ASYMMETRIC DEPROTONATION OF ORGANO-MOLYBDENUMAND ORGANO-IRON COMPLEXES

Gunjan Bansal

Research Scholar, Calorx Teachers' University, Ahmedabad, Gujarat

INTRODUCTION:

Optically active carbonyl compounds present an important group of intermediates for asymmetric synthesis. The most commonly used methods for chiral carbonyl compound synthesis involve the use of chiral auxiliaries. Chiral oxazolidinones, oxazolines and hydrazonesare the most studied and useful chiral auxiliaries developed so far.Though these methodologies provide excellent solutions to the problem, they require multistep reaction sequences for preparation and recovery of the chiral auxiliaries. Another approach to prepare optically active carbonyl compounds is the use of chiral lithium amide bases. Hindered secondary amide bases e.g., LDA, KHMDS etc., have been widely used for kinetically controlled deprotonations. Chiral Li-amides distinguish between two enantiotopic a-protons of pro-chiral cyclic ketones in a kinetically controlled deprotonation step generating chiral enolates which, on reaction with an electrophile, yield the product in optically activeform.

Chiral Li-amide bases have been used for various enantio selective transformations.These reactions can be classified into four broad categories:

1) Enantio selective rearrangements of pro-chiral epoxides
2) enantio selective deprotonations of pro-chiral ketones
3) enantio selective dehydrohalogenations
4) enantio selective [2,3] - Wittig rearrangements.

These bases have also been used for kinetic resolution of racemic epoxides and ketones but these are omitted from this discussion.

Chiral lithium amides give better region selectivity than LDA in deprotonation of optically active 3-ketosteroids.Other uses are: (a) as non-covalently bound chiral auxiliaries in enolate reactions and in the additions of alkyl lithiums to aldehydes; (b) asymmetric deprotonations of carboxylic acids; (c) enantioselective reduction of non-enolizableprochiral ketones and (d) diastereoselective Michael additions to acrylates.

1.1.ENANTIOSELECTIVE REARRANGEMENTS OF PRO-CHIRAL EPDXIDES:

Rearrangement of an epoxide to allylic alcohol with a lithium amide involves removal of a proton *syn*to the oxgen atom. This reaction is thought to proceed *via* a six-membered ring

transition state (Figure 1). Use of chiral lithium amides in the rearrangements of pro-chiral epoxides generate optically active allylic alcohols.

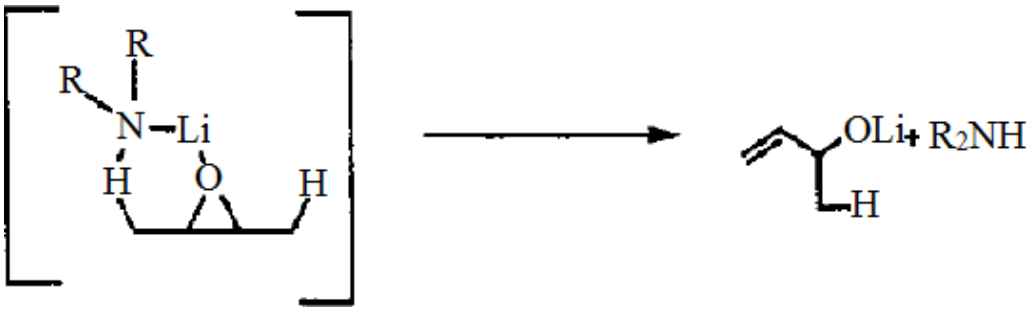
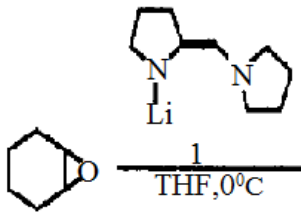
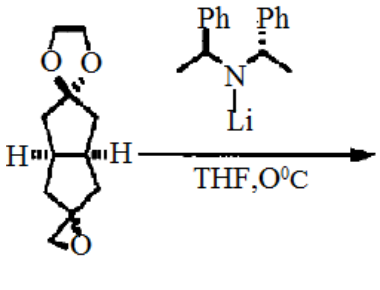
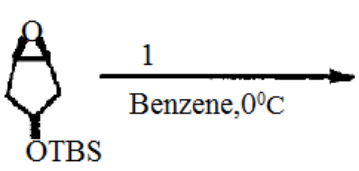
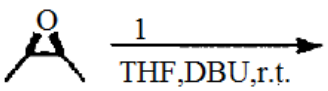
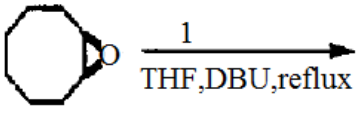


Figure 1.1

The most extensively studied system is the rearrangement of cyclohexene oxide to cyclohexenol. In general, these reactions are very slow at low temperature and are carried out at 0 ^{0}C. Interestingly, carrying out the reaction in refluxing THF also generates optically active product (e.e. = 31%). Use of lithium amide bases with internal chelating ligands and additive (DBU) is very successful. Some epoxides studied and the corresponding results are summarized in Scheme 1.1

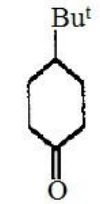
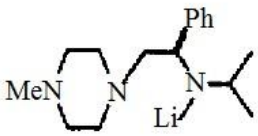
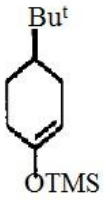
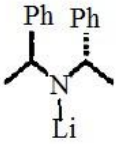
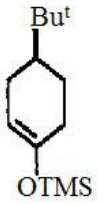
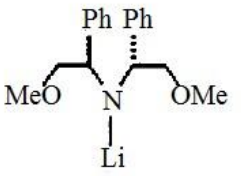
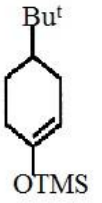
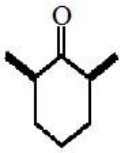
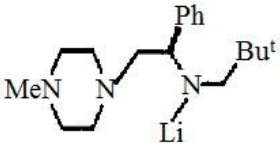
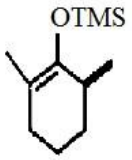
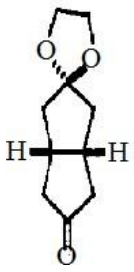
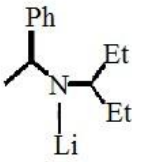
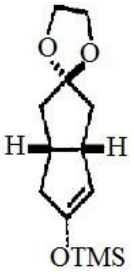
SCHEME-1.1:

Reaction	Yield	e.e.	Ref.
	78%	92%	13,14
	50%	76%	15
	73%	76%	16
	60%	72%	17
	84%	50%	17

ENANTIOSELECT1VE DEPROTONATION OFPRO-CHIRALKETONES:

A major use of chiral Li-amide bases involves reactions in which a cyclic, conformationally locked pro-chiral ketone is directly converted to an optically active product by selective removal of one of the two a- protons. The products were found to have higher optical purity when an *in situ* quench technique with TMS-Cl was used as compared to quenching a pre-formed enolate. Enantiomeric excesses were highly dependent on solvent and reaction temperatures. Most reactions were carried out in THF at -75 ^{0}C to -100 ^{0}C. Some examples are presented in Table 1.1.

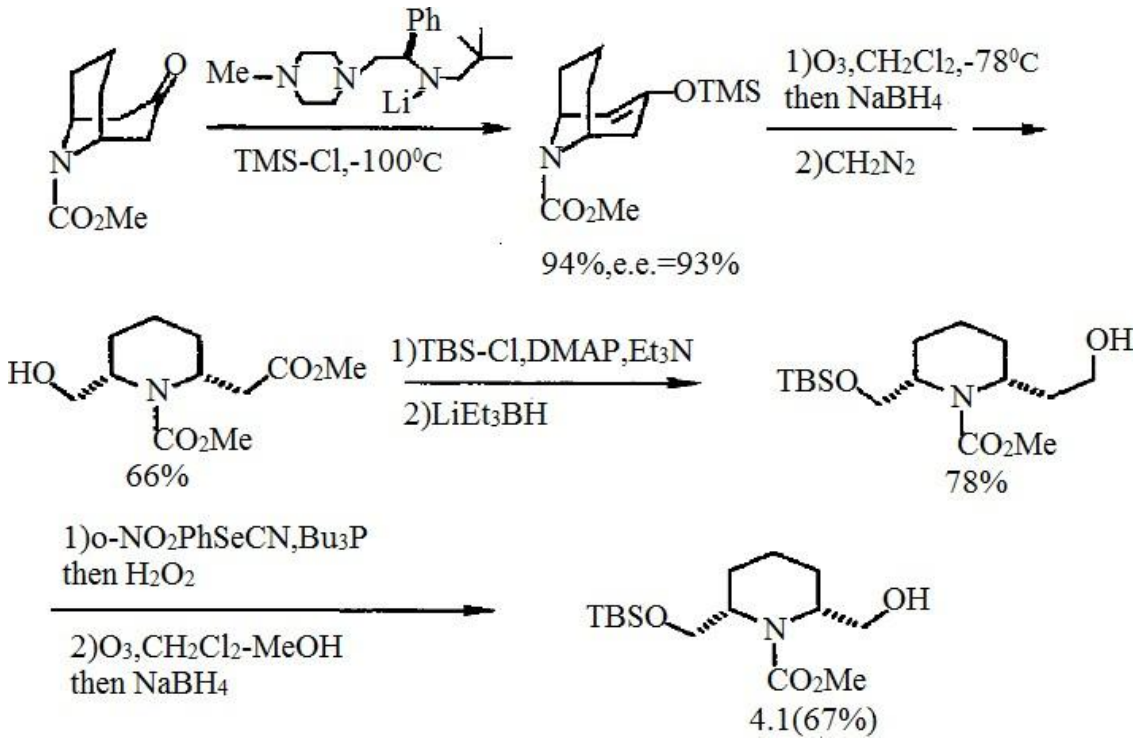
TABLE-1.1: Asymmetric Deprotonation of Prochiral Ketones

Ketones Used	Bases and Conditions	Products	e.e.	Ref.
	 THF,HMPA,-100^{0}C		97%	19
			88%	18
			84%	20
	 THF,HMPA,-75^{0}C		96%	21
	 THF,-75^{0}C		95%	22

This method is already finding use in enantioselective synthesis of natural products.An example is the synthesis of cis-2,6- bis(hydroxymethyl)piperidine derivative **4.1** in 93% e.e. as illustrated in Scheme 1.2. Compound **4.1** is an important building block for the synthesis of many naturally occurring

piperidine alkaloids. Using asymmetric deprotonation methodology, it would be possible to synthesize either enantiomer of natural products possessing the cis-2,6- disubstitutedpiperidine skeleton.

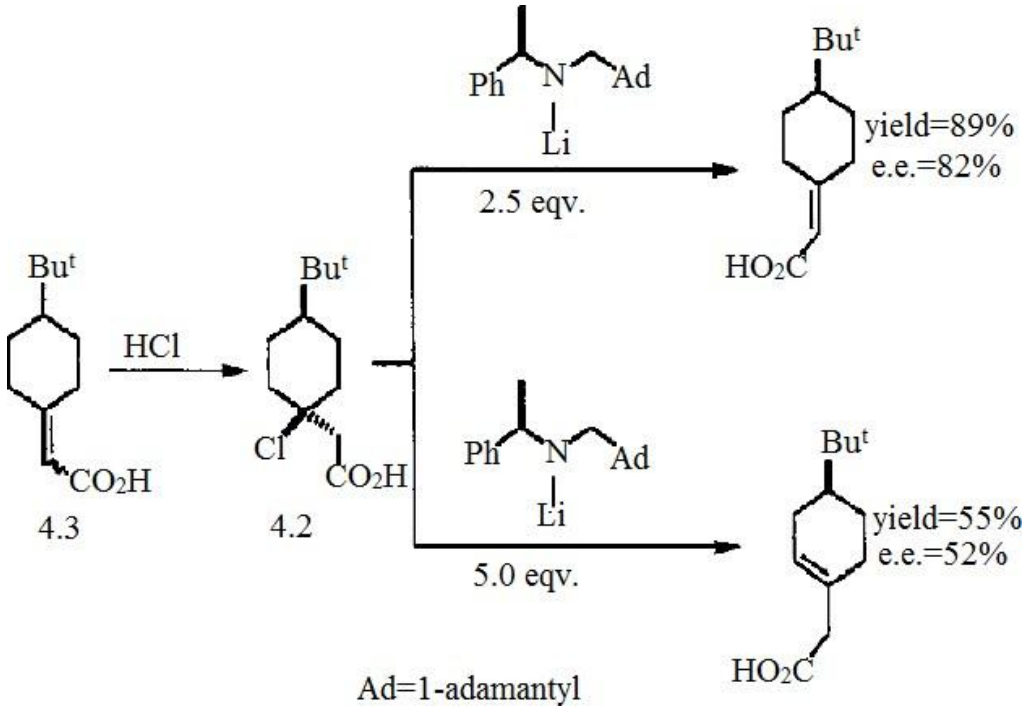
SCHEME-1.2:



ENANTIOSELECTIVE DEHYDROHALOGENATION:

Duhamel and co-workers reported enantio selective dehydrohalogenation of the compound **4.2.** This method has been used to deracemise 4-tert-butyl-cyclohexylidene acetic acid **(4.3)** as shown in Scheme 1.3. To achieve the optimum level of asymmetric induction, more than one equivalent of the Li-amide base was necessary. Bromo compounds corresponding to **4.2** gave lower levels of induction.

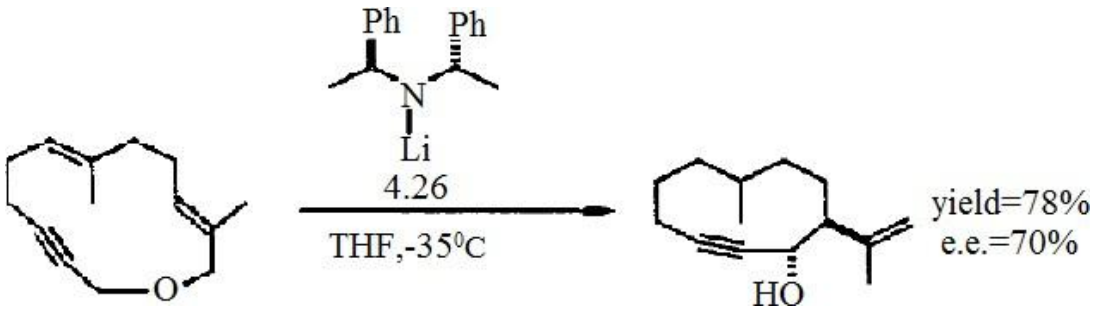
SCHEME-1.3:



ENANTIOSELECTIVE [2,3]-WITTING REARRANGEMENT

Marshall reported enantio selective synthesis of macro cyclic propargylic alcohols (up to 70% optical purity) by Wittig rearrangement of macro cyclic allylic propargylic ethers. The use of chiral Li-amide bases for the initial deprotonation step was studied. The C-2 symmetric amide **4.26**,used with a 13-membered *ring* ether gave the best result (Scheme 1.4). Other ring sizes gave lower levels of asymmetric induction (e.e. 23-33%) and acyclic systems showed no asymmetric induction.

SCHEME-1.4:

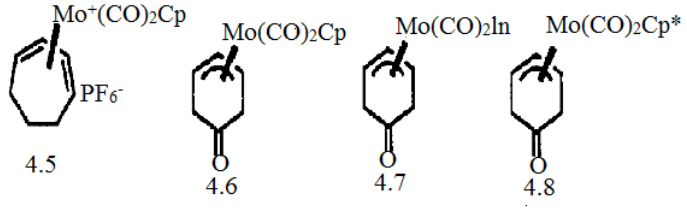


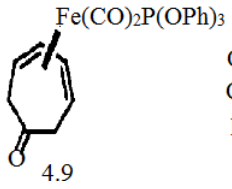
2 ASYMMETRIC DEPROTONATION OF ORGANO-MOLYBDENUM AND ORGANO-IRON COMPLEXES:

PREPARATION OF THE COMPLEXES:

Several pro-chiral organo-molybdenum complexes and one pro- chiral organo-iron complex were prepared for this study. These complexes are shown in Scheme 1.5

SCHEME-1.5:

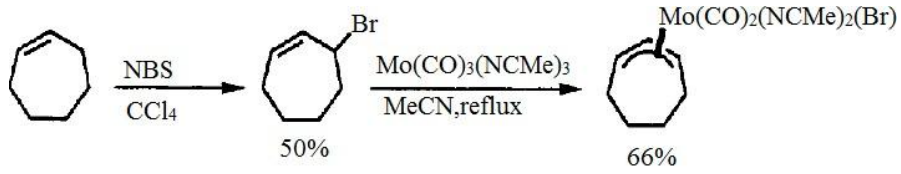


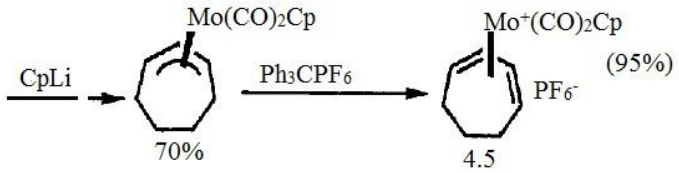


Cp=η^5-cyclopentadienyl
Cp*=η^5-pentamethylcyclopentadienyl
In=η^5-indenyl

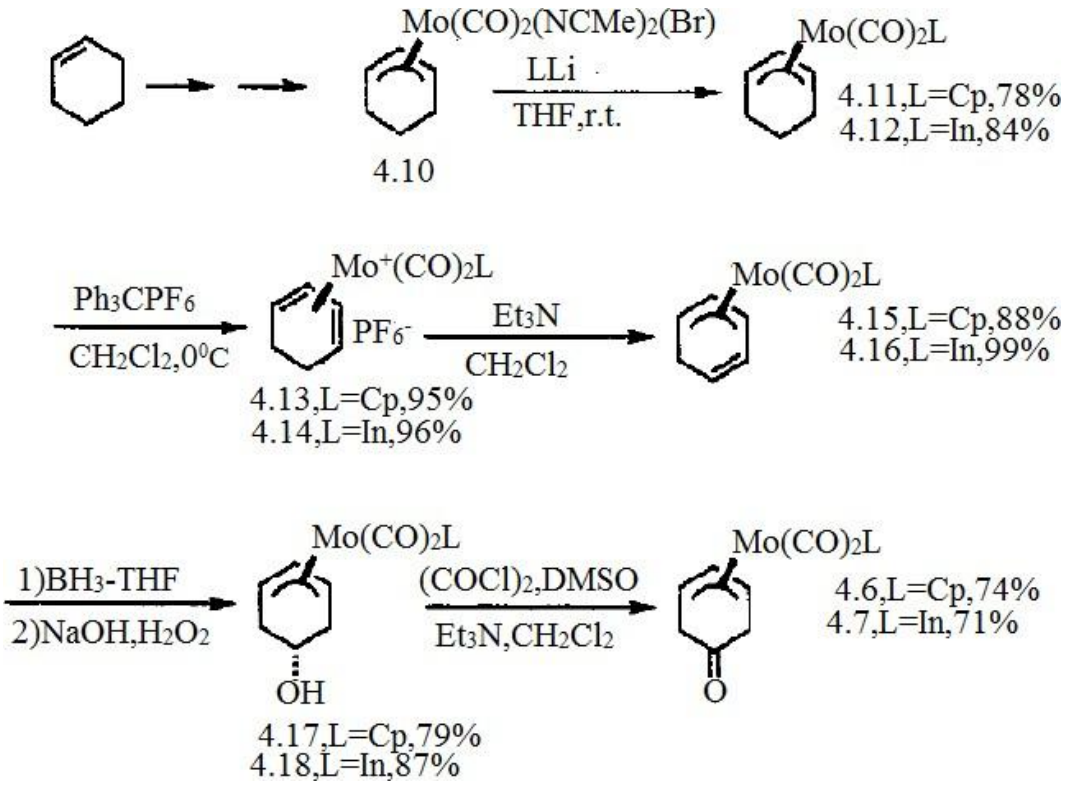
Compounds **4.5, 4.6,** and **4.9** were prepared by methods developed by Pearson et.al. and was prepared by a method analogous to that used for **4.6**. Complex **4.8** was prepared by a procedure analogous to that developed by Green et. al.These are shown below:

1) **Preparation of 4.5:**



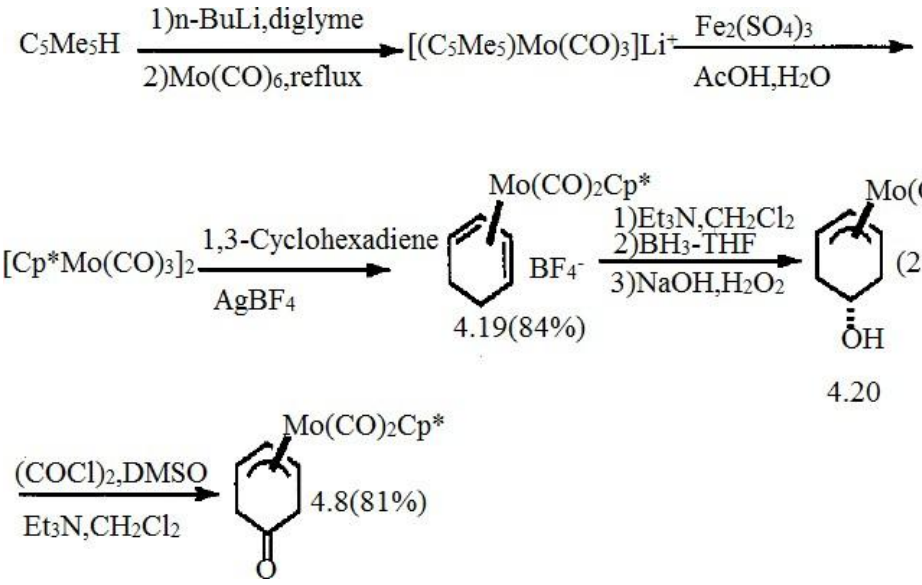


2) **Preparation of 4.6 and 4.7:**

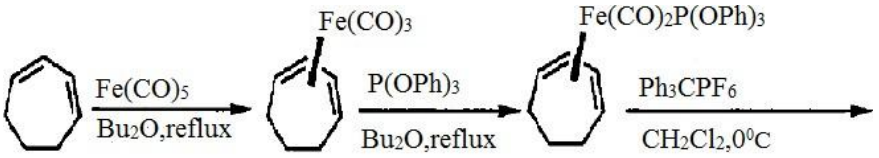


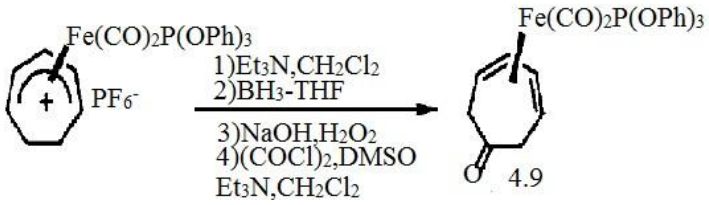
3) <u>Preparation of 4.8:</u>

Treatment of the complex **4.10** with pentamethylcyclopentadienyllithium (C_p* Li) in THF or diglyme (room temperature or reflux) led to unidentifiable products. Therefore a different and more direct route was followed. This is summarized in the following scheme.



4) Preparation of 4.9:

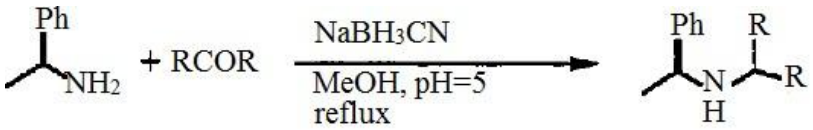




PREPARATIONOFTHEAMINES:

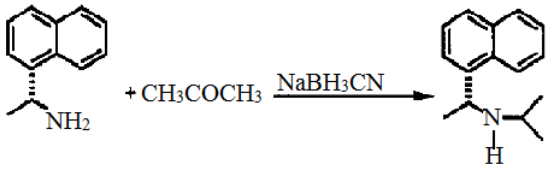
Reaction of Li-amides with the complex **4.5** led to its decomposition. For this compound, therefore, chiral 3^0 amines were used as bases. The amines tested are: (-)-strychnine, (+)-cinchonine, (S,S)-1,2-dimethoxytetramethylethylenediamine, (-)-brucine, (-)-sparteine, and (S)-(-)-N,N-dimehtyl a-phenylethylamine. All these amines are commercially available from either Aldrich or Sigma and were used as received.

For asymmetric deprotonations of all other ketones, a variety of 2^0- chiral amines were prepared. Most of the amines were synthesized starting from (S)-(-)-a-phenylethylamine*via* reductive amination with the appropriate carbonyl compound in presence of $NaBH_3CN$.

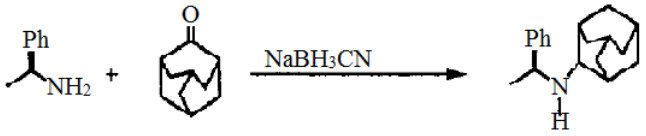


R=Me,4.21,81%,$[\alpha]_D$=-61^0,c=4.4,$CHCl_3$
Lit:-61.4^0,c=4.23,$CHCl_3$(ref.18).
R=Et,4.22,88%,$[\alpha]_D$=-60^0,neat
Lit: not given (ref.19).

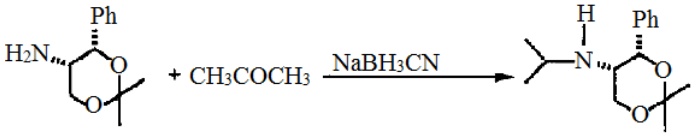
Several other amines prepared *via* reductive amination are shown below. Compound **4.23**was reported by Koga without its specific rotation. Since the $[\alpha]_D$ for **4.21**(-60.9^0) matches well with the value reported in literature (-61.4^0), reductive amination with $NaBH_3CN$proceeds without racemization. On this basis, compounds **4.24**and **4.25**were also presumed to be optically pure (these amines are not reported in the literature). Compound **4.24**was synthesized to study the effect of a bulky N-substituent on the degree of asymmetric induction.



4.23,88%,$[\alpha]_D$=-62^0,c=7.0,CH_2Cl_2
Lit: not mentioned(ref.19).



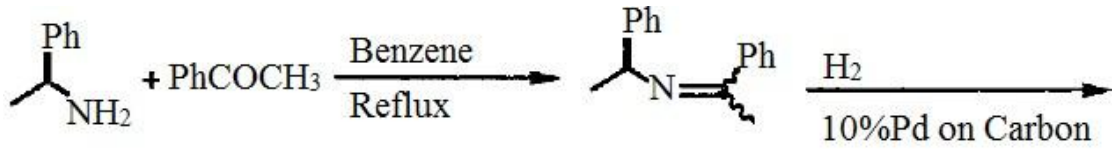
4.24,25%,$[\alpha]_D$ =-50^0,c=1.0,CH_2Cl_2

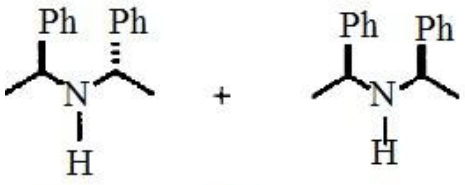


4.25,97%,$[\alpha]_D$=+85^0,c=2.3,$CHCl_3$

Amine**4.26**was prepared following Marshall's procedure. The C-2 symmetric amine was separated from the meso isomer by fractional recrystallization of their hydrochloride salts from

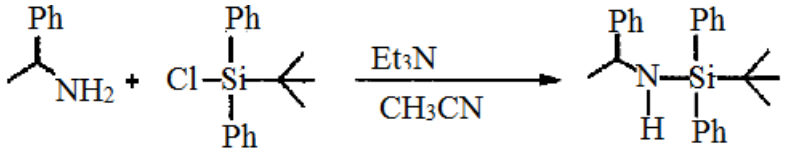
water. The $[\alpha]_D$ for the regenerated amine (-166^0) matched well with the reported literature value (-167^0).



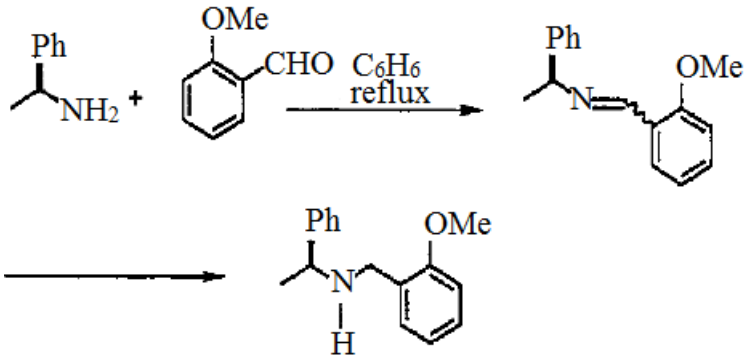


4.26 4:1

Amines **4.27**and **4.28**were prepared by literature methods. The rationale behind synthesizing 4.27 was twofold: (a) introduction of a bulky substituent on the nitrogen atom; (b) the negative charge on nitrogen atom in the Li-amide will be stabilized by the adjacent Si atom making the amide less basic than **4.24**; this, in turn, might increase the free energy difference between the two diastereotopic transition states for the deprotonation of **4.6.**

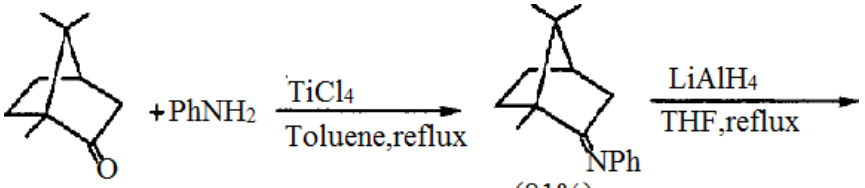


87%,4.27,$[\alpha]_D$=-79^0,c=2.8,$CHCl_3$
Lit: not given (ref.30)



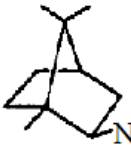
83%,4.28
$[\alpha]_D$ =-76^0,c=7.8,cyclopentane
Lit:-74^0,c=4.8,cyclopentane

The (R)-camphor derived amine **4.29** was also prepared by $LiA1H_4$ reduction of the imine **4.30** in refluxing THF. The optical rotation for the amine was 18% lower than the value reported in the literature. No efforts were made to improve the optical purity of the amine since **4.29** did not give good asymmetric induction in the deprotonation step. For the imine formation, $TiCl_4$ was used because conventional procedures led to little or no imine.



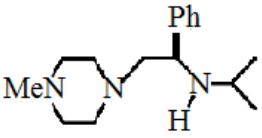
(81%)

4.30



70%,4.29,$[\alpha]_D$=-85^0,c=1.9,$CHCl_3$

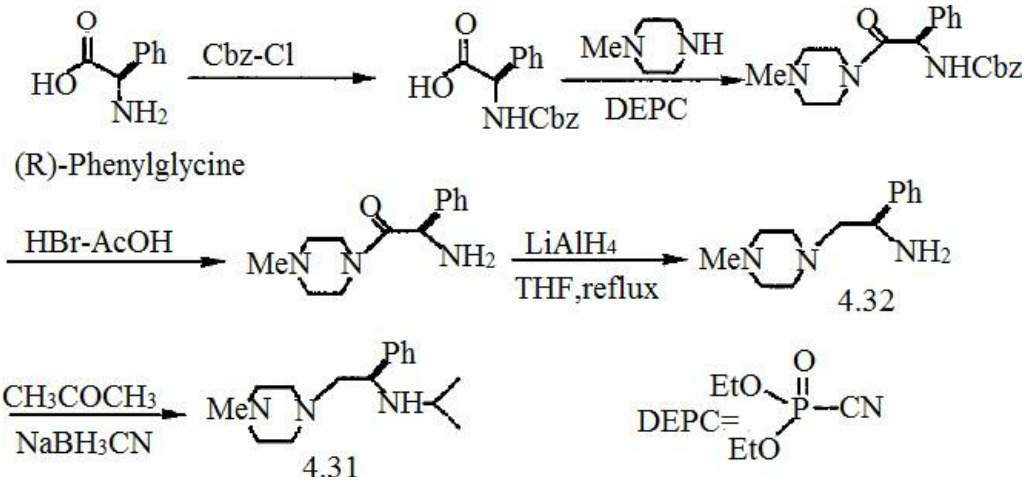
Lit:-103^0,c=1.6,$CHCl_3$



4.31

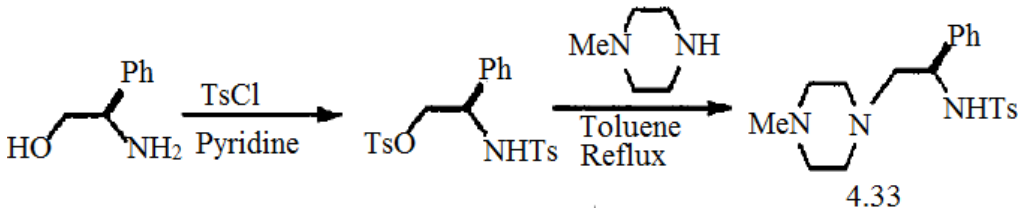
Synthesis of the phenylglycinol-derived amine **4.31** proved to be somewhat difficult. Prof. Koga kindly provided us with a procedure (unpublished) in a personal communication (Scheme 1.6). We could not execute the synthesis following his method owing to our failure to locate a reliable literature preparation for the unstable peptide-coupling reagent, diethyl phosphorocyanidate (DEPC).

SCHEME-1.6:



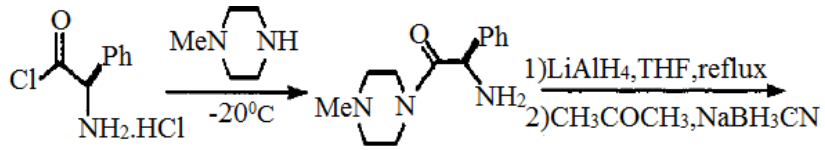
Following a similar route but using DCC as the peptide-coupling reagent was also not very successful. DCC gave an inseparable mixture of the starting material, product and dicyclohexyl urea. Use of isobutyl chloroformate/Et_3N in the coupling stage gave racemic products. Another approach was briefly pursued as indicated in Scheme 1.7, starting from (R)-phenylglycinol.

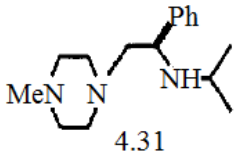
SCHEME-1.7:



Deprotection of the amino group of**4.33**was not very encouraging. Among the methods tested (KOH/MeOH/reflux, HBr-AcOH/70 ^{0}C, Al- Hg, Ca-liq.NH_3), only Ca-liq.NH_3 gave the desired product in low yield (30%). So, a more direct approach was pursued (Scheme 1.8). (R)-phenylglycine chloride hydrochloride (commercially available from Aldrich) was treated with an excess of 1-methyl piperazine at -20 ^{0}C to give a 7:1 mixture of the desired product and dipeptide. This mixture can be directly reduced with $LiA1H_4$ in refluxing THF and the product can be purified at this stage. Reductive amination with acetone gave **4.31** in 44% overall yield. The specific rotation of **4.31** (-71^0, c=3.0, EtOH) was somewhat lower than that indicated by Prof. Koga (-82^0, c=1.3, EtOH). We did not attempt to modify the synthesis because of the low asymmetric induction obtained in the target reaction.

SCHEME-1.8:





(Overall yield=44%)

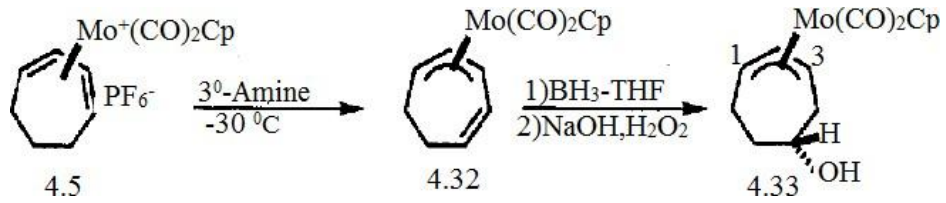
4.31

RESULTS:

1) Asymmetric Deprotonation of **4.5**:

Tertiary amines react with **4.5** to abstract a proton a to the dienemoiety and *anti* to the metal (Scheme 1.9).

SCHEME-1.9:



4.5 4.32 4.33

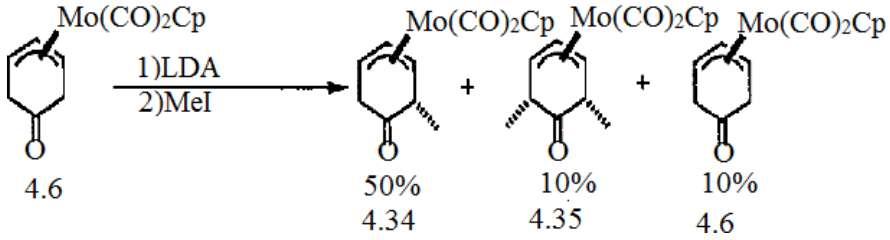
Asymmetric induction in this deprotonation step was studied and the results are shown in Table 1.2. The alkene complex **4.32** was found to be unstable in solution. Also the chiral shift reagent (+)-Eu(hfc)$_3$ did not show any separation of any hydrogens in its NMR spectrum because **4.32** does not have any atom that can coordinate to europium. Consequently, this compound was converted to the alcohol **4.33** and the e.e.'s were determined at this stage. The H-5 resonance broadens and the signals for the enantiomers separate with (+)-Eu(hfc)$_3$. The enantiomeric excesses were determined by integration of the two peaks. Since the level of induction was low in these preliminary experiments, this was not studied further.

TABLE-1.2:Asymmetric Deprotonationof 4.5

Bases Used	Yield(4.32)	$[\alpha]_D$	e.e.
(-)-Strychnine	86%	$+0.8^0$	~5%
(S,S)-1,2-Dimethoxy tetramethyl-ehtylenediamine	72%	$+0.8^0$	~5%
(-)-Brucine	70%	$+0.7^0$	-
(-)-N,N-Dimethyl α-phenylethylamine	65%	-0.5^0	-
(-)-Sparteine	79%	-6^0	~30%

2)Asymmetric deprotonation ofpro-chiral ketones **4.6, 4.7, 4.8,** and **4.9:**

The ketone **4.6**, when treated with 1.2 equivalents of LDA in THF at -100 ^{0}C, generates a deep red colored enolate. Addition of MeI and warming the reaction mixture to -20 ^{0}C gives the monomethylatedproduct **4.34** in about 50% yield together with about 10% of recovered starting ketone and about 10% of the dimethylated ketone **4.35** .



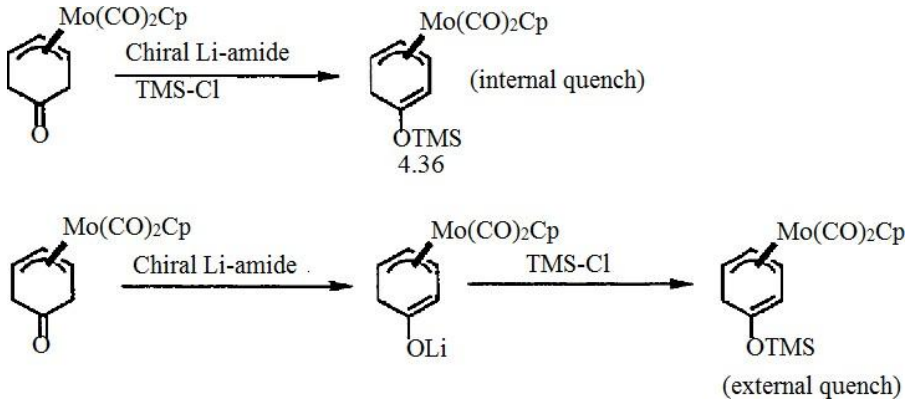
Enolization of **4.6**was studied using chiral Li-amide bases followed by quenching the reaction by methyl iodide. The results are shown in Table 1.3. Several important features of this reaction were noted.

a) The temperature during deprotonation was found to be very important; deprotonating at -75 ^{0}C instead of -100 ^{0}C mostly leads to decomposition of the ketone.

b) The quality of the BuLi used to generate the Li-amide bases significantly affected the levels of asymmetric induction. The results were consistent ($[\alpha]_D$ difference within 0.5^0 between successive runs with the same chiral Li-amide) when a fresh bottle of BuLi was used. Old batches of butyllithium gave

racemic products.

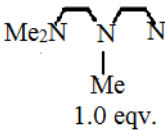
c) In all literature reports, 'internal' quench methods were used instead of quenching a pre-formed enolate.



All attempts to isolate the enolsilane**4.36(**generated either by internal quench or by external quench) were unsuccessful due to its extremely unstable nature. The same instability was observed for the TBS-enol ether.

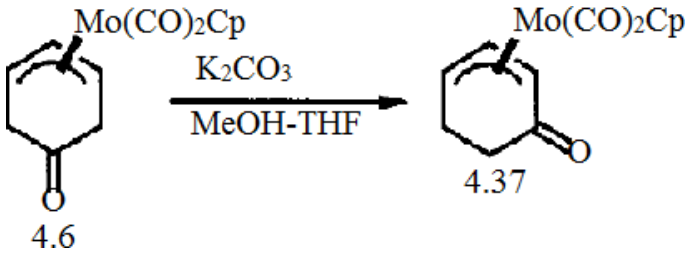
d) Since quenching the enolate with methyl iodide was not complete till -20 ^{0}C, equilibration of enolates cannot be totally ignored. Reactions with more reactive electrophiles (Me-OTf, NC-CO_2Me, CH_3COCl) were tested. All led to inseparable mixtures of C- and O- alkylated products which were not suitable for NMR chiral lanthanide shift studies.

TABLE-1.3:Asymmetric Deprotonation of 4.6

Amine Used	Additive	Yield of 4.34	$[\alpha]_D$	e.e.[a]
4.21	-	56%	$+7^0$	17%
4.22	-	40%	$+12^0$	30%
4.23	-	54%	-6^0	~16%
4.23	 1.0 eqv.	42%	0	0
4.24	-	54%	$+10^0$	25%
4.25	-	48%	0	0
4.26	-	53%	$+16^0$	40%
4.27	-	48%	-8^0	~20%
4.28	-	53%	$+6^0$	16%
4.29	-	55%	-2^0	-
4.31	HMPA 1.0 eqv.	53%	$+4^0$	~10%

a) Estimated using NMR methods-See experimental section

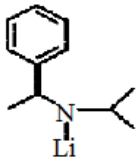
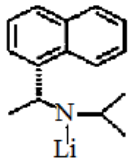
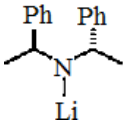
One possible reason for not observing useful levels of asymmetric induction with ketone **4.6** as compared to 4-tert-butyl cyclohexanone(both conformationally locked ketones) was thought to be the greater acidity of the a-protons of **4.6**. Stabilization of a carbanion α-to the π-allyl-$Mo(CO)_2Cp$ moiety has been well documented. In fact, compound **4.6** can be completely isomerized to the compound **4.37** by treating it with methanolic K_2CO_3 at room temperature.



To test this hypothesis, the pentamethylcyclopentadienyl (Cp*) substituted ketone **4.8** was prepared. C_p* being more electron releasing than Cp, was expected to increase the electron density on molybdenum. This, in turn, should decrease the acidity of the protons a-to the carbonyl group (these protons are adjacent to π-allyl-Mo(C0)$_2$Cp moiety also) in the compound **4.8**.

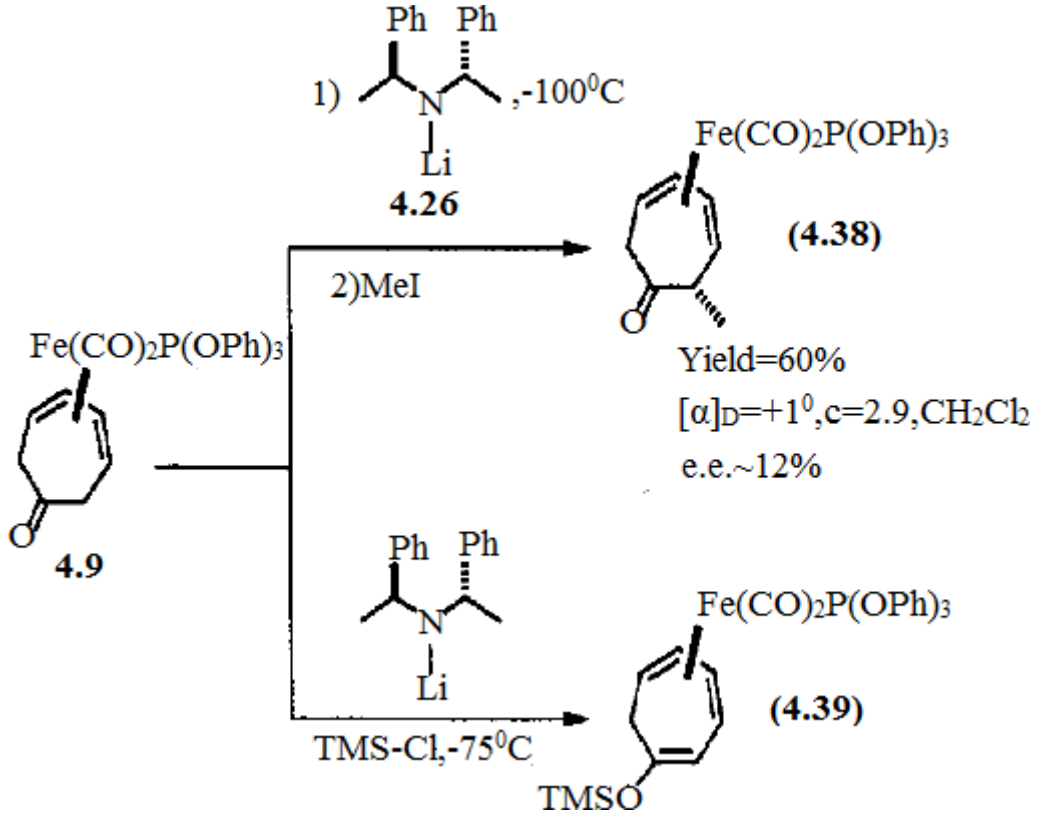
Methylation reactions of this ketone using chiral Li-amide bases were studied. A comparision is presented in Table 1.4. The indenylsubstituted ketone **4.7** was worse than **4.6** and its asymmetric deprotonation was not investigated in detail.

TABLE-1.4: Comparison between 4.6 and 4.8

Base Used	E.e. obtained	
	4.8 (Cp* ketone)	4.6 (Cp ketone)
	29%	17%
	21%	16%
	41%	40%

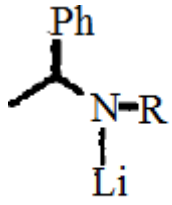
Iron complex **4.9** was also subjected to the monomethylationreaction. The C-2 symmetric amine **4.26**, which gave 40% e.e. in the molybdenum system **4.6**, gave 12% e.e. with **4.9**. The silylenol ether **4.39**from **4.9**, generated by internal quench with TMS-C1, was too unstable to handle. Attempts to oxidize the crude product **4.39** with mCPBA to the α-hydroxy ketone were unsuccessful. This is summarized in Scheme 1.10. Clearly, further studies in this area are needed. However, since the reactions involving chiral Li-amide bases are poorly understood, and since these bases are not all readily available, this project was abandoned.

SCHEME-1.10:



3 DISCUSSION:

One of the major problems in designing a base to get optimum enantiomeric excess is the lack of knowledge regarding the structure of the transition state. Thus, it is not possible to predict which enantiomeric product will result from a particular deprotonationexperiment. The only trend observed during the course of this study is that for bases of general structure **4.40**, the steric bulk of the R- group plays an important role.



4.40

R=iPr,e.e.=17%
R=2-Adamantyl,e.e.=25%
R=Et2CH,e.e.=30%

But, when R was changed to tert-butyl-diphenylsilyl, the sense of induction was reversed.

(IJABAS) 2017, Vol. No. 1, Issue No. I, Oct-Dec **ISSN: 2457-0451**

Lithium amide bases in the solid state exist as supramolecularcomplexes. These were found also to maintain their integrity in solution also.Enolates exist as mixed aggregates in solution and in the solid state; the structure of the aggregate is determined by the ratio of the enolizable compound and the lithium amide base. Solid state structures of Li-enolates of pinacolone are shown in Figure 1.2

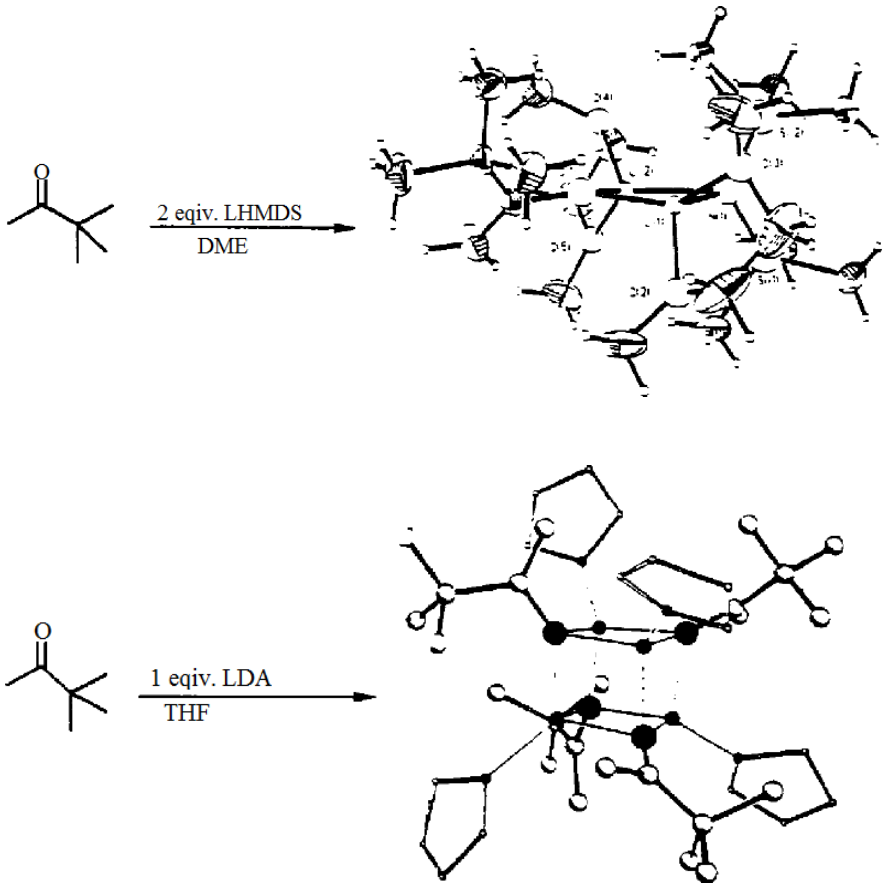
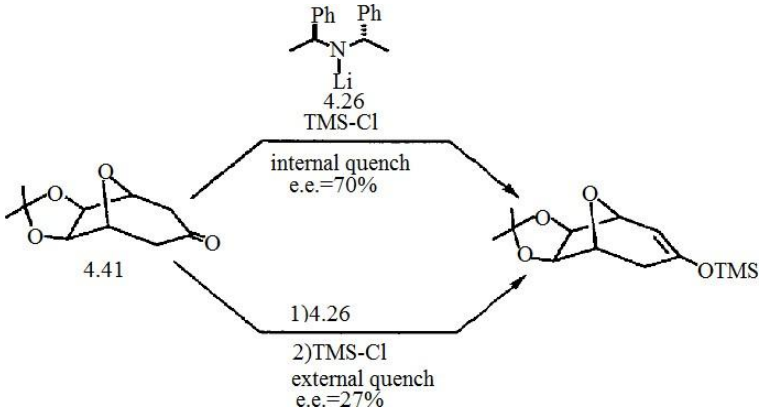
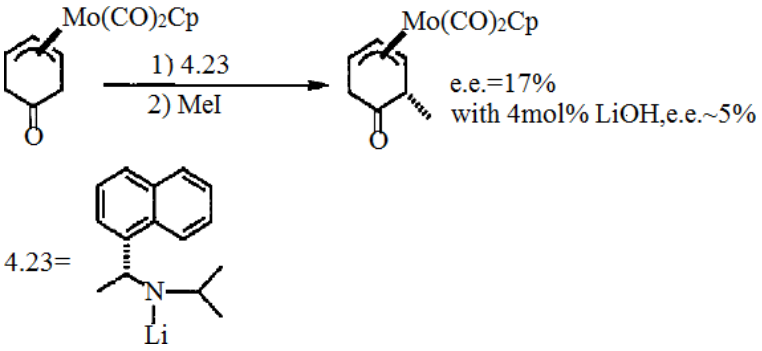


Figure-1.2. Solid State structures of Li-enolates

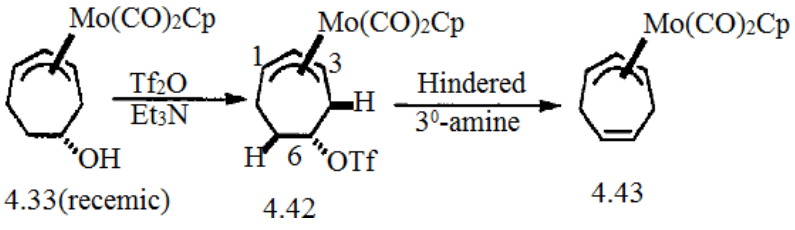
Thus, when a solution of a ketone is added to the Li-amide base for deprotonation (as is the case for all asymmetric deprotonationexperiments), the nature of the species responsible for deprotonationchanges as the reaction proceeds. Internal quench may solve this problem leading to a higher degree of asymmetric induction. There is some experimental evidence in support of this hypothesis. In asymmetric deprotonation of the ketone **4.41** using the chiral Li-amide **4.26**, internal quench with TMS-Cl furnishes the product in 70% e.e. Under identical conditions, when TMS-Cl was added to a solution of the pre-formed enolate, the isolated product showed only 27% optical purity.



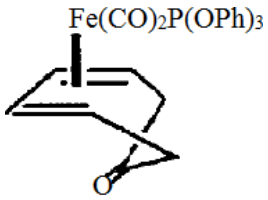
As mentioned earlier, the quality of BuLi used to generate the chiral lithium amide strongly affected the levels of asymmetric induction. This is probably due to the presence of small amounts of LiOH in older batches of BuLi. To test this possibility, asymmetric deprotonation of **4.6** was carried out with the Li-amide **4.23** containing 4mol% LiOH. This leads to the monomethylated product in 5% e.e.



A possible approach to synthesize the alcohol **4.33** in optically enriched form would be asymmetric hydroboration followed by peroxide oxidation of the prochiral complex **4.43**. Although there are two protons in 4.42 that can be abstracted by a base to effect the elimination (H-4 and H-6), H-4 is situated closer to the sterically hindering metal than H-6. Use of a sterically hindered 3^0-amine should generate **4.43**.



Future work should be directed to the iron complex **4.9** due to the similarity of its conformation (shown below) with that of the ketone **4.41**. Though the silylenol ether **4.39** (Scheme 4.10) was unstable, the crude reaction mixture (the amine can be removed by washing with saturated $CuSO_4$ solution) can be directly treated with MeLi to generate the Lienolate. Quenching the Li-enolate with methyl iodide should generate **4.38** in optically enriched form.



Conformation of 4.9

Another problem that is specific to the molybdenum ketone **4.6** is its poor solubility in ether or toluene which limits the deprotonationexperiments to THF solvent only. The iron complex **4.9** does not suffer from this problem. Solvents have very pronounced effects on the optical purity of the product obtained in asymmetric deprotonationexperiments. Thus, **4.9** can be used to study the dependence of the optical purity of the monomethylated product **4.38** on reaction solvents also.

Another area for future work in this project is the design of the chiral amines. Though a review of the literature reveals that each system is unique and the base used for optimum asymmetric induction had to be separately determined, the C-2 symmetric amine **4.26** seems very encouraging. This amine gave the highest e.e. in asymmetric deprotonation of **4.6** and also showed useful levels of asymmetric induction with pro-chiral ketones of varied structures (compare **4.41**with 4-tert-butyl cyclohexanone). It is worthwhile to note the conformational similarity of **4.9** with **4.41**. The complex **4.9** exists in a boat conformation as shown above. A detailed study of the role of C-2 symmetric amines[40] in asymmetric deprotonation should be a future goal of this project.

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