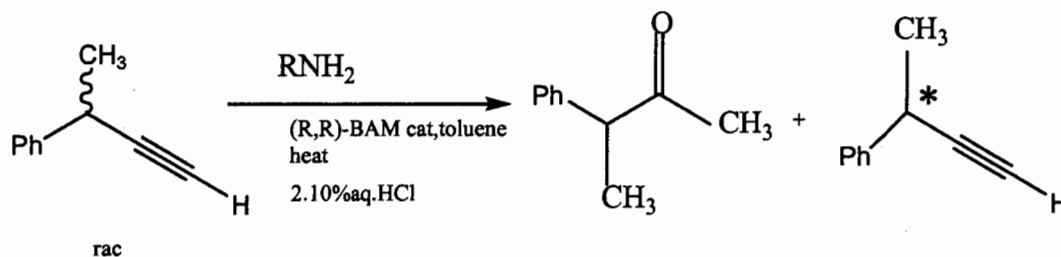
group and Doy's<sup>3</sup> group extensively. Titanium complex has been used extensively and it has several advantages over other metals. Titanium is the fourth most abundant element in the earth's crust and it is quite inexpensive relative to many other metals. In both of the latter titanium and zirconium systems it has been proposed that the critical intermediates are 16-electron imido complexes of the type  $\text{Cp}_2\text{M}=\text{NR}$ . In the presence of catalysts intermolecular and intramolecular hydroamination are possible. (scheme2)

### Scheme2



If the hydroamination is done in presence of an asymmetric catalyst, a racemic  $\alpha$ -substituted alkynes can be separated into its two enantiomers. The 3-phenyl-1-butyne can be prepared by Corey-Fuchus reaction according to literature procedures.<sup>4</sup>

For the synthesis of highly enantiomerically enriched chiral compounds we focused our attention on asymmetric hydroamination which can give kinetically resolved alkyne .i.e one part of the racemic mixture will be hydroaminated and the other part will be completely intact without taking part in the reaction.



### Ligand design for Kinetic Resolution and Hydroamination Reactions

The ligand bis amidine, BAM (BAM = N,N'-bis(phenanthrolin-2-yl)-1,2-cyclohexanediamine) (figure 1) is a potential asymmetric ligand for the purpose of hydroamination as it is asymmetric in its nature. (R,R)-BAM is a variety of the ligand where relative stereochemistry around the neighboring carbon centers of cyclohexyl ring in the ligand is (R,R). Our first goal was to prepare Ti-imido complexes with this type of ligand and to use these complexes as hydroamination catalysts. To reach this goal we have synthesized Ti-imido complex according to the known procedure by Mountford and co-workers.<sup>5</sup>

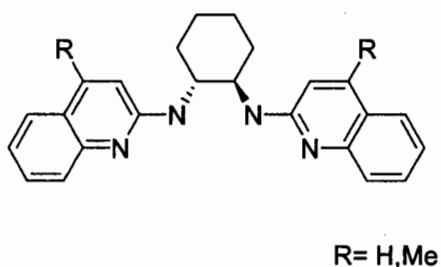
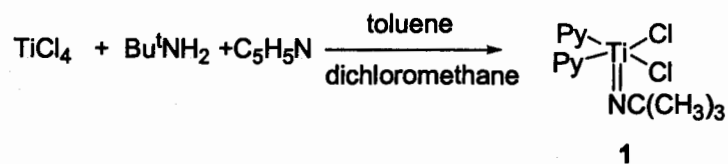


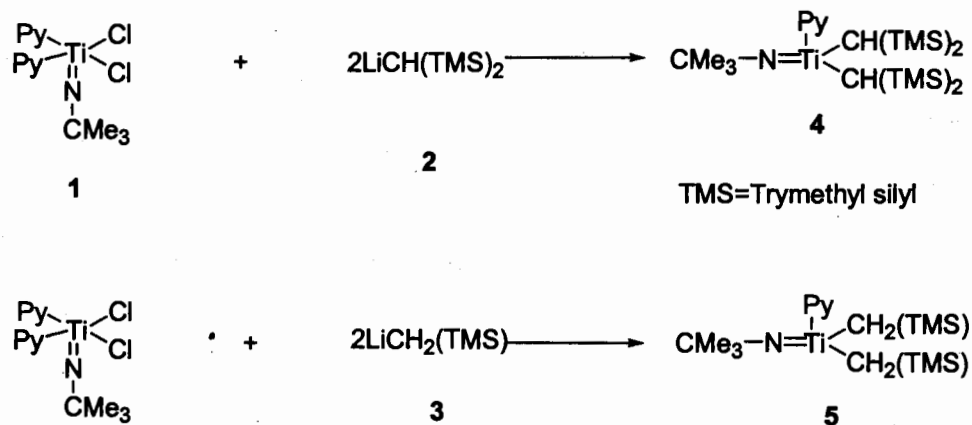
Fig 1 BAM ligand

Initial studies focused on the dianionic salt of the ligand BAM and incorporation with Ti-imido complex (1). The preparation reaction of the Ti-imido (1) compound is provided below.



Probably under the treatment of this strong base  $^n\text{BuLi}$  the ligand BAM cleaves and gives some undesired products. We then attempted the complex by replacing the chloro groups with some good leaving group such as an alkane (Scheme 3). Lithium salt of bis(TMS)methane (TMS = trimethyl silyl), **2** was treated with  $\text{RN}=\text{TiCl}_2\text{Py}_2$  ( $\text{R} = ^t\text{Bu}$ ) (**1**). In both reactions substitution of the chloro groups took place to afford imido alkyl complexes.

### Scheme 3



To determine the degree of aggregation we collected the X-ray data which has been shown below in fig 2.

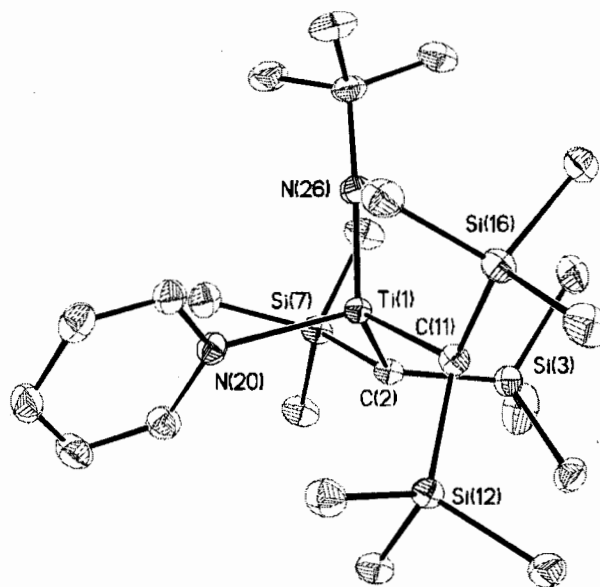


Fig2 Crystal structure of 2. Molecular structure of 2 with thermal ellipsoids at the 50% probability level. All H-atoms have been omitted for clarity.

This imido complex 4 was appearing very promising as the surrounding of the Ti center was hindered by the sterically demanding bulky groups which may play some prominent role in catalyzing some reaction. As the good leaving groups are incorporated, further reactions particularly the coordination with the ligand BAM is more feasible to attain.

Formation of the imido complex 5 by lithium salt of mono(TMS)methane 3 might be in the dimeric form which was not conclusively proved.

Reaction of the ligand BAM with compound 1 was monitored by NMR spectroscopy with certain interval of time. With the progressing time a big peak was appearing in the spectral region 0 ppm. At the same time the proton peaks attached with the  $\alpha$ -nitrogens were vanished which gave an indication of the formation of the complex. To detect the nature of the evolved gas, the gas produced in the reaction was transferred in a separate NMR tube in vacuum. That experiment proved conclusively that trimethyl-silyl-chloride was being evolved. Still the crystal

structure of the ligand coordinated Ti imido complex need to be determined before testing its catalytic activity in hydroamination.

To investigate the C-H activation by complex **4**, this complex was mixed in  $C_6D_6$  and the progress of reaction was by NMR spectroscopy. In that case no evident change was found during the course of the reaction. This solution was heated after that in different temperatures and the activation property was under probation. But in that case also no C-H activation was found out.

In addition to our target ligand BAM we tried to make the same Ti-imido complex with more cheap and commercially available Schiff base ligand, salen (salen=(S,S)Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexdiamine)structure of which has been shown in fig.3.<sup>6</sup> Already several groups reported versatile uses of salen complexes for several purposes. Asymmetric epoxidation<sup>7</sup>, asymmetric synthesis of acetylcyanohydrin<sup>8</sup>, pinacol coupling of aryl aldehydes, asymmetric oxidation of racemic 2-substituted 1,3-oxathianes, asymmetric trimethylcyanation of PhCHO are few among those. Our initial attempt was to form the Ti-complex with the readily available ligand and to use it as active hydroamination catalyst.  $TiCl_2$  complex has been synthesized from  $TiCl_4(THF)_2$  with salen in the presence of a mild base  $Et_3N$ . The final product was obtained by extraction from Soxhlet apparatus.

Synthesis of Ti- imido complex of the salen ligand is still under the process of investigation by treating with lithium salt of P-tolyaniline. Other method of reaching the same target molecule is to form the disodium salt of the ligand first by treating with NaH and to make complex with Ti-imido(**1**) (Scheme 4). There is no indubitable proof of forming the disodium salt of the salen ligand during treating with NaH but after that when it was treated with the Ti-imido complex (**1**),

instantaneous color change supports the belief that the complex is being formed. The structure of the final product is yet to be proved conclusively.

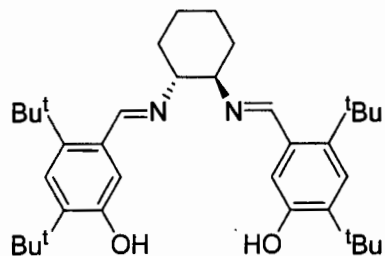
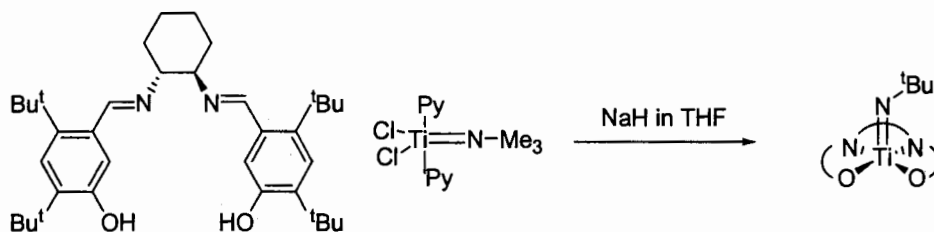
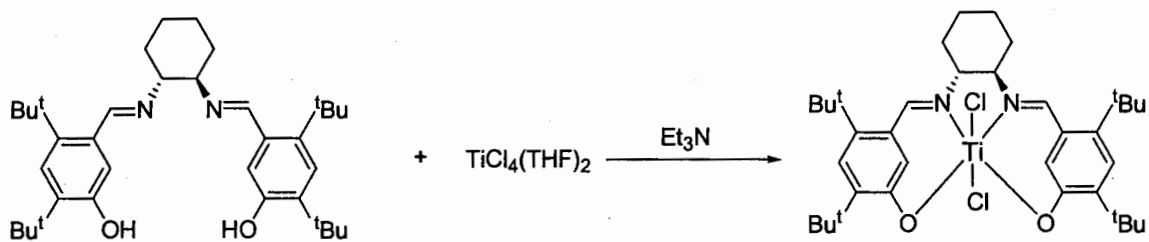


Fig3 Salen ligand

#### Scheme4





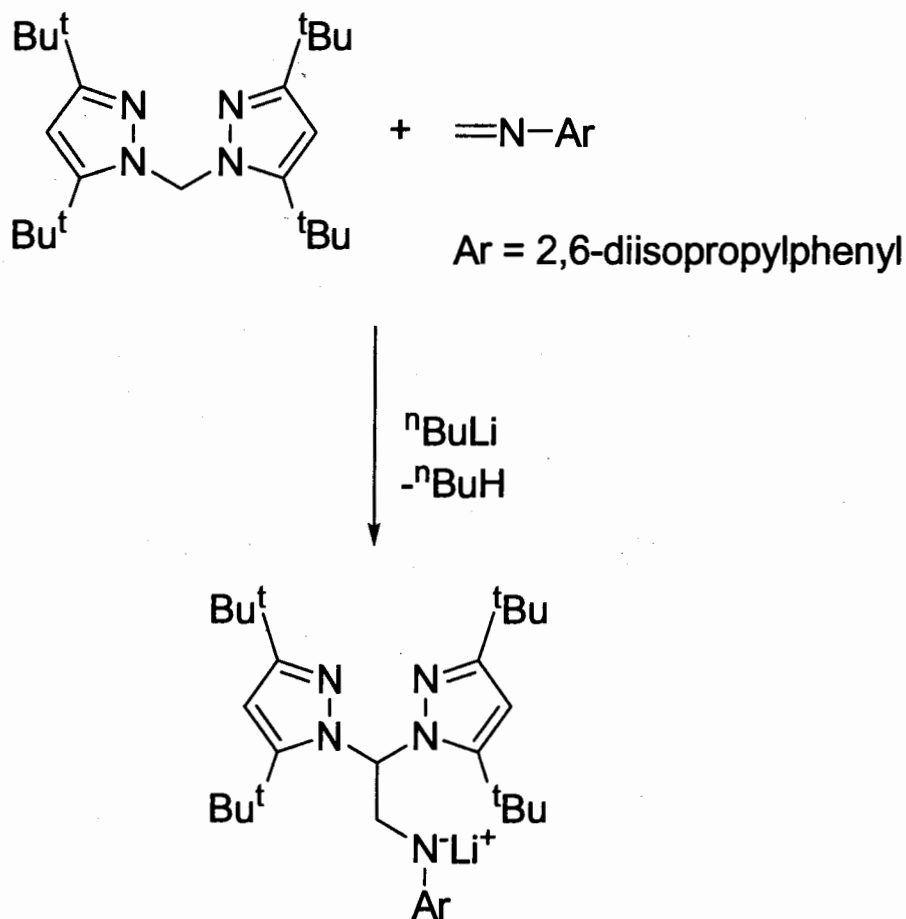
## Synthesis of Challenging complexes with Scorpionate ligand

### Background

There has been a continuous tendency in the field of macrocyclic chemistry to undertake the synthesis of new ring systems which exhibit ever-increasing structural diversity. Sometimes these contain some appended groups or side chains incorporating additional donor functional groups. Such compounds have been obtained both from structural modification of selected rings as well as via synthetic procedures designed to produce the required macrocycle directly from non-cyclic precursors. Many of the complexes exhibit the kinetic inertness which is typical to cyclic systems while still showing some of the coordination flexibility frequently associated with open chain ligands. First introduced in 1967<sup>9</sup>, poly (pyrazolyl)-borates are important ligands in coordination chemistry. This is not only because of the flexibility to functionalize the pyrazole ring by different R groups which can control the bulky nature of the ligand; at the same time pyrazole ring can be functionalized by one or two R groups to form asymmetric ligand. This is electron rich but robust after coordination with metals. Because of the three arms all are the same, this will deeply decrease the complexity of NMR spectroscopy. A representative synthesis of this ligand is given in the reference<sup>10</sup>. Another salient feature of this ligand is that pyrazole is a bio-active molecule in life science. Its coordination chemistry will help enormously to understand its bio-significance from its interaction with different metals. The improved design of these ligands has less steric hindrance and should be easier to coordinate with transition metals. The third arm of this ligand is different from the other two. This will increase complexity in NMR spectroscopy, but it will increase the

flexibility to design some interesting ligands with special features. First attempt was using the bis(3,5-di-<sup>t</sup>Bu-pyrazole)methane, upon deprotonation and reaction in situ with  $\text{H}_2\text{C}=\text{N}-\text{Ar}$  a three armed ligand scorpionate (scorpionate = N-(2,2-bis(3,5-di-tert-butyl-1H-pyrazol-1-yl)ethyl)-2,6-diisopropylbenzenamine) was prepared. (scheme5). For apparent similarity with the structure of scorpions these kinds of ligands are popularly called scorpionates.

### Scheme 5

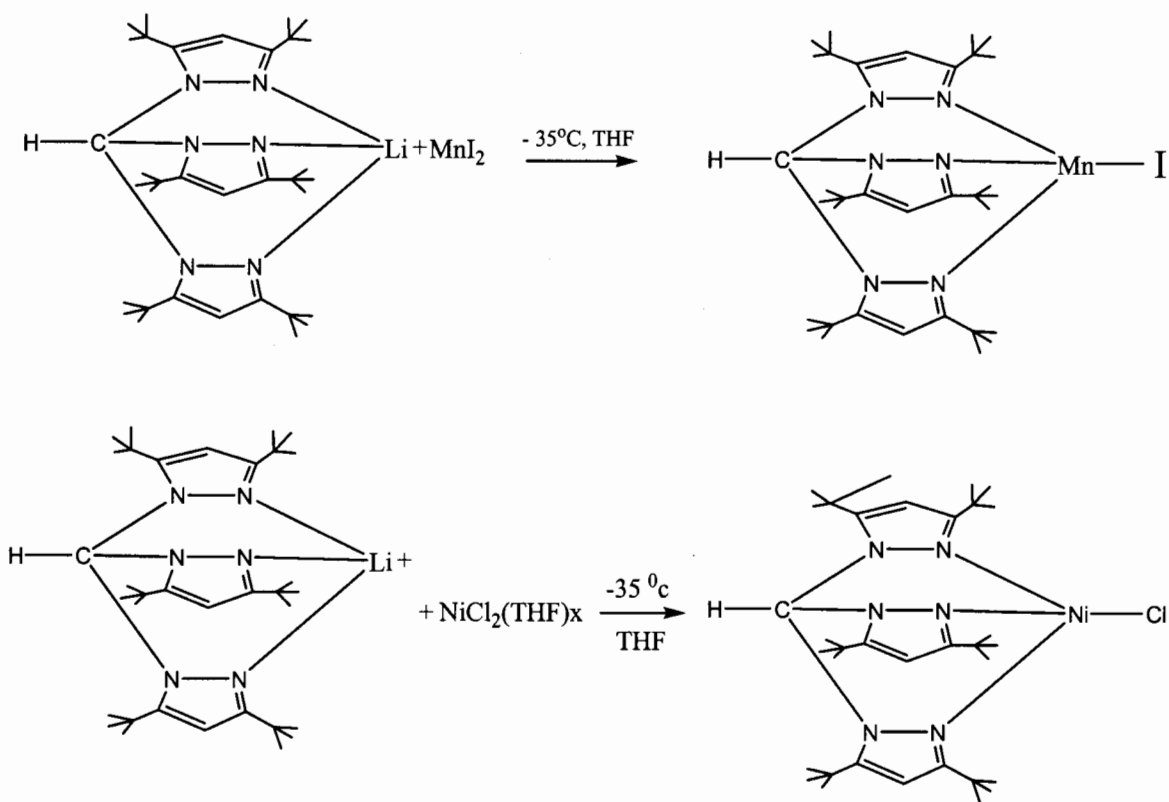


This tripodal ligand scorpionate (6) has a beautiful characteristic of giving low coordination complexes with the late transition metals. It is a good  $\pi$ -donor as well as

hard donor. So from that viewpoint of donicity this ligand is really a focus of attention and need to be studied. Our first attempt was to synthesize Ni complex of the tripodal scorpionate (**6**) ligand (Scheme 6). For that a soluble source of Ni(II) was needed and THF adduct of NiCl<sub>2</sub> was prepared by refluxing NiCl<sub>2</sub> in THF for one day. This Ni(II) source was sparingly soluble in THF and approximate formation was NiCl<sub>2</sub>(THF)<sub>1.5</sub>. This was reacted with scorpionate ligand which gave a paramagnetic complex evident from the broad signals in NMR. X-ray quality crystals were obtained from toluene and structure was determined crystallographically. Crystal structure has been shown in fig 4. The structure shows that it is a tricoordinated metal complex having excellent features of being functionalized. Our next goal is to synthesize oxo-compound of that complex. One problem that was encountered during this reaction was that the yield for the reaction was exceedingly small and the plausible reason was the proneness of the ligand for protonation. A major part of the ligand abstracted proton from the solvent THF and became incapable of forming the complex. To get rid of this problem the reaction was set in very inert solvent toluene but the NiCl<sub>2</sub>(THF)<sub>1.5</sub> was not stable in toluene and the color of the reaction mixture became black very soon. The optimization of the procedure to get a considerable yield is yet to explore and we have several plans to be implemented. Nextly Mn complex of the same ligand was synthesized and we were successful to come up with a tricoordinated complex of manganese. As a soluble source of Mn(II), MnI<sub>2</sub> was used which is mostly soluble in THF giving an orange solution. The structure of the compound was characterized by the paramagnetic NMR which is very possible for a d<sup>5</sup> system in the tetrahedral environment. X-ray quality crystals were obtained from toluene and the structure of the complex was determined by X-ray crystallography which has

been shown in fig 5. This Mn-I bond is pretty long ( $2.646 \text{ \AA}$ ) and hence believed to be labile which is really promising in light of developing new functionality. But the same kind of problem of the ligand protonation was still there and different methods are being used to overcome the problem. One potentially very efficient technique is to transmetallate with TI complex which is still under the process of investigation.

### Scheme 6



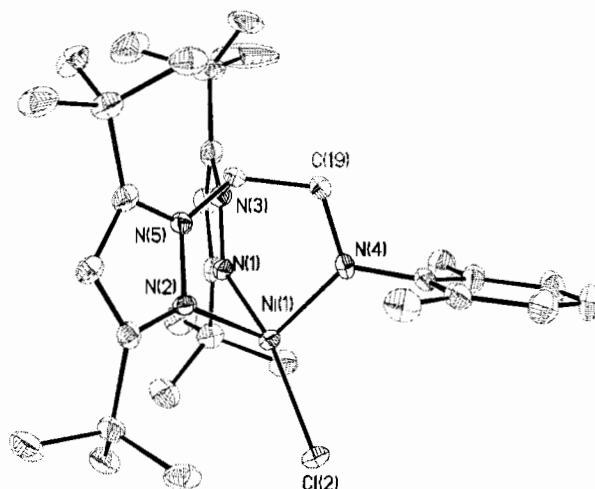


Fig 4 Crystal structure of NiCl(scorpionate)complex . Crystal structure of 2.Molecular structure of 2 with thermal ellipsoids at the 50% probability level. All H-atoms and isopropyl methyl groups have been omitted for clarity.

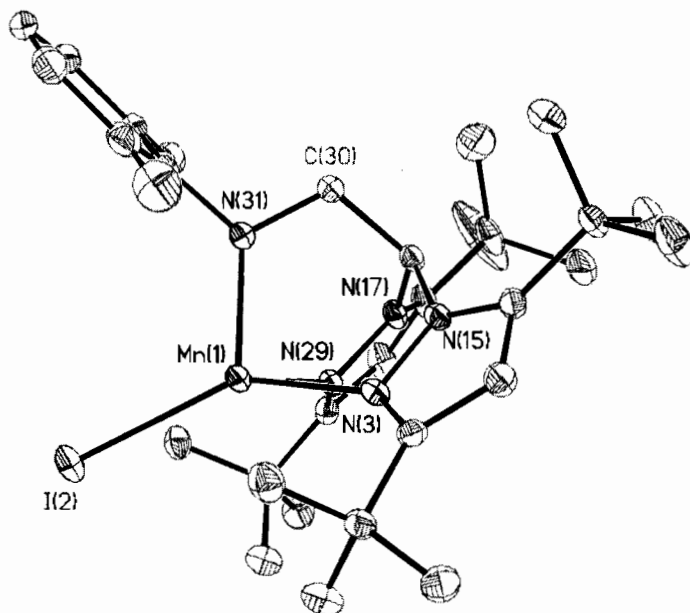


Fig 5 Crystal structure of MnI(scorpionate) complex. Crystal structure of 2. Molecular structure of 2 with thermal ellipsoids at the 50% probability level. All H-atoms and isopropyl methyl groups have been omitted for clarity.

### **Future Work**

1. For hydroamination catalysts both BAM and salen ligand would be used. Several methods are yet to be employed to prepare the complexes and to use those as active hydroamination and kinetic resolution catalysts.
2. In biological enzymes often intermediacy of the Ni-oxo species are believed but they are not yet conclusively proved. Our future goal is to use our tricoordinated NiCl (scorpionate) complex to make the desired oxo complex of nickel. Once we know the reduction potential of the complex, this Ni(II) complex will be reduced to Ni(I) complex and then will be treated by dioxygen. Direct use of some peroxide reagent also can be employed to synthesize the desired compound. Similarly from the same biological viewpoint terminal Mn-oxo complexes are drawing attention and same strategies will be employed for the MnI(scorpionate) complex also.

### **Experimental Procedures**

#### **General Considerations:**

All reactions were done under a N<sub>2</sub> atmosphere in a M. Braun Lab Master glove box, or using standard Schlenk techniques. Solvents were dried by passage through alumina columns, except THF which is kept in a still and dried under sodium metal. Sodium benzophenone ketyl was used to ensure dryness. Deuterated solvents are purchased from Cambridge Isotope Laboratory, degassed, dried over molecular sieves and with CaH<sub>2</sub>. <sup>1</sup>H

and  $^{13}\text{C}$ , spectra were done on Varian 400 or 300 MHz NMR spectrometers. X-ray diffraction data sets were collected on a SAMRT6000 (Bruker) systems under a stream of  $\text{N}_2$  at low temperatures.

### Synthesis of 1-H-3,5-di-*tert*-butylpyrazole

To a solution of 5 mL (24 mmol) of 2,2,6,6-tetramethyl-3,5-heptanedione (dipivaloylmethane) dissolved in ethanol (30 mL) were added 2 mL (40 mmol) of hydrazine hydrate and three drops of concentrated hydrochloric acid (35%,  $d=1.18$  g/ml). The reaction mixture was heated to reflux for 10 h. After evaporation of the solvent, the residue was dissolved into dichloromethane. The solution was washed with water, dried over  $\text{Na}_2\text{SO}_4$  and solvent was evaporated to yield 4.21 g (97%) product.

Melting point: 195°C.

### Synthesis of Bis(3,5-di-*tert*-butylpyrazol-1-yl)methane (dtbpzm): 5-di-*tert*-

butylpyrazole (3.00 g, 16.64 mmol), KOH (3.60 g, 64.16 mmol),  $\text{K}_2\text{CO}_3$  (9.00 g, 65.12 mmol) and benzyltriethylammonium chloride (0.5 g) were dissolved in dichloromethane (100 mL) and heated under reflux for 5 hours. Salts were removed by filtration and the filtrate was concentrated in vacuum to dryness. The white residue was dissolved in water and extracted with pentane (2 x 150 mL). The organic layer was dried with  $\text{MgSO}_4$  and the solvent removed in vacuum. The white residue was recrystallized from pentane to yield dtbpzm as a white powder (2.40 g, 77%). m.p. 132 °C,  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 250 MHz):  $\delta$  1.21 (s, 18 H,  $\text{CH}_3$ ), 1.25 (s, 18 H,  $\text{CH}_3$ ), 5.90 (s, 2 H,  $\text{CH}_2$ ), 6.52 (s, 2 H,  $\text{H}_{\text{pz}}$ ).

**Deprotonation of dtbpzm:** 1 equivalent of dtbpzm in  $-78\text{ }^{\circ}\text{C}$  was added Butyl lithium (1 equivalent), 30 minutes later, 1 equivalent of  $\text{CH}_2=\text{N-Ar}$  was added, keep this temperature for 10 minutes, then reaction was allowed to warmed up to  $0\text{ }^{\circ}\text{C}$  for another 1 hour. Solvent was removed and product was washed with hexanes to yield a light yellow solid.

### Acknowledgements

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