STEREOCONTROLLED ALKYLATION OF ENOLATES ATTACHEDTO π-ALLYL-$Mo(CO)_2Cp$ SYSTEMS

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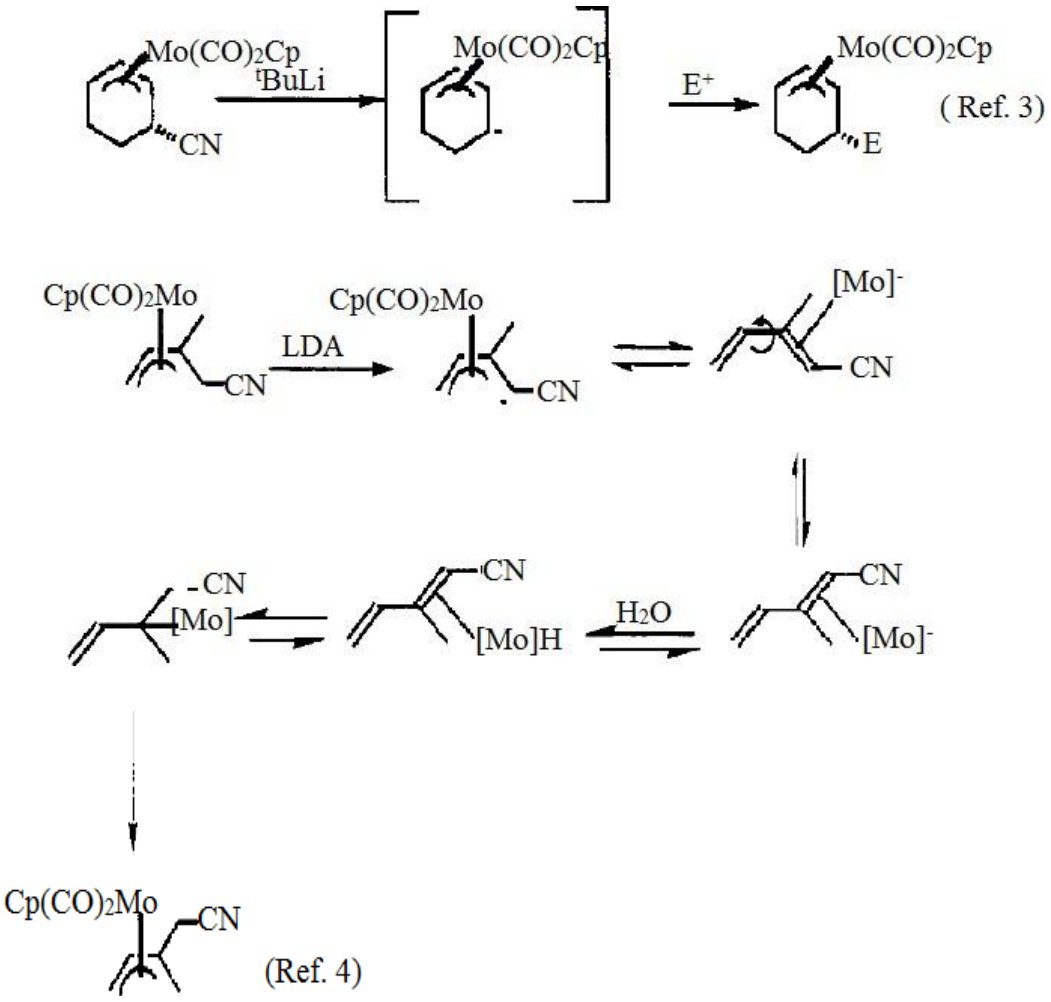
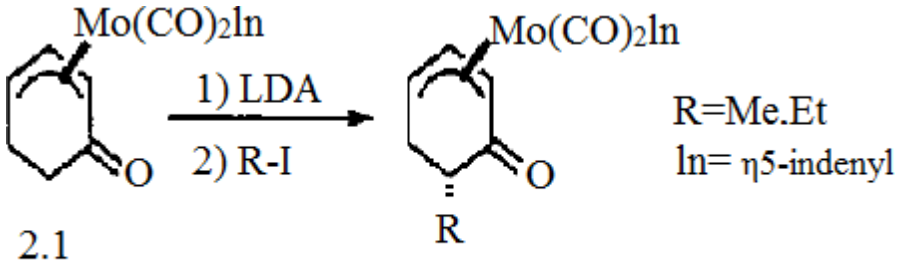
INTRODUCTION:

Various transition metals e.g., Cr,Fe, Mn, etc. stabilize neighboring carbanions. The π-allyl-$Mo(CO)_2Cp$ has also been found tohave this stabilizing property. Some reactions illustrating this stabilizing property are presented below:

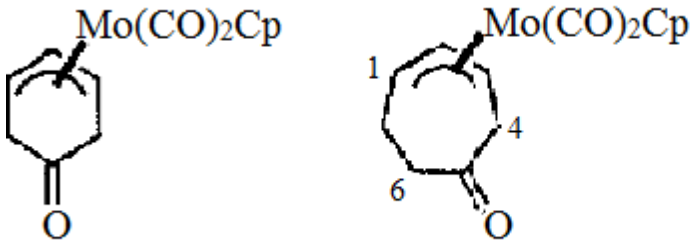


Green reported alkylations of the enolate derived from the ketone complex **2.1,** which proceed with complete diastereofacial selectivity; the incoming electrophile approaches the enolate*anti* to the metal. But multiple functionalization using enolate chemistry is not possible with this compound due to the position of the ketone carbonyl (Scheme 2.1). Pearson has used the ketone complex **2.2** for multiple functionalization where the metal is used to control the stereochemistry.

SCHEME-2.1:



2.1



2.2 2.3

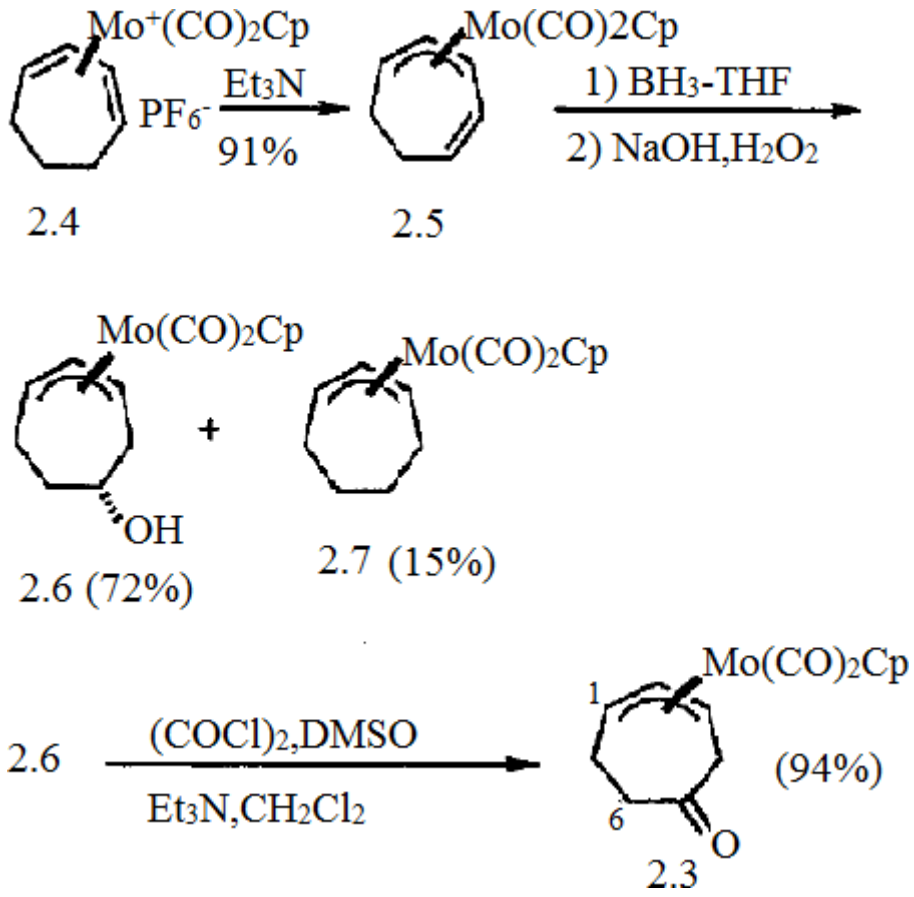
For the seven membered ring analog, complex **2.3,** the two positions α- to the carbonyl group are non-equivalent. Protons on C-4 should be considerably more acidic than protons on C-6 due to the presence of the π-allyl-$Mo(CO)_2Cp$ moiety. Thus, for the complex **2.3,** the metal can be used to control both regio- and stereochemistry for enolatereactions. This also gives a method for stereocontrolled multiple functionalization of the seven membered ring using organo - molybdenum chemistry. It should be noted that all of these reactions are stoichiometric in molybdenum. Trost has used various molybdenum-isonitrile complexes as *catalysts* for the alkylation of allylic acetates and sulfones*via* the intermediary of electrophilic π-allylmolybdenum complexes.

2.2 PREPARATION OF THE COMPLEX 2.3.

The keto derivative **2.3** was prepared from [cycloheptadiene$Mo(CO)_2Cp]^+PF_6^-$**(2.4)** in a manner analogous to the synthesis of **2.2**(Scheme 2.2). All steps are high yielding although the

hydroboration of **2.5** gave a mixture of the desired alcohol **2.6** and cycloheptenyl-Mo(CO)$_2$Cp **(2.7)** in 5:1 ratio. The latter presumably results fromhydrolysis of the organoborane intermediate. Use of disiamylborane or thexylborane did not improve the selectivity. The compounds **2.6** and **2.7**can be readily separated by flash chromatography and **2.7** can be reconverted to **2.4** by treatment with Ph_3CPF_6, thereby allowing recycling.

SCHEME-2.2:



NMR data for the compound **2.6** was very difficult to interpret (Figure 2.1). The peaks were assigned with the help of a 400 MHz H- COSY experiment, shown in Figure 2.2. This did not permit unambigous assignment of the stereochemistry of **2.6** and this was determined by X-ray crystallography. Two half-chair conformations were observed in the solid state (Figure 2.3) but in both conformations the hydroxy group was antito the metal. Selected bond lengths and bond angles are given in the Appendix. This half-chair conformation is consistent with the earlier conformational analysis of seven membered π-allyl-Mo(CO)$_2$Cp systems based on NMR coupling constants

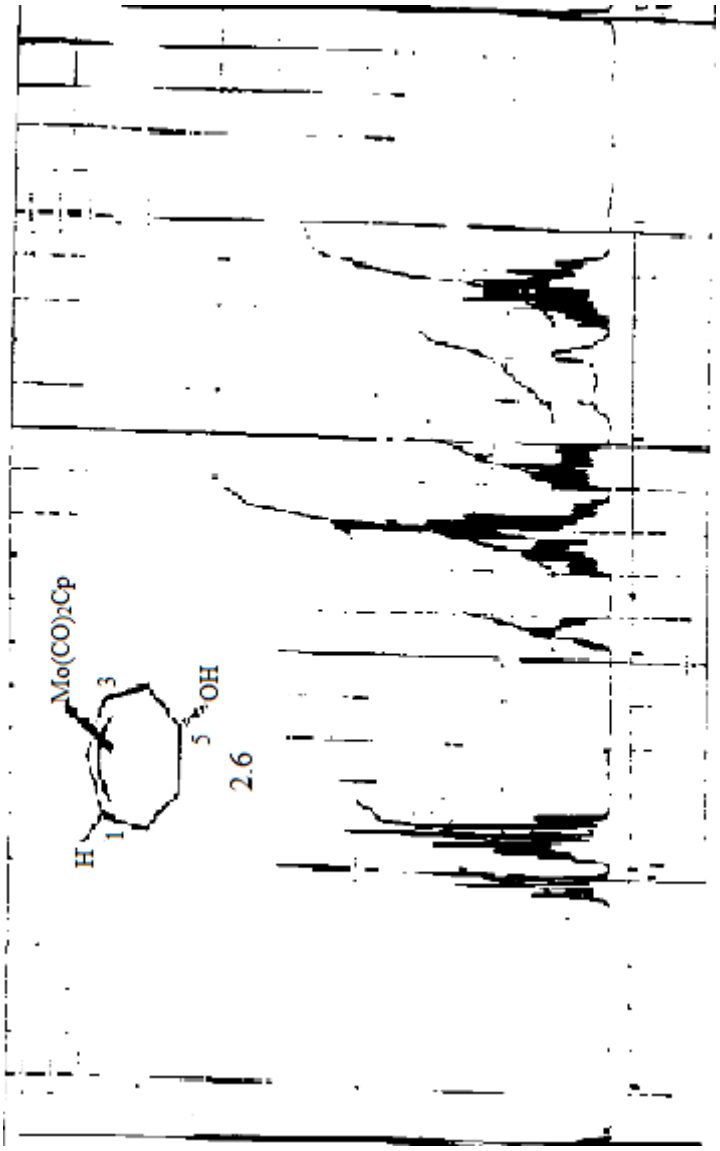


Figure 2.1. 200 MHz ^{1}H NMR spectrum of 2.6

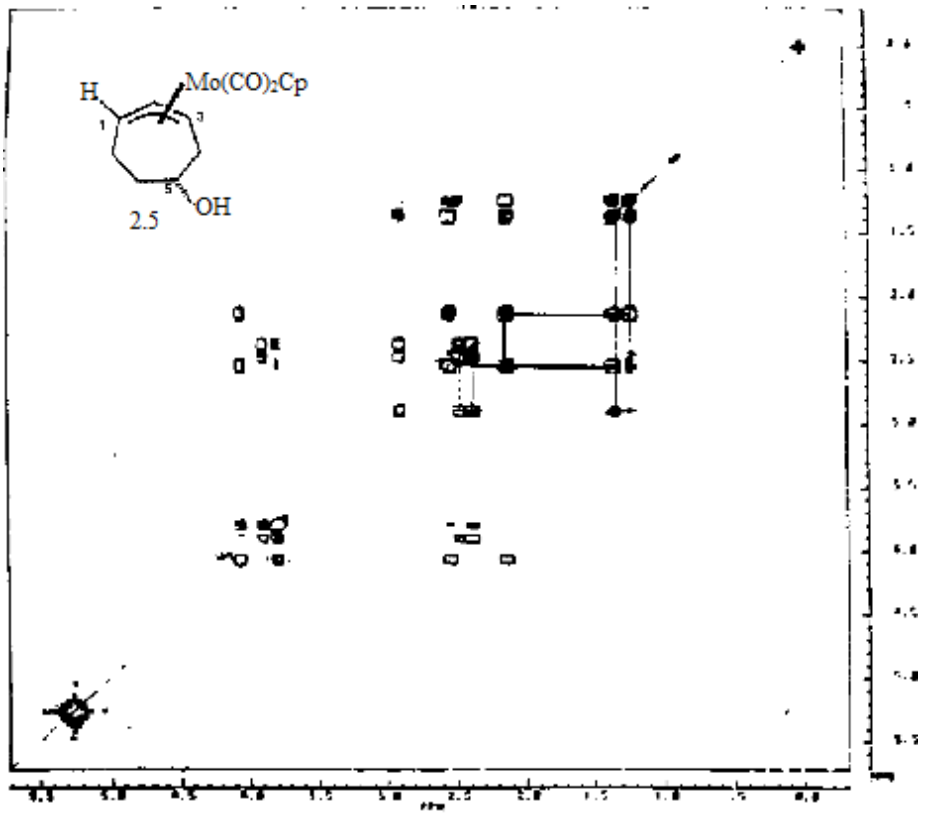


Figure 2.2. 400 MHz H-COSY spectrum of 2.6

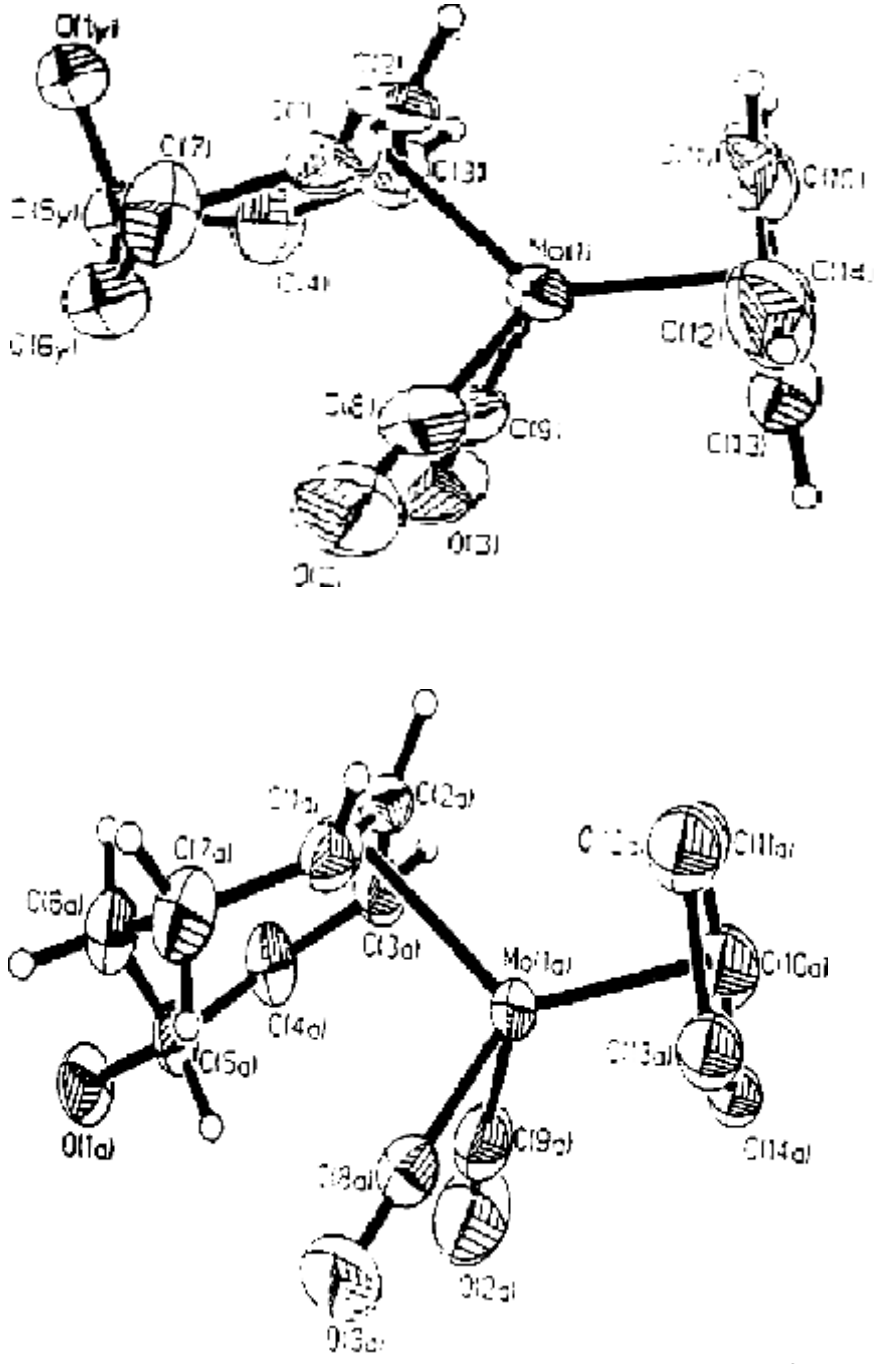


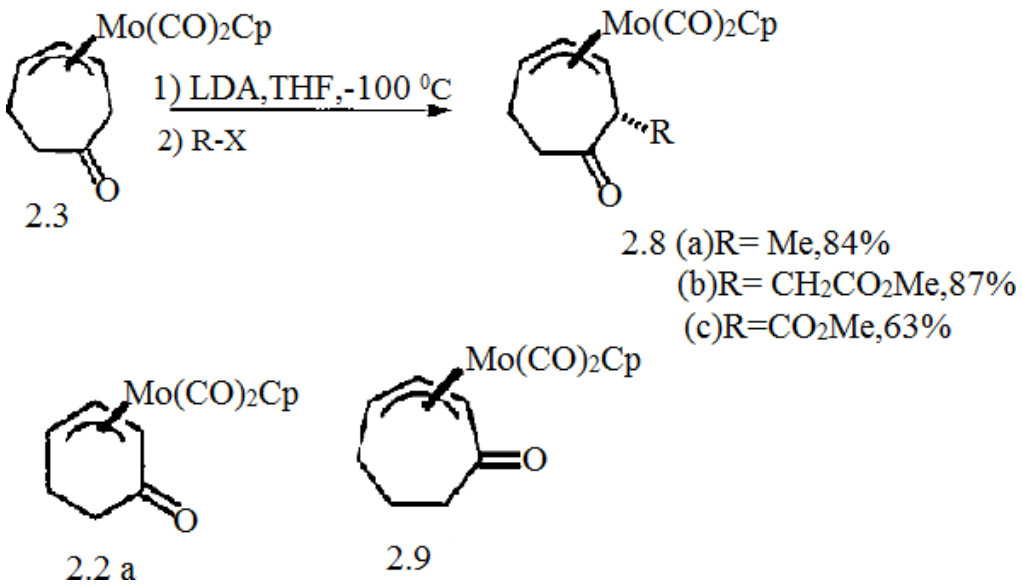
Figure 2.3. X-ray structure of 2.6

REACTIVITY OF THE KETONE 2.3 .

On the basis of the supposition that the π-allyl-$Mo(CO)_2Cp$ moiety participates in carbanion stabilization, deprotonation was expected to occur regioselectively at C-4. Treatment with LDA or $KOBu^t$ at -100 ^{0}C followed by quenching with electrophiles generates exclusively the

substituted complexes **2.8** (Scheme 2.3). Excess of LDA (up to 5 equivalents) also gave exclusive mono alkylation at C-4.

SCHEME-2.3:

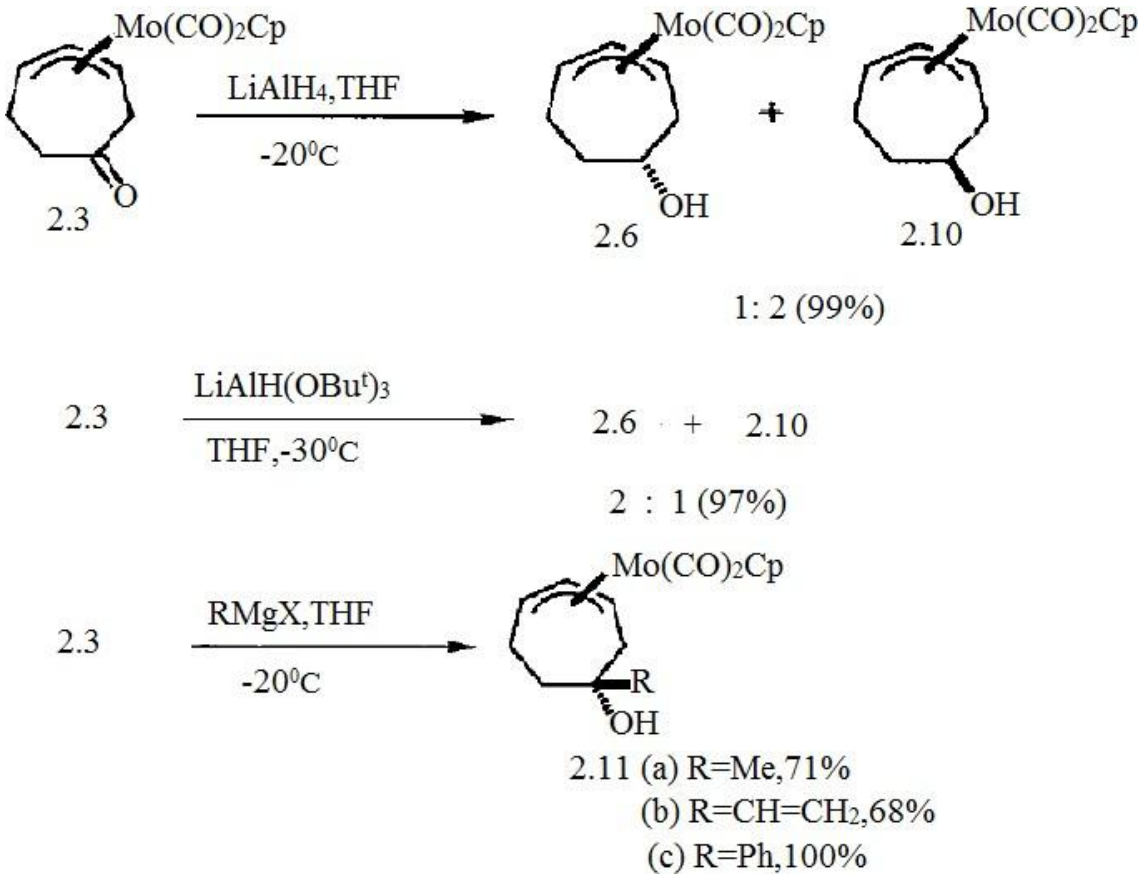


Attempts toeffect hydride abstraction from**2.3**using Ph_3CPF_6 were unsuccessful. These reactions gave products unidentifiable byNMR. Attempts torearrange**2.3** to **2.9** with KOH-H_2O-MeOH were partially successful. The desired product **2.9**could be obtained in about45% yield but it was found to be very difficult to purify due to its polar nature. The analogoussix-membered ring complex **2.2** can be completely rearranged to the conjugated ketone **2.2a**under identical reaction conditions.

The stereochemistry of **2.8**was assigned by analogy with hydroboration results and was confirmed by X-ray crystallography of a later derivative. Thus the stereochemical outcome of additions to C=C adjacent to $Mo(CO)_2Cp$ is dictated by the bulky metal moiety.

Additions of nucleophiles to**2.3** were notdirected by the steric bulk of the metal (Scheme 2.4). Reduction of **2.3** with $LiA1H_4$ at -20 ^{O}C gave a mixture of **2.6**and **2.10**in 1:2 ratio. Reaction of a stericallydemanding reducing agent, $LiA1H(OBu^{t})_3$ gave **2.6**and **2.10** in 2:1 ratio.

SCHEME- 2.4:



Grignard reagents are presumed to be more sterically demanding than $LiA1H_4$. In all reactions with Grignard reagents, only one stereoisomer was observed (as judged by the NMR spectra of crude reaction product). The stereochemistry of the products were assigned as shown in the structure **2.11**where the incoming nucleophile attacks the carbonyl group *syn*to the metal. It appears that the outcome of nucleophilic addition reactions is dictated by the conformation of the ketone **2.3**, rather than the steric bulk of the metal (see later discussion).

Addition of nucleophiles to the monomethylated compound **2.8a**was governed by the conformation of the molecule and an additional steric effect from the neighbouring methyl group. Addition of MeMgBr at -30 ^{0}C gave only one product (Scheme 2.5). Again NMR data were inconclusive with regard to stereochemistry (Figure 2.4) and the tertiary alcohol was submitted for X-ray crystallography. This showed that the nucleophile has again added *syn*to the metal to give **2.13a**and not **2.12**as might be expected based on steric effects alone. The X-ray structure is shown in Figure **2.5**, and selected bond lengths and bond angles are given in the Appendix.

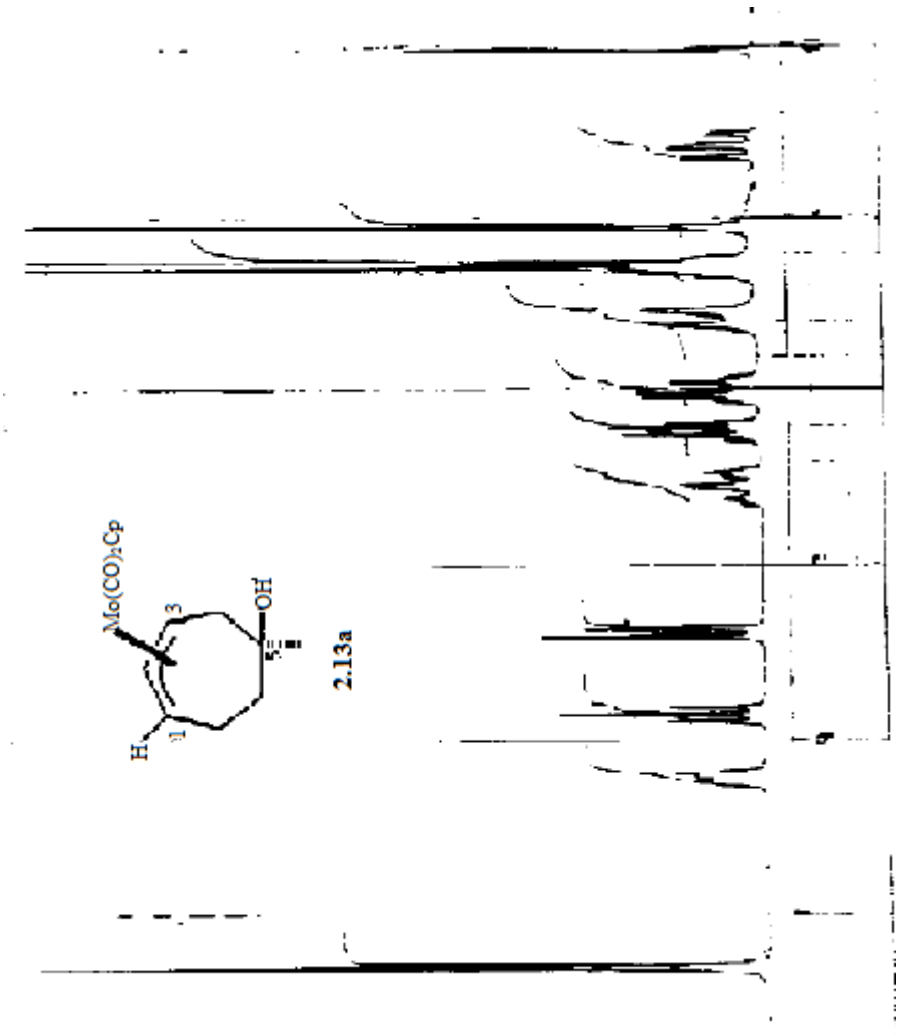


Figure 2.4. 200MHz ^{1}H NMR spectrum of **2.13a**

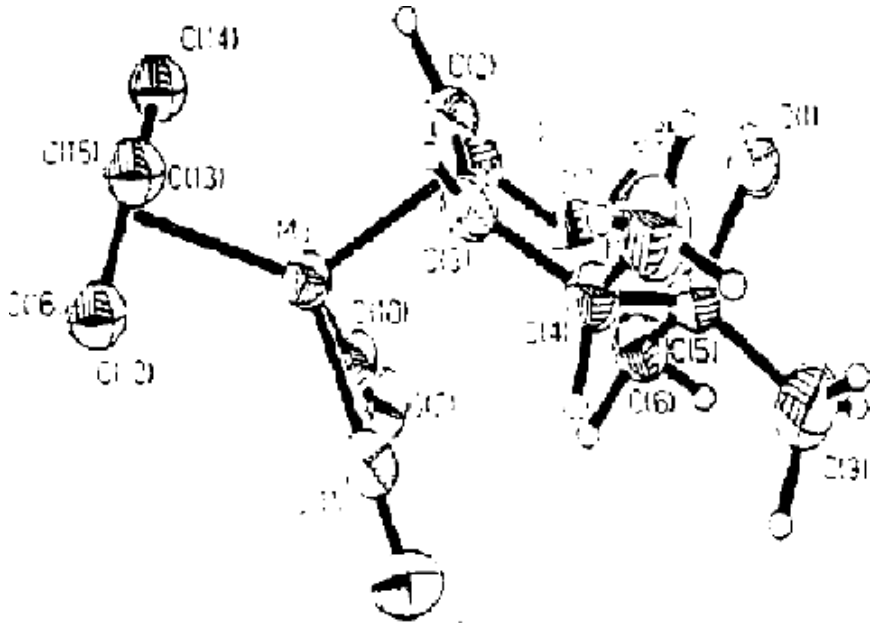
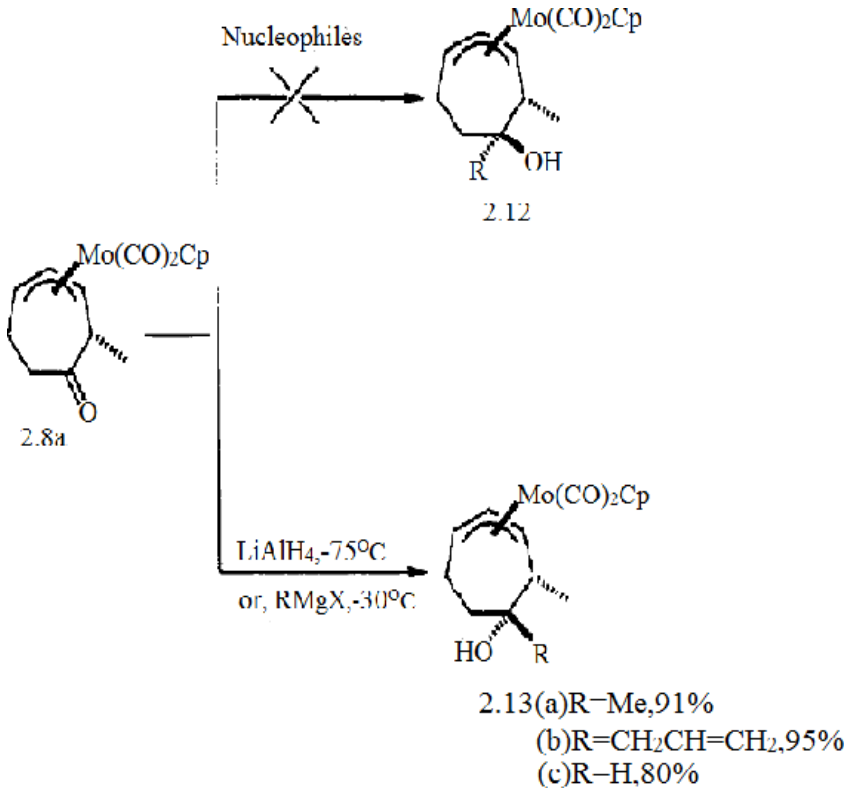


Figure 2.5. X-ray structure of **2.13a**

SCHEME-2.5:

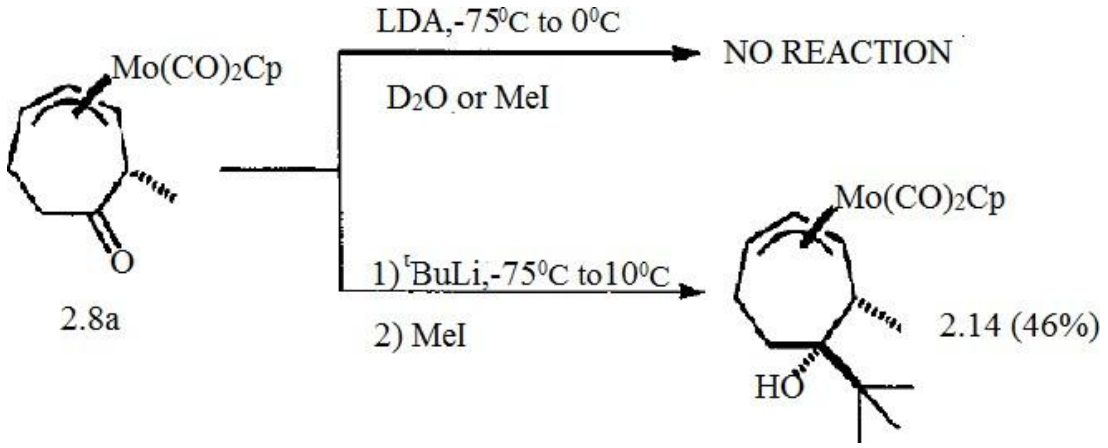


2.13(a)R=Me,91%
(b)R=$CH_2CH=CH_2$,95%
(c)R=H,80%

By analogy, the products from all nucleophilic additions to **2.8a**were assigned the structure **2.13**. Reduction of the ketone **2.8a** with $LiA1H_4$ at -75 ^{0}C gave only one product **(2.13c),** whereas reduction at 0 ^{0}C furnished a 2:1 mixture of epimers favoring **2.13c**.

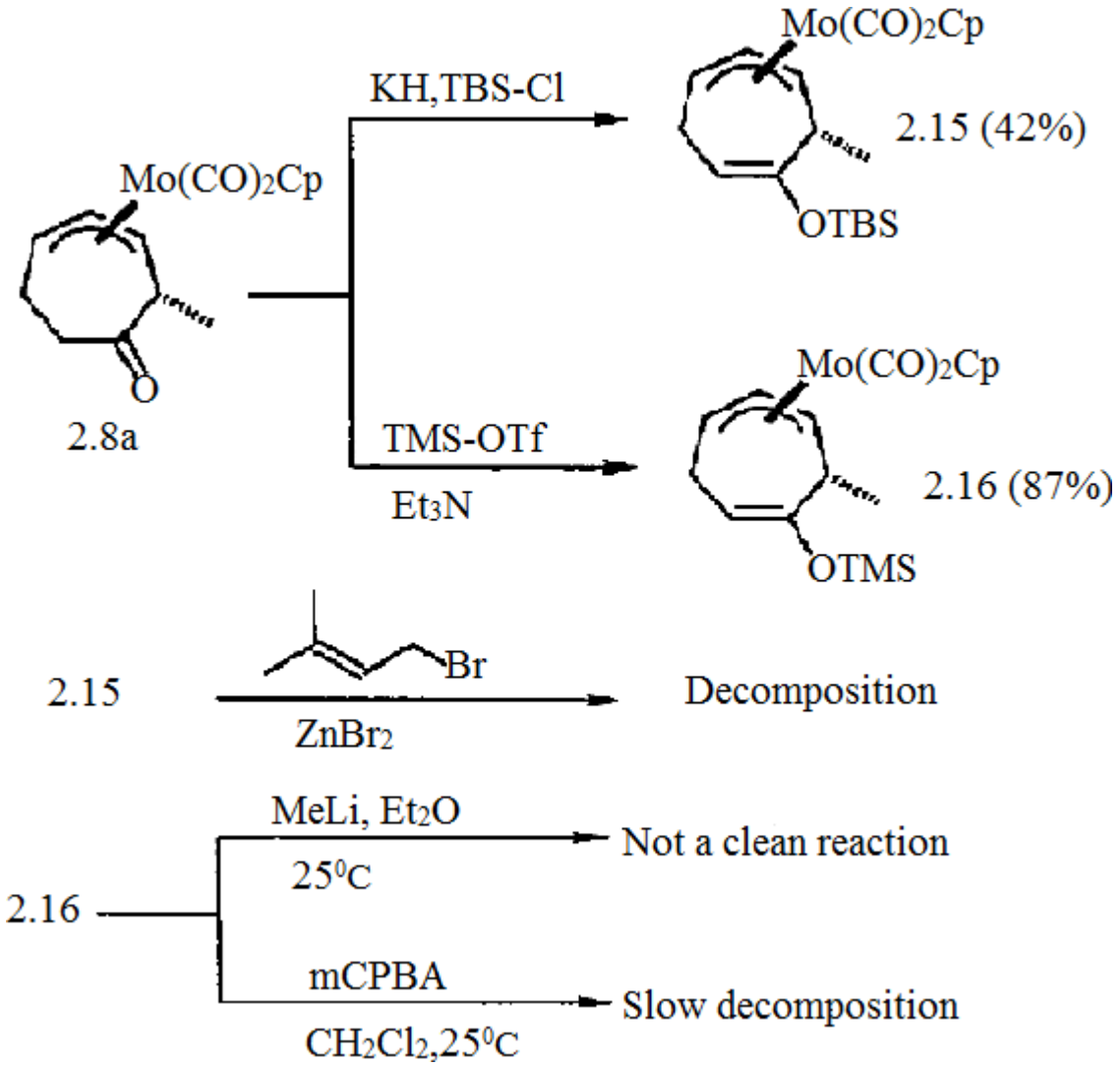
Deprotonation of **2.8a** was found to be very difficult. Treatment with LDA at low temperature followed by D_2O quench gave no deuteratedproduct and attempted methylation also failed. Raising the temperature to 0 ^{0}C during LDA treatment did not lead to any improvement. Treatment with ^{t}BuLi (-75 ^{0}C to 10 ^{0}C) led to the tertiary alcohol **2.14**from nucleophilic addition. Deprotonation attempts at low temperature or at room temperature using NaH or KH led to decomposition of **2.8a**(Scheme 2.6).

SCHEME-2.6:



Compound**2.8a** was converted to the TBS-enol ether **2.15** with KH at room temperature in the presence of TBS-C1.[10,12] Attempted alkylation of **2.15** with isoprenyl bromide in the presence zinc bromide[11]led to its decomposition. Complex **2.8a** was also converted to the TMS-enolether**2.16** by treatment with TMS-OTF/Et_3N in ether.[13] Treatment of **2.16** with MeLi to generate the lithium enolate[14] was not clean. Considerable attack on the Cpring bymethyllithium was observed[15] by the ^{1}H NMR spectra of the crude reaction products. Direct oxidation of the TMS-enolether with mCPBA[16] to an α-hydroxy ketone was also unsuccessful (Scheme 2.7).

SCHEME-2.7:



Alkylation of **2.8a** was eventually achieved by treatment with excess potassium hydride in THF at room temperature in the presence of excess alkylating agent. However, the stereoselectivity was not good in this case. With methyl iodide,anequimolar mixture of the two epimers**2.17** and **2.18** was obtained. Benzyl bromide gave two epimericproducts (**2.19** and **2.20**) in the ratio of 3.5:1. No attempts were made to determine the stereochemistry of the major product. This is summarized in Scheme 2.8. The benzylationreaction was carried out in the presence of nBu_4NI; without it, no products were observed. Allylation reaction gave the monoallylated product **2.34** and the unexpected diallylated product **2.35** in 1:1 ratio. No attempts were made to determine the stereochemistry of the monoallylated compound **2.34**.

SCHEME-2.8:

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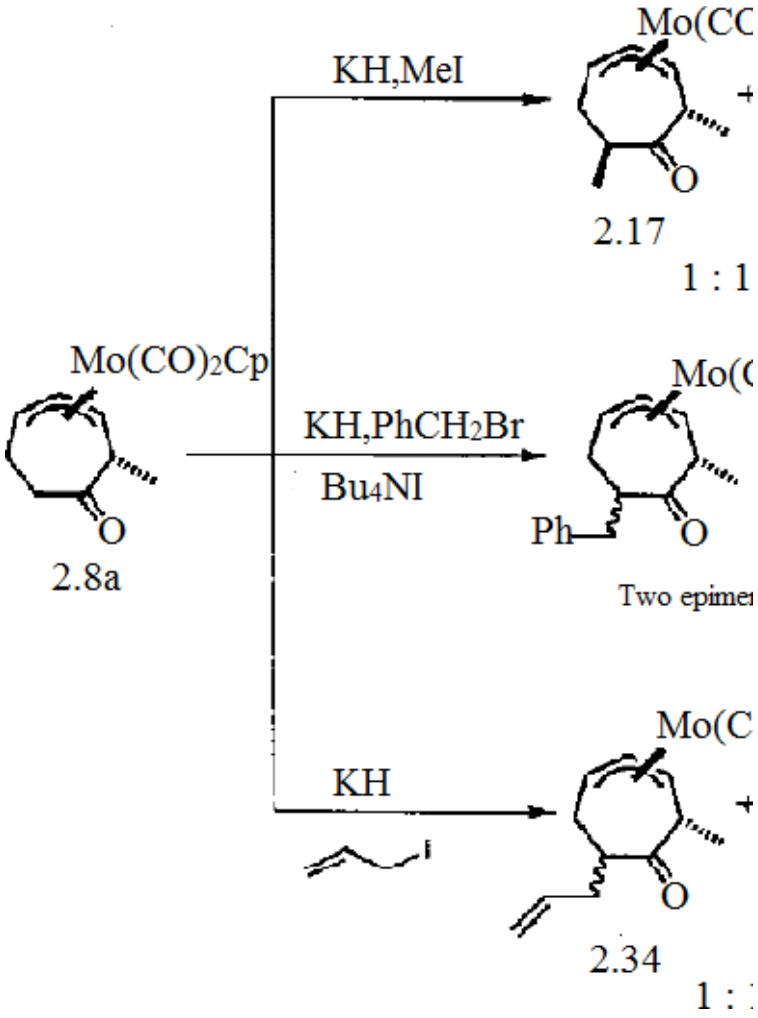
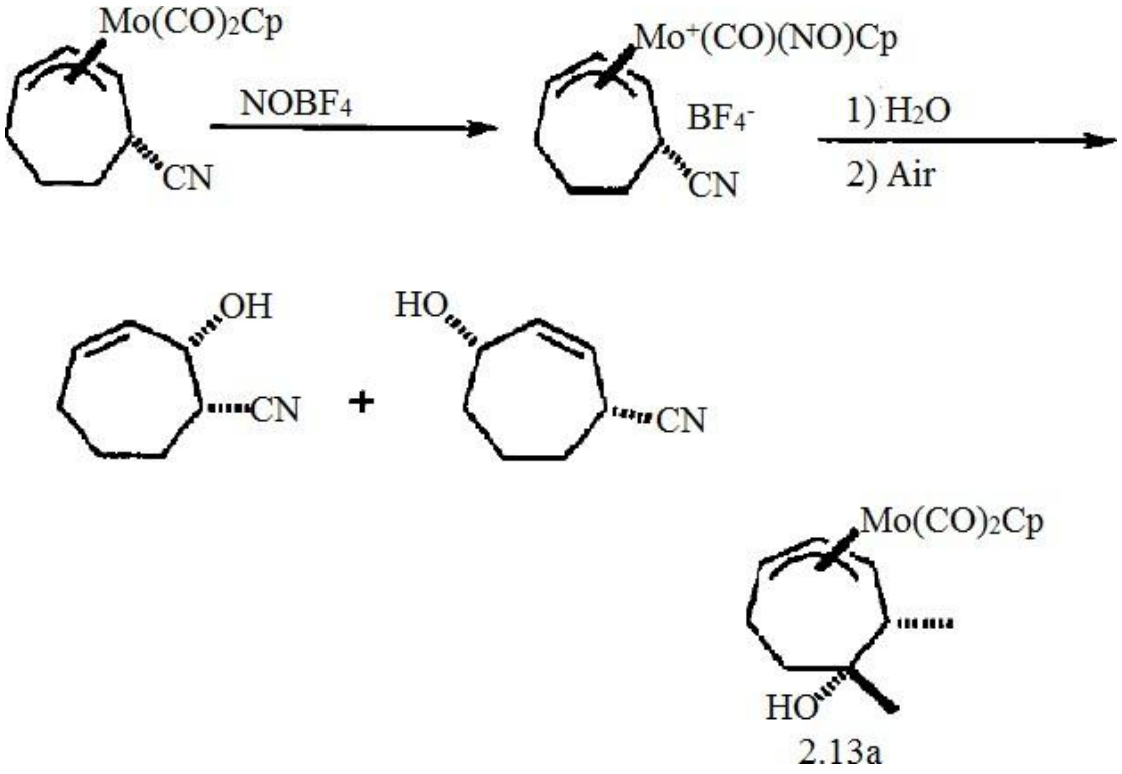


2.4 DECOMPLEXATION:

The π-allyl-$Mo(CO)_2Cp$ does not translate directly to a stable organic moiety upon demetallation. So, decomplexation generally involves simultaneous introduction of additional functionality.Faller *et.* al. and Pearson *et. al.* have treated π-allyl-$Mo(CO)_2Cp$ complexes with $NOBF_4$ to generate cationic molybdenum complexes. Here the π-ally1 group is sufficiently activated for attack by nucleophiles to generate an alkene-molybdenum complex which is oxidized by air to release the organic molecule (Scheme 2.9, taken from ref. 4).

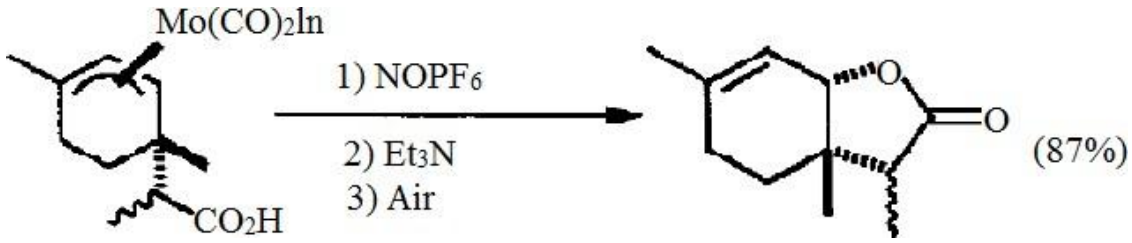
SCHEME-2.9:



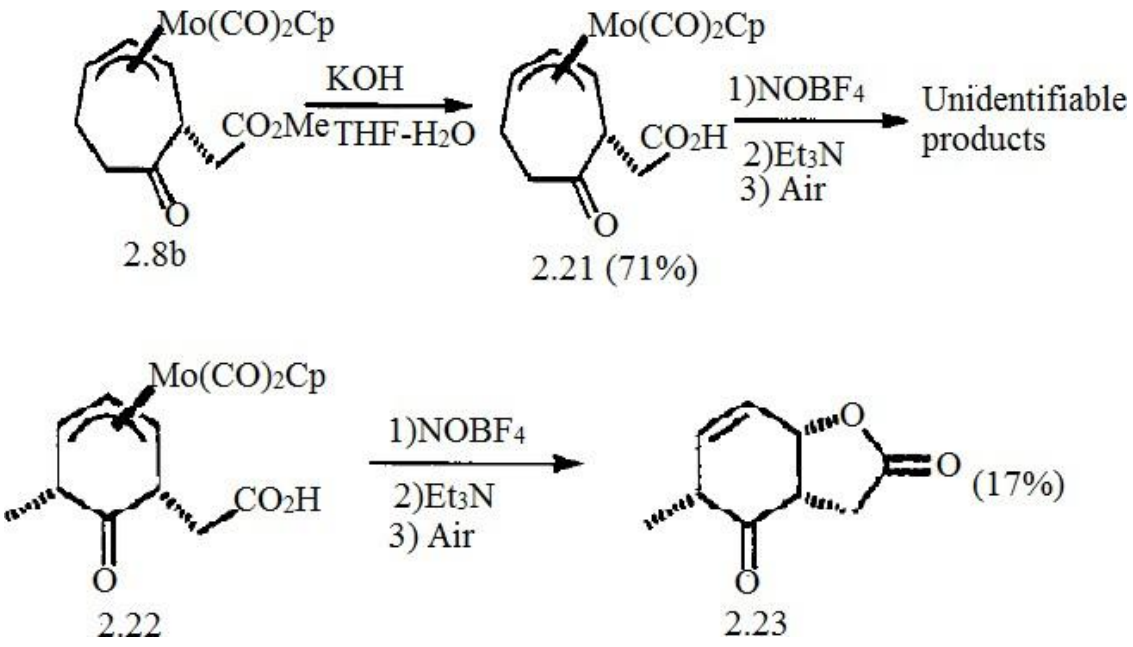
2.13a

Application of this procedure to **2.13a**led to unidentifiable products possibly due to the presence of a hydroxyl group in **2.13a**.

This method suffers from the drawback that two regioisomericproducts are obtained. To obviate this difficulty, Pearson has developed an alternative procedure involving an internal nucleophile as illustrated below:

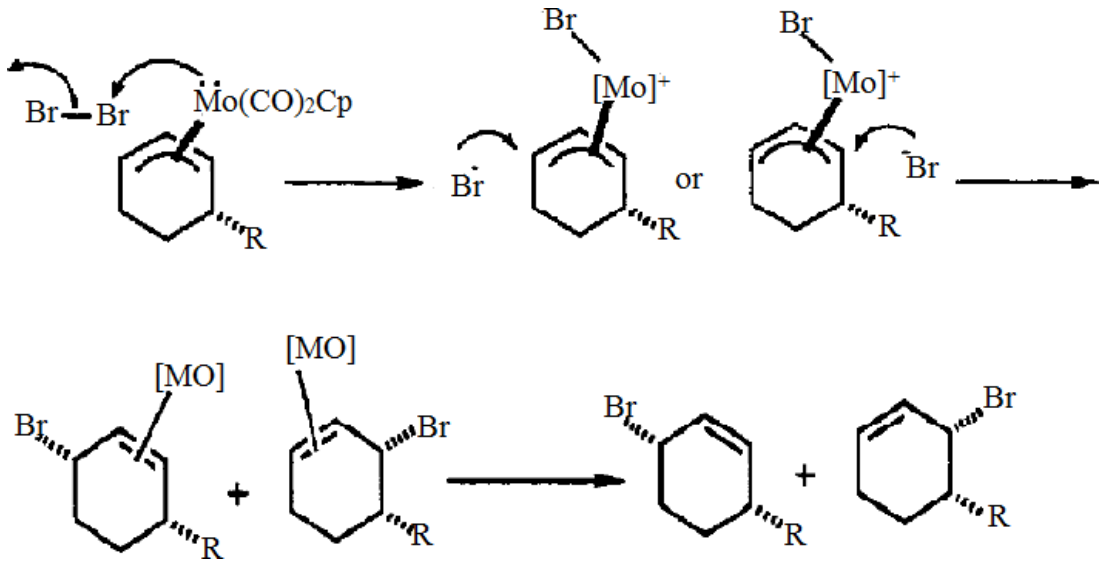


Attempted decomplexation of**2.21**using this lactonizationprocedure was also unsuccessful. This is presumably due to the presence of the ketone carbonyl group in the molecule. It is worthwhile to note that the demetallation of**2.22**using this procedure gave the desired product**2.23**in only 17% yield.



Bromine or iodine can also be used to decomplex π-allylMo(CO)$_2$Cp systems giving allylic bromide or iodide as the product as illustrated in Scheme 2.10.

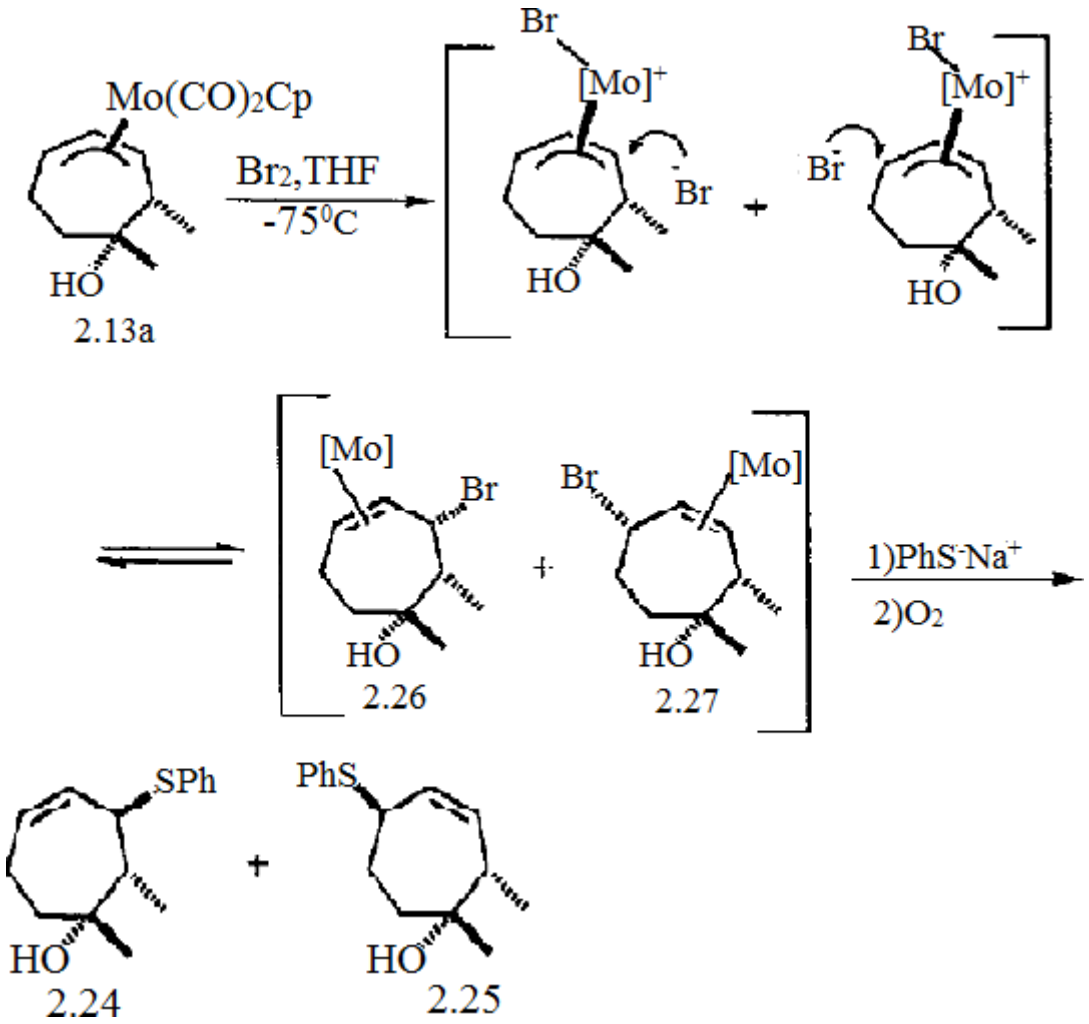
SCHEME-2.10:



Treatment of the tertiary alcohol **2.13a** with bromine gave a mixture of allylic bromides which could not be purified chromatographically owing to their facile

rearrangement on silica gel. Reaction of **2.13a** with bromine followed by in *situ* treatment with sodium thiophenoxide gave good yields of the stable allylicthioethers**2.24** and **2.25.** The ratio of the two products was found to depend on reaction temperature; at -75 ^{0}C, a 3:1 mixture in favor of **2.24** was obtained while at 0 ^{O}C, a 2:1 mixture was produced. Selectivity for the reaction was lost when carried out under oxygen atmosphere at -75 ^{0}C. This implies that the second step in the reaction mechanism (Scheme 2.10) is probably reversible and in the absence of oxygen, a thermodynamic mixture of the two allylic bromides is obtained. Oxygen decomplexes the alkene complexes (**2.26** and **2.27**) faster than the rate of equilibration (Scheme 2.11).

SCHEME-2.11:



Temprature	**2.25 : 2.24**	**Yield[a]**
-75^{0}C	3 : 1	89%
0^{0}C	2 : 1	72%
-75^{0}C,O_2	1 : 1	97%

a) based on recovered starting material

DISCUSSION:

There are marked differences in the stereodirecting power of $Mo(CO)_2Cp$ attached to six or seven membered ring π-allyl ligands. In six membered rings, both unsubstituted and mono substitute complexes were found by X-ray crystallography to have a chairconformation for the cyclohexenyl ring. The conformation of the 4β,6β-dimethyl cyclohexenyl ring was also deduced to be a chair form (by NMR analysis) where the two methyl groups are axially oriented (Figure 2.6). The same is also true for monosubstituted complexes. It appears that the effective bulk of the $Mo(CO)_2Cp$ moiety is the controllingfactor in all these cases, which is also responsible (in part) for all nucleophile additions to diene-molybdenum complexes to occur *anti* to the metal.

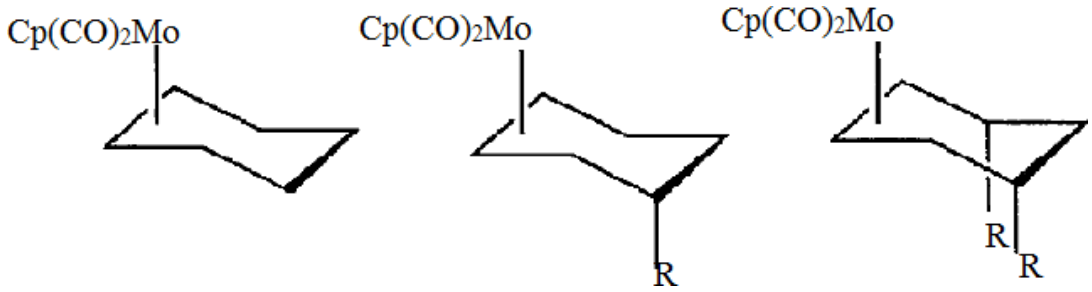
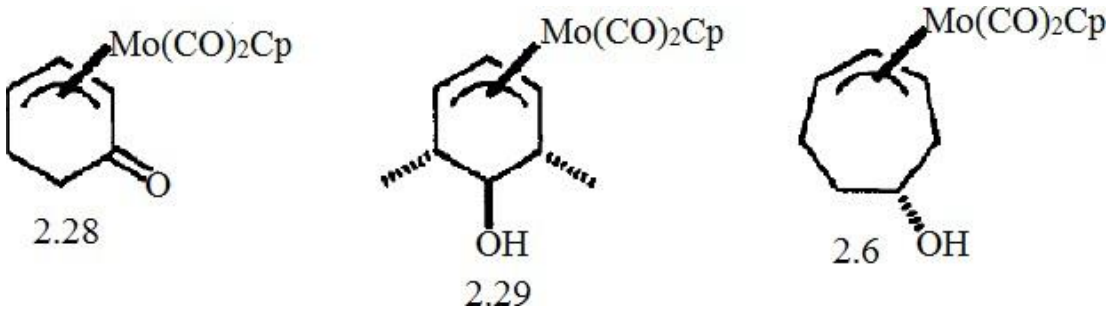


Figure 2.6. Chair conformation for cyclohexnyl – $Mo(CO)_2Cp$

The six membered ring ketone complex **2.28** was found to have a flattened chair conformations and the compound **2.29** also showed a chair conformation (determined by NMR analysis) in which all substituents are axial.[7]



Theseven membered ring in cycloheptenyl-$Mo(CO)_2Cp$ appears to be conformationally more mobile. Introduction of substituents leads to C-C bond rotations to place the ring in a half-chair conformation (e.g., see X-ray structure of **2.6**). For **2.6**, this relieves the eclipsing

interactions between C-OH and C-6-H bonds, between C-4 - C-5 and C-6 - C-7 bonds and between C-Mo and C-4 - C-5 or C-6 - C-7 bonds (Figure 2.7).

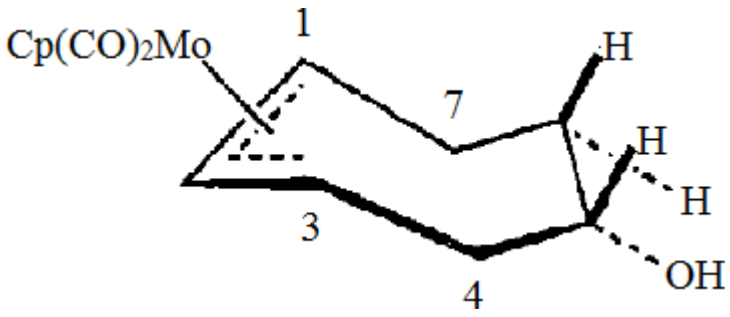


Figure 2.7. Chair conformation of 2.6 showing eclipsing interactions

The mono substituted complexes **2.8** seem to adopt a half chair conformation as shown in Figure 2.8. Nucleophiles now attack *syn*to molybdenum because *anti* attack is hindered by the ring carbons.

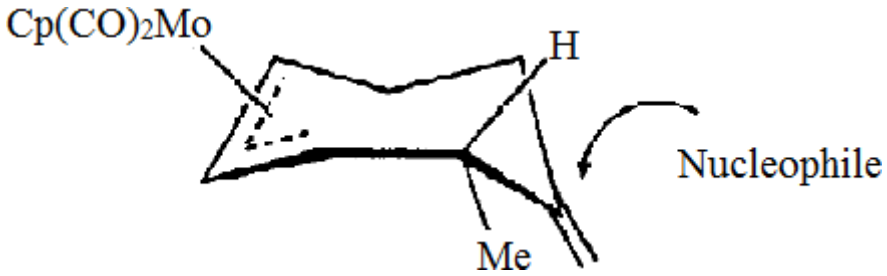
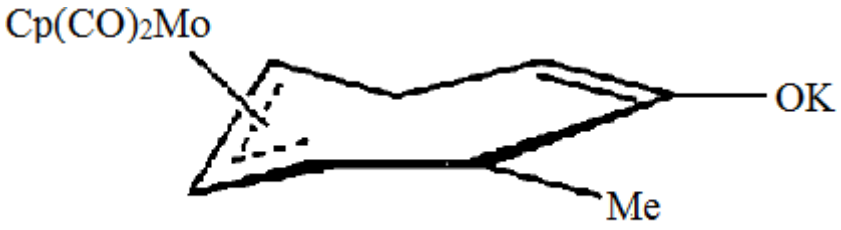


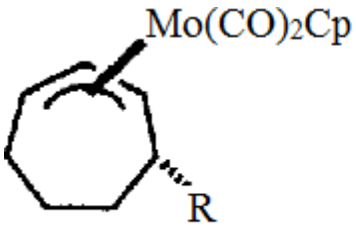
Figure 2.8.Half chair conformation of **2.8** showing quasi-equatorial methyland endo nucleophile approach

This conformation places the methyl group in quasi equatorial position and the two C-6-H bonds almost orthogonal to the ketone π-system. So, deprotonation is expected to be slow as was indeed observed. The proton on C-4 is not abstracted due to steric hindrance. The enolate, once formed under forcing conditions, possibly adopts a conformation (**2.34**) where there is very little steric bias for the two diastereotopicfaces.Thus, the alkylations were not stereoselective.

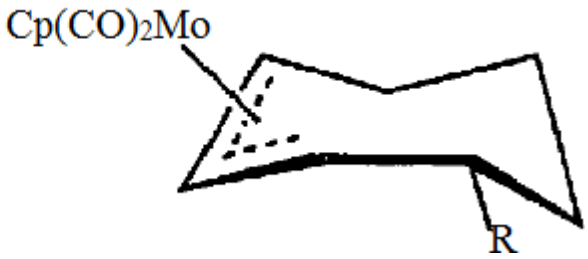


2.34

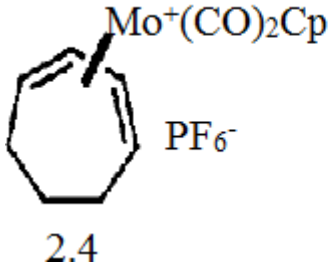
The tertiary alcohol **2.13a** was found to have a half chair conformation by X-ray crystallography. It is interesting to note that mono substituted cycloheptenyl-$Mo(CO)_2Cp$ complexes of the type **2.30**also adopt a half chair conformation as evidenced by NMR spectroscopy.[8] This places the substituent R in a quasi equatorialposition.



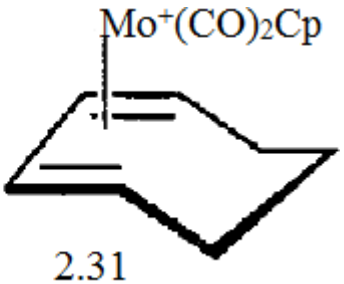
2.30



It is also worthwhile to note the conformation of the cationic cycloheptadienyl-$Mo(CO)_2Cp$ complex **2.4**. Though no X-ray data areavailable, analysis of coupling constants in the NMR spectrum strongly suggests of a chair conformation **2.31**.[8]



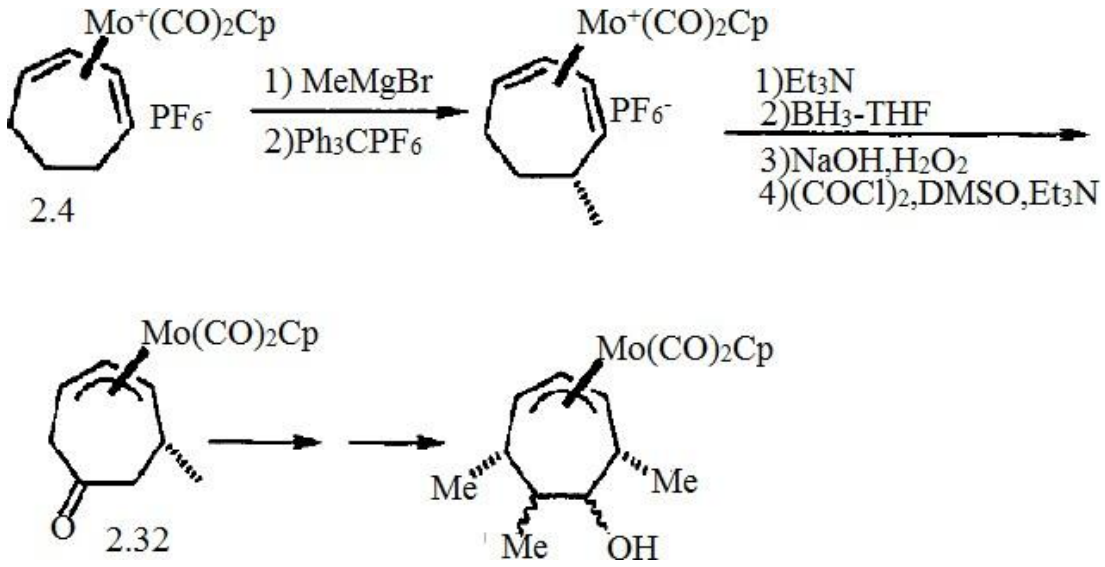
2.4



2.31

With these precedents, it would be interesting to study the enolate chemistry of the ketone **2.32**. Preliminary experiments conducted in our laboratory indicate that **2.32** can be synthesized in a fashion analogous to **2.3** (Scheme 2.12) starting from **2.4**. Enolate formation and alkylation followed by demetallation will lead to a cycloheptene ring with five carbon atoms functionalized.

SCHEME-2.12:



As mentioned earlier, the π-ally1 moiety is not transformed directly to a stable organic molecule upon decomplexation. Though several methods exist for demetallation accompanied by the introduction of new functionality, they are often limited in scope with regard to the new functionality introduced. Thus decomplexation of π-allyl$Mo(CO)_2Cp$ complexes is another area of future research.

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