Organolanthanide Reagents and the Mukaiyama Reaction

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Abstract

The bis(pentamethylcyclopentadienyl) lutetium halide complex $[(C_5Me_5)_2LuCl \cdot THF]$ was synthesized and characterized. The crystal structure of this complex shows that the Lu is at the center of a distorted tetrahedron consisting of the centroids of two cyclopentadienyl rings, the oxygen atom of a tetrahydrofuran molecule and a chlorine atom. All of the methyl groups on the cyclopentadienyl rings are bent out of the planes of the rings, away from the lutetium atom, such that the least-squares planes through the methyl groups are on an average 0.22 Å farther away from the lutetium atom than the plane of the cyclopentadienyl rings. This bending phenomenon may be attributed to steric effects as well as an electronic effect.

1H NMR studies of toluene- d_6 solutions of $(C_5Me_5)_2LuCl(THF) + THF$, $(TMS_2Cp)_2LuCl(THF) + THF$, and $(MeCp)_2LuCl(THF) + THF$ at various temperatures showed exchange processes between co-ordinated THF and free THF with average values of $\Delta G^\ddagger$ of 13.0 ± 0.3 kcal/mol, 11.1 ± 0.1 kcal/mol and < 11 kcal/mol at 0 °C, respectively. This increase in activation energy with increase in steric crowdedness suggests that a concerted associative pathway is a possible mechanism.

It has been found that under the influence of a catalytic amount (1-5 mol %) of $(TMS_2Cp)_2YbCl$ dimer, silyl enol ethers $(R_1R_2C=C(OR_3)(OSiMe_3))$ react with benzaldehyde smoothly in dichloromethane at room temperature, giving >99% of the aldol silyl ether (isolated yield: 90%) within 3 h. At -78°C, the reaction gives kinetically controlled diastereoselectivity, which was not observed in the

TiCl_4 -mediated aldol reaction. A cyclic transition state model is, therefore, postulated. This cross aldol reaction finds some generality. For example, both aromatic aldehydes and aliphatic aldehydes are usable as receptors. When α , β -unsaturated aldehydes were used, only 1,2-addition products were formed (50-70%). This reaction also displays some chemoselectivity. Aldehydes undergo the aldol reaction quite readily, while ordinary aliphatic or aromatic ketones do not form the aldol adducts at all. In addition, silyl enol ethers derived from ketones or the cyclopropane derivative do not react with aldehydes.

The mechanism of this aldol reaction catalyzed by $[(\text{TMS}_2\text{Cp})_2\text{YbCl}]_2$ has been studied in detail. In dichloromethane- d_2 , the reaction between the silyl enol ether of methyl isobutyrate and benzaldehyde proceeds with pseudo-first order kinetics in the silyl enol ether in the presence of 5-10% of the catalyst and an excess amount of trimethylchlorosilane (TMSCl). The excess TMSCl is essential to facilitate the reaction, and to insure that the reaction undergoes first-order kinetics. A study with a series of substituted benzaldehydes in the reaction with the silyl enol ether of methyl isobutyrate demonstrates that the reaction rate is slightly dependent on the electronic nature of the substituents (small Hammett ρ value of 0.36 ± 0.05), with electron-withdrawing groups increasing the rate. Evidence suggests that the course of the reaction follows a three-step pathway: fast complexation, slow addition, and fast subsequent equilibrium.

The use of organoytterbium enolates shows promise result with respect to increased stereoselectivity, and indicates the importance of the bulky ligands on the metal center. In addition, Yb(III) species can retard retroaldol reaction owing to its mild Lewis acidity.

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Chapter 1

Structure of $(C_5Me_5)_2LuCl(THF)$ and Exchange of Coordinated Solvent in Three Associated Systems

1.1 Introduction

One of the most rapidly developing areas of organometallic chemistry currently is organolanthanide chemistry. In the past few years, interest in this field has been expanded from an area involving a narrow range of ionic cyclopentadienyl species such as $(C_5H_5)_3Ln$, $[(C_5H_5)_2LnCl]_2$, and $[(C_5H_5)_2LnR]_2$ (Ln =Lanthanide metal ions; R =alkyl or aryl), to an area encompassing a wide variety of new classes of organometallic complexes which often have unique structures and spectacular reactivities [1].

The lanthanides are generally defined as those 14 elements ($Z=58-71$) which follow lanthanum in the Periodic Table. Lanthanum ($Z=57$) is not, strictly, a lanthanide element because there is no f-electron in its ground electronic configuration ($Ln^0=[Xe]5d^16s^2$). However, its chemical and physical behavior is so similar to that of the lanthanide elements that it is usually included in the lanthanide series. For the same argument, yttrium is also treated as a lanthanide-like element. The lanthanide elements differ from other metals in that their valence electrons are in 4f orbitals. Calculations of the $[Xe]4f^n$ electron

configurations of the lanthanides indicate that the 4f orbitals do not have significant radial extension beyond the filled $5s^25p^6$ orbitals of the xenon inert gas core [2]. As a result, in their most common oxidation state, the external appearance of a lanthanide ion is like that of an inert gas with positive charges. In this sense, the lanthanides are similar to alkali or alkaline earth ions. Lanthanide chemistry is, therefore, predominantly an ionic chemistry [3]. In addition, a given class of lanthanide complexes usually displays similar chemical behavior regardless of the particular metal or 4fⁿ configuration involved due to the limitation of the radial extension of 4f orbitals. Thus, a single symbol, Ln, is designated for all lanthanide elements. However, a recent close examination reveals differences in the chemistry of the lanthanides due to the gradually changing radial size of the elements, which decreases from 1.061 Å for La³⁺ to 0.848 Å for Lu³⁺ [4]. Another similarity across the series is that +3 oxidation state is the most stable for every element [3] although there are two nontrivalent oxidation states, +2, +4 accessible under normal conditions: Ce⁴⁺(4f⁰), Eu²⁺(4f⁷), Yb²⁺(4f¹⁴), Sm²⁺(4f⁶).

There are two generalizations used to judge the stabilization of organometallic complexes of the lanthanide elements. First, in these ionic systems, the +3 charge must be balanced, and electrostatic interactions must be optimized. These can be achieved with the use of stable organic anions as ligands. Second, the stability of a complex must be enhanced with proper choices of ligand sizes to fill the coordination sphere of the metal ion. Either overcrowdedness or undercrowdedness will lead to the decomposition of organolanthanide complexes. Since the second requirement is not that easy to fulfill, Lu, Yb and Er are studied more often than the other elements in the series. For these small elements, it is less

difficult to sterically saturate their centers [1].

The highly ionic nature of organolanthanides makes them difficult to handle since they are extremely air and moisture sensitive. In addition, the lanthanides are generally unable to undergo two-electron oxidation-reduction cycles, which are so important in catalytic transition metal chemistry in 18 $\rightarrow$ 16 electron complexes. Moreover, the diversity of chemical reactivity found in transition metals as the metal changes across the series or as the oxidation state of a given metal changes is not found in the lanthanide series, where all of the metals have similar chemistry and a single oxidation state predominates [1]. These facts appear disadvantageous and disappointing.

More recently, however, it has been realized that the lanthanide elements have great potential for unique chemistry [5], which cannot be achieved with transition elements. For example, the similarity of organolanthanide chemistry among the lanthanide series offers the potential to vary reactivity precisely by selecting the appropriately sized metal from the 14 choices. It has been shown that reactivities can be altered quite substantially [5]. Furthermore, the large size, ionic, and electropositive character of the lanthanides, properties which cause the chemistry to be experimentally difficult, make the lanthanides strongly electrophilic and oxophilic. These properties, in fact, can also impart unusual chemistry.

Due to the uniqueness of the lanthanide chemistry, the synthesis of organolanthanide complexes appears more interesting. Many types of these complexes have been successfully synthesized with different choices of ligands such as cyclopentadienyl, mono-, di-, penta-substituted cyclopentadienyls, different substituted cyclooctatetraenes, halides, alkyls and aryls [6, 7, 8].

Since the bis(cyclopentadienyl) lanthanide halide complexes are basic precursors in the organometallic chemistry of these elements [9], here we just focus on this type of complex.

The bis(cyclopentadienyl)lanthanide(III) halide complexes fall into three main classes: (i) homometallic complexes of formula $[\text{Ln}(\eta^5\text{-Cp}')_2(\mu\text{-X})]_2$ (Ln =a lanthanide element(III), Cp' =cyclopentadienyl or substituted cyclopentadienyl ligand), (ii) heterometallic complexes of formula $[\text{Ln}(\eta^5\text{-Cp}')_2(\mu\text{-X})_2\text{ML}_2]$, (L =a monodentate neutral ligand such as THF, or L_2 =a bidentate neutral ligand such as TMEDA, M =alkali metal ions such as Li^+ , Na^+ , K^+), and (iii) monometallic complexes of formula $[\text{Ln}(\eta^5\text{-Cp}')_2\text{XL}]$.

Preparation and Properties of Class (i) Complexes. Most of the earlier preparations were directed at unsubstituted cyclopentadienyls, (C_5H_5), although in few instances simple derivatives such as MeC_5H_4 analogues were also sought. Lately, there has been much interest in bulky or rigid cyclopentadienyl ligands such as $(\text{C}_5\text{Me}_5)^-$, $[1,1'-(\text{CH}_2)_3(\text{C}_5\text{H}_4)_2]^{2-}$, or $[\text{C}_5\text{H}_3(\text{TMS})_2]^-$. These bulky ligands may kinetically stabilize early ($4f^0$ – $4f^3$) lanthanocene(III) halides, which are inaccessible for $(\text{C}_5\text{H}_5)^-$ or simple derivatives [8].

There are various routes available to produce class (i) complexes, as illustrated by the preparations shown below:

(1) salt elimination [10] (which may involve an intermediate heterometallic Ln-M complex)

Cp' =cyclopentadienyl or substituted cyclopentadienyl.

(2) ligand redistribution [11]

(3) Ln-Cp' cleavage using HCl or NH₄Cl [11]

There are two more types, which are available for organoytterbium(III) iodides, namely (4) cleavage by I₂ [11] and (5) Ln(Cp')₂ oxidation by I₂ [12].

The lanthanocene(III) chlorides are mostly colored, volatile, air and moisture-sensitive solids. They are monomeric in coordinating solvents such as THF, but dimeric in non-polar solvents (e.g., benzene) and in the solid state. The substituted derivatives are significantly more soluble in non-polar solvents than those of the Cp analogues, and the trimethylsilyl derivatives, TMSCp and TMS₂Cp, offer particularly good hydrocarbon solubility.

Preparation and Properties of Heterometallic Complexes. The general synthetic method for this class of complex is shown below [13, 14]:

An alternative procedure for iodo-complexes has used the oxidative addition reaction of eq. 1.7 [15], but these compounds are also accessible from

$\text{LnI}_3 + 2\text{MCp}'$ [16].

The heterometallic complexes, in most cases, melt with decomposition in the range of 100–250 °C. All are soluble in common organic solvents. The coordinated tetrahydrofuran molecules in $[\text{Ln}(\eta^5\text{-Cp}')_2(\mu\text{-Cl})_2\text{Li}(\text{THF})_2]$ can be displaced by OEt_2 (excess), 1/2 DME, or 1/2 TMEDA [14].

The effect of heat on the complexes $[\text{Ln}(\eta^5\text{-Cp}')_2(\mu\text{-Cl})_2\text{Li}(\text{THF})_2]$ is to drive off the THF; the resulting solids, in some cases, have been crystallized from a toluene extract [10], or sublimed, affording the homometallic complex $[\text{Ln}(\eta^5\text{-Cp}')_2(\mu\text{-Cl})_2]$. An alternative procedure for removing ligated THF or OEt_2 is by prolonged vigorous stirring in hexane or toluene as shown in eq. 1.8.

Preparation and Properties of Monometallic Complexes. There are several ways to make this type of complex.

(i) Elimination of coordinated alkali halide [13]

It has been found that this method is applicable only when $\text{M}=\text{Na}$. In other words, the analogous lithium salts are much more stable with respect to loss of

LiCl since they do not undergo this disproportionation in toluene.

(ii) Addition of THF [17]

(iii) Oxidation with alkyl halides [9]

(iv) Decomposition of methyl halide [19]

This type of complex is soluble in toluene and somewhat soluble in hexane. The halides can be replaced by nucleophilic reagents to provide routes to lanthanocene complexes having Ln-C, Ln-N, Ln-P, Ln-O, Ln-H bonds.

It is well known that a given class of lanthanide complex exhibits similar chemical behavior. Recently, it has been realized that small changes in the size of the metal and the steric crowding caused by ligands can have substantial effects on the reactivities [18].

An illustrative example [18] of how small changes in steric crowding can have large effects on stability is provided by the comparison of $(\text{C}_5\text{H}_5)_2\text{Yb}(\text{CH}_3)(\text{THF})$ with the lutetium analogue $(\text{C}_5\text{H}_5)_2\text{Lu}(\text{CH}_3)(\text{THF})$. The lutetium complex is reported to decompose below 20 °C [19], whereas a room temperature crystal structure of the ytterbium analogue was readily obtained. The main difference between these two complexes is the 0.008-0.01 Å difference in ionic radius of the metals. This small change in the size of the metal ions causes the lutetium derivative to be slightly more sterically crowded. The crowding may

enhance the THF extrusion process and cause the decomposition to occur more readily. Similarly, both $[(C_5H_5)_2LuH(THF)]_2$ and $(CH_3C_5H_4)_2Lu(t-C_4H_9)(THF)$ are less stable than the analogous erbium or yttrium complexes [20].

Another example is the hydrogenolysis of organolanthanide complexes. The structural data indicate that, for a given metal, the $(C_5H_5)_2Lu(t-C_4H_9)(THF)$ complex is significantly more crowded than $(C_5H_5)_2Lu(CH_2SiMe_3)(THF)$ or $(C_5H_5)_2Lu(CH_3)(THF)$ [20]. Consistent with the crystallographically established steric congestion, it is found that $(C_5H_5)_2Lu(t-C_4H_9)(THF)$ is unreactive towards H_2 in THF in which it is likely to be fully solvated; however, a rapid hydrogenolysis was observed in toluene to give a good yield of $[(C_5H_5)_2LuH(THF)]_2$ product. The rapid reactivity towards H_2 in toluene is probably derived from $(C_5H_5)_2Lu(t-C_4H_9)$, a highly reactive, sterically unsaturated, unsolvated species. The same phenomenon was found in the reactivity of $[(CH_3C_5H_4)_2Yb(\mu-CH_3)]_2$. This species reacted rather sluggishly in toluene, but rapidly in THF/toluene (1:10) mixed solvents. In the later case, the presence of coordinated solvent THF could effect a bridge cleavage, leading to $(C_5H_5)_2Yb(CH_3)(THF)$ and $(C_5H_5)_2Y(CH_3)$, species more reactive, less sterically saturated than the double bridged dimer. This example clearly indicates that the solvent and degree of association of a complex can be as important as the size of the metal and the alkyl ligand.

In conclusion, there are several ways to finely manipulate the reactivity of organolanthanide complexes, providing a level of control unusual in organometallic chemistry. The fact that the lanthanide elements constitute the largest series of metals with similar chemistry but a gradually changing radial size makes these metals ideal for this sterically based variation of reactivity [5].

1.2 Results and Discussion

1.2.1 Structure Analysis. As stated before, the halide derivatives of organolanthanides are important starting materials for further synthetic transformations. Several such bis(pentamethylcyclopentadienyl) lanthanide(III) halides have been crystallographically characterized as alkali halide complexes of the general formula $(C_5Me_5)_2LnX_2ML_2$ ($X=Cl, I$; $M=Li, Na$; L =coordinated solvent molecules) [16, 21, 22]. For the simple parent solvated bis(pentamethylcyclopentadienyl) lanthanide halide complexes, $(C_5Me_5)_2LnX \cdot L$, the corresponding ytterbium complex had been reported but crystals suitable for X-ray structure determination were not obtained [13, 16]. In order to study this type of compound, $(C_5Me_5)_2LuCl(THF)$ was synthesized and characterized by X-ray structure determination. Lutetium was chosen to work with because Lu(III) compounds are diamagnetic and permit 1H NMR studies. Lately, several compounds of this type have been reported [9]. They provide some interesting structural comparisons.

$(C_5Me_5)_2LuCl \cdot THF$ was made by Tilly and Andersen's method [13]. A THF solution of $LuCl_3$ and NaC_5Me_5 in 1:2 molar ratio was refluxed for 15 h, followed by removal of THF. The residue was extracted with toluene, a non-polar solvent assisting the elimination of the NaCl salt. The toluene filtrate was then concentrated and cooled to $-30^\circ C$ overnight, giving transparent, needle crystals of $(C_5Me_5)_2LuCl \cdot THF$. The synthetic process can be best illustrated by the following scheme:

The structure of $(\text{C}_5\text{Me}_5)_2\text{LuCl} \cdot \text{THF}$ solved by Dr. A. Zalkin at Lawrence Berkeley Laboratory shows that the lutetium atom is at the center of a distorted tetrahedral array of two pentamethylcyclopentadienyl rings, a chloride atom, and an oxygen atom of a tetrahydrofuran molecule. The structure has average lutetium-carbon distances of 2.63 Å; the distance of the lutetium atom to the least-squares plane of the C_5Me_5 ring is 2.34 Å. The $\text{C}_5\text{Me}_5\text{--Lu--C}_5\text{Me}_5$, $\text{C}_5\text{Me}_5\text{--Lu--Cl}$, and $\text{C}_5\text{Me}_5\text{--Lu--THF}$ angles are 137, 105 and 105°, respectively.

The orientation of the two pentamethylcyclopentadienyl rings is fully staggered as shown in figure 1.1.

Fig.1.1 ORTEP Diagram of $(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF})$ from top view

However, Watson [16] has observed that in $(\text{C}_5\text{Me}_5)_2\text{Yb}(\mu\text{-Cl})_2\text{Li}(\text{OEt})_2$ and

$(C_5Me_5)_2Yb(\mu-Cl)_2AlCl_2$, the two rings do not show a perfectly staggered conformation. Her assumption was that nonbonded repulsion between the halide and the methyl groups causes deviation from the fully staggered conformation in which ring methyl groups were maximally distant from each other. This assumption was further proved by the fact that the replacement of chlorine atoms (van der Waals radius 1.8 Å) [31] by large iodine atoms (van der Waals radius 1.95–2.12 Å) as in $(C_5Me_5)_2Yb(\mu-I)_2Li(OEt)_2$ imposes an even greater steric constraint [16]. In the iodine complex, the two rings are eclipsed. The staggered orientation in $(C_5Me_5)_2LuCl \cdot THF$ suggests that the non-bonded repulsion between methyl groups and chloride atom do not overcome the repulsion between methyl groups although it will be shown later that both groups (Me–Cl and Me–Me) are in close van der Waals contacts.

The average lutetium-carbon length in $(C_5Me_5)_2LuCl \cdot THF$ is 2.634 Å, yielding 1.657 Å for the effective ionic radius of a pentamethylcyclopentadienyl ring. This value is compared to those found in $(C_5Me_5)_2YCl \cdot THF$, $(C_5Me_5)_2SmCl \cdot THF$, and $(C_5Me_5)_2SmI \cdot THF$ [9] in Table 1.1.

Table 1.1
X-ray Diffraction Data

entry	complex	D(Ln-C)	R(Ln(III)) (Å)	R(Cp) (Å)
1	$(C_5Me_5)_2LuCl \cdot THF$	2.634	0.977	1.657
2	$(C_5Me_5)_2YCl \cdot THF$	2.655	1.019	1.636
3	$(C_5Me_5)_2SmCl \cdot THF$	2.72	1.079	1.641
4	$(C_5Me_5)_2SmI \cdot THF$	2.725	1.079	1.646

The ionic radius in these structures for the C_5Me_5 ligand is essentially invariant with an average value of 1.645 ± 0.007 Å.

Table 1.2 gives all the Ln-X and Ln-O bond lengths in these four analogues.

Table 1.2
X-ray Diffraction Data (Å)

Complex	D(Ln-X)	R(Ln(III))	R(X)	D(Ln-O)	R(O)
$(C_5Me_5)_2LuCl \cdot THF$	2.529	0.977	1.552	2.340	1.363
$(C_5Me_5)_2YCl \cdot THF$	2.578	1.019	1.559	2.41	1.39
$(C_5Me_5)_2SmCl \cdot THF$	2.737	1.079	1.658	2.46	1.28
$(C_5Me_5)_2SmI \cdot THF$	3.048	1.079	1.969	2.45	1.27

The ionic radii for the chloride atoms in these three compounds are within the range of 1.55–1.69 Å, which is typical for terminal chlorides [18]. The average ionic radii for the oxygen atoms vary from about 1.37 Å for relatively small metal ions (Lu^{3+} , Y^{3+}) to 1.28 Å for a relatively big metal ion (Sm^{3+}).

The most striking feature of the $(C_5Me_5)_2LuCl \cdot THF$ molecular structure is that the pendant methyl groups of the C_5Me_5 rings are significantly bent from the C_5 ring planes, lying on the opposite sides of the C_5 rings from Lu. The least-squares planes through the methyl groups are on the average 0.22 Å farther away from the lutetium atom than the plane of the cyclopentadienyl ring. The molecular structure and atom numbering scheme for this molecule are shown below.

Fig.1.2 ORTEP Diagram of $(\text{Me}_5\text{C}_5)_2\text{LuCl}(\text{THF})$

Table 1.3 presents all the deviations of methyl groups from C_5 planes.

Table 1.3
Bending Angles and Distances ($\text{\AA}$)

	Angle	Distance		Angle	Distance
C(11)	8.880	0.2404	C(16)	4.902	0.1380
C(12)	5.439	0.1491	C(17)	7.922	0.2226
C(13)	12.97	0.3591	C(18)	5.408	0.1489
C(14)	8.574	0.2345	C(19)	4.578	0.1270

The largest deviation in each ring is $0.36 \text{ \AA}$ (13°) for C(13) and

0.33 Å (12°) for C(19). Such out-of-plane displacements have been explained previously for the related system $[(C_5Me_5)_2Yb \cdot THF]$ in terms of mutual repulsions of the methyl groups in the two coordinated C_5Me_5 rings from intramolecular contacts for the methyl groups [26]; in other respects the C_5Me_5 groups have normal geometries. Similar distorted tetrahedral structures and out-of-plane displacements have also been observed for $(C_5Me_5)_2YbCl_2Li(OEt)_2$ [16], $(\mu-N_2)[(C_5Me_5)_2ZrN_2]_2$ [27], and $(C_5Me_5)_2TiCl_2$ [28], in which the distances between the metal and C_5 rings are 2.61, 2.54, 2.44 Å, respectively. For large metal atoms, such as thorium in bis[(but-2-ene-2,3-diolato)bis(pentadienyl)thorium] with $Th-C_{av.}=2.84$ Å, however, the methyl groups lie in the plane of the C_5 rings [29]. Obviously, the ring-ring distances play a critical rule in these bending phenomena. From Table 1.4, one can see that the closest distances between two methyl groups on each C_5 ring are 3.42 [C(13)–C(18)] and 3.50 Å [C(13)–C(19)]. In addition, the distances of chlorine and oxygen atoms from the nearest methyl groups on each C_5 ring are 3.23 [C(11)–Cl], 2.67 [C(16)–O], 2.95 [C(15)–O], and 2.73 Å [C(17)–O].

Table 1.4
Interatomic Distances (Å)

atoms	distance	atoms	distance
C(11)-C(16)	5.765	C(14)-C(18)	4.090
C(11)-C(20)	5.536	C(14)-C(17)	5.391
C(12)-C(20)	4.349	C(15)-C(17)	5.328
C(12)-C(19)	3.910	C(15)-C(16)	6.530
C(13)-C(19)	3.497	C(15)-O	3.323
C(13)-C(18)	3.420	C(17)-O	2.734
C(16)-Cl	2.674	C(11)-Cl	3.232

These distances are close to or within the sum of the van der Waals radii listed in Table 1.5.

Table 1.5
van der Waals radii and distance(Å)

	R		R(sum)
<i>CH₃</i>	2.0	<i>CH₃-CH₃</i>	4.0
<i>Cl</i>	1.8	<i>CH₃-Cl</i>	3.8
<i>O</i>	1.4	<i>CH₃-O</i>	3.4

Consequently, the corresponding methyl groups are bent away significantly because of steric repulsions. Similar comparisons, however, show that some of the methyl groups are in positions where no obvious steric hindrance effects

exist, [C(14), C(20)], yet they are still bent significantly away from the ring planes. An *ab initio* SCF MO study of cyclopentadienyllithium showed that a similar bending of the ring hydrogens away from the lithium could be explained simply on the basis of an ionic model. This ionic model consists of a cyclopentadienyl anion and a point positive charge at the lithium location; such bending puts more negative charge on the face of the ring towards the lithium cation [30]. The same interpretation may apply in the present case to explain why those methyl groups that are not within the van der Waals contact distance of methyl groups are nevertheless bent away from the highly charged Lu^{3+} ion. In the case of thorium, this Coulombic effect is expected to be diminished by the larger distance between ligand and cation.

1.2.2 Exchange Process of Coordinated Solvent. Mass spectrum, IR, and ^1H NMR spectra of $(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF})$ are in good agreement with the solid state structure. The ^1H NMR spectrum at room temperature of a toluene- d_6 solution shows chemical shifts of the coordinated THF that are different from those of free THF in toluene- d_6 as listed below:

Table 1.6
Chemical Shifts

	$\delta_{\text{coord.}}$ (ppm)	δ_{free} (ppm)
α	3.37	3.50
β	1.26	1.44

A variable temperature 200 MHz ^1H NMR study of a solution in toluene- d_6 , 0.008 M in $(\text{C}_5\text{Me}_5)_2\text{LuCl}\cdot\text{THF}$ and 0.023 M in free THF showed single NMR peaks for the α - and β -protons due to the rapid exchange at room temperature, but separate peaks at -30°C : α -protons, δ_{free} 719.5, $\delta_{\text{coord.}}$ 680.0 Hz, coalescence temperature -5.1°C ; β -protons, δ_{free} 285.0, $\delta_{\text{coord.}}$ 220.0 Hz, coalescence temperature 9.8°C .

Theoretically, rates and activation parameters for the exchange process can be determined by computer simulated line-shape analysis of the broadened exchange peaks. By inputting frequency values for non-exchanging peaks, along with natural line widths, one can get best fit-curves generated by computer for specific mean nuclei lifetimes. At different temperatures, different exchange rates can be determined by the conversion of different nuclei lifetimes. Therefore, associated activation parameters can be obtained. In this case, however, the simulation method can not be applied due to the uncertainty in natural line widths of THF. This is because the splitting pattern of THF is rather complicated (AA'BB'EE'FF').

Fortunately, rate constants can be approximated from the following expressions:

$$k = 2^{-0.5} \pi \Delta\nu \quad \text{eq. 1.13}$$

$$-\Delta G^\ddagger = RT \ln \left(\frac{kh}{Kk_B T} \right) \quad \text{eq. 1. 14}$$

Thus, an average value for $\Delta G^\ddagger$ at 0°C for the following exchange process shown by eq. 1.15 is 13.0 ± 0.3 Kcal/mol.

Owing to the different chemical shift changes involved, the coalescence temperatures differ for the α - and β -protons of the THF. This result provides the first estimation of the bond strength of coordinating solvent in such lanthanide complexes.

In order to compare exchange rates in different systems, $(\text{TMS}_2\text{Cp})_2\text{LuCl}(\text{THF})$ and $(\text{MeCp})_2\text{LuCl}(\text{THF})$ were synthesized. The corresponding exchange processes shown by eq.1.16 and eq.1.17 were then studied.

Again, a variable temperature 200 MHz ^1H NMR study of a toluene- d_6 solution, 0.016 M in $(\text{TMS}_2\text{Cp})_2\text{LuCl}(\text{THF})$ and 0.024 M in free THF showed single NMR peaks for the α - and β -protons due to the rapid exchange at room temperature, but separate peaks at -60°C : α -protons, δ_{free} 713.9, δ_{coord} 661.2 Hz, coalescence temperature -45.4°C ; β -protons, δ_{free} 262.5, δ_{coord} 201.3 Hz, coalescence temperature -40.0°C . Rate constants were approximated according to eq.1.14. The substitution of the rate constants in eq.1.13 gave an average value for $\Delta G^\ddagger$ of 11.1 ± 0.1 Kcal/mol at 0°C for the exchange process in eq.1.16,

However, a similar ^1H NMR study of a toluene- d_6 solution, 0.0701 M in $(\text{MeCp})_2\text{LuCl}(\text{THF})$ and 0.140 M in free THF showed single NMR peaks for the

rapidly exchanging α - and β -protons at room temperature as well as at -40°C . The broadening exchanging peaks observed in $(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF})$ and $(\text{TMS}_2\text{Cp})_2\text{LuCl}(\text{THF})$ exchanging systems at low temperature were not seen in the exchange process shown by eq.1.17. This indicates that THF molecules exchange so rapidly in this case that the exchange process cannot be frozen out at low temperature. This also implies that the $\Delta G^\ddagger$ value for this exchange process must be less than 11 Kcal/mol. A summary of the results for these exchange processes is presented in Table 1.7.

Table 1.7
Activation Energy

Complex	$\Delta G^\ddagger$ (Kcal/mol)
$(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF}) + \text{THF}$	13.0 ± 0.3
$(\text{TMS}_2\text{Cp})_2\text{LuCl}(\text{THF}) + \text{THF}$	11.1 ± 0.1
$(\text{MeCp})_2\text{LuCl}(\text{THF}) + \text{THF}$	< 11

Several conclusions can be made based on the study of these three systems.

First, the chemical shifts of coordinated THF molecules are different in different molecules as shown in Table 1.8.

Table 1.8

Chemical Shifts of Coordinated THF in toluene-d₈ (ppm)

	α	β
$(Me_5Cp)_2LuCl(THF)$	3.37	1.26
$(TMS_2Cp)_2LuCl(THF)$	3.27	1.00

This phenomenon was also observed in the molecules summarized in Table 1.9.

Table 1.9
Chemical Shifts (ppm) [19]

entry	complex	α proton	β proton
1	$Cp_2LuCH_3(THF)$	3.57	1.53
2	$Cp_2LuC_2H_5(THF)$	3.41	1.41
3	$Cp_2LuCH(CH_3)_2(THF)$	3.80	1.41
4	$Cp_2LuC_6H_5(THF)$	3.45	1.45
5	$Cp_2LuC(CH_3)_3(THF)$	3.32	1.13
6	$Cp_2LuCH_2C(CH_3)_3(THF)$	3.21	1.17
7	$Cp_2LuCH_2Si(CH_3)_3(THF)$	3.16	1.15
8	$Cp_2LuCH_2C_6H_5(THF)$	3.27	1.24
9	$Cp_2LuC_6H_4-4-CH_3(THF)$	3.21	1.10
10	$Cp_2LuCl(THF)$	3.55	1.37
11	free THF*	3.50	1.44

* = in toluene- d_8

It appears that as the ligand changes from less bulky groups ($-CH_3$, $-C_2H_5$) to more bulky groups such as $-C(CH_3)_3$, $-CH_2C(CH_3)_3$ and $-CH_2Si(CH_3)_3$, the chemical shifts differ greatly both for α -protons and for β -protons. However, the directions of the shift are not predictable.

This perhaps can be interpreted on the basis of Lu-O bond strength. When there is enough space accessible for a THF molecule to come close to lutetium, a

strong interaction between Lu and O is established. Likewise, when ligands are bulky and limit the available space, the Lu-O interaction is weaker. Consequently, the Lu-O bond strength differences may result in chemical shift differences for α - and β -protons of THF molecules in these various complexes.

The same phenomenon has also been found in zerovalent nickel phosphorus complexes ($\text{Ni}(\text{PZ}_3)_4$) [36]. The ^{31}P chemical shifts of the coordinated ligands vary with different substitutes on phosphorus atoms. For example, the ^{31}P chemical shifts found in $\text{Ni}[\text{P}(\text{CH}_3)_3]_4$, $\text{Ni}[\text{P}(\text{OCH}_3)_3]_4$, and $\text{Ni}[\text{P}(\text{O}-p\text{-C}_6\text{H}_4\text{OCH}_3)_3]_4$ are -41.1, -22.9, -3.4 ppm, respectively. It has been concluded that there is no general correlation between the ^{31}P chemical shifts with its electron donor or acceptor character. It is best accounted for by the size of the ligands.

Furthermore, close examination of the bond lengths in several organoluthetium THF complexes shows a correlation between the Lu-O bond length and the steric bulkiness around THF molecules in Table 1.10.

Table 1.10
Lu-O bond length (Å) [19, 32]

entry		D(Lu-O)
1	$\text{Cp}_2\text{Lu}\cdot\text{C}_6\text{H}_4\cdot 4\text{-CH}_3(\text{THF})$	2.288
2	$\text{Cp}_2\text{LuCH}_2\text{Si}(\text{CH}_3)_3(\text{THF})$	2.265
3	$\text{Cp}_2\text{LuC}(\text{CH}_3)_3(\text{THF})$	2.312
4	$(\text{C}_6\text{Me}_6)_2\text{LuCl}(\text{THF})$	2.340

The more crowded the complex is, the longer the Lu-O bond, and the weaker the

interaction between lutetium and the oxygen atom of THF molecules.

Second, the exchange rates are different in three systems as indicated in Table 1.7. If electronic effects play a role in these exchange processes, the exchange rate of $(\text{TMS}_2\text{Cp})_2\text{LuCl}(\text{THF})$ with THF should be slower than that of $(\text{MeCp})_2\text{LuCl}(\text{THF})$ and $(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF})$ with THF. The TMS_2Cp anion is a weaker base than the methylated cyclopentadienyls. With weakly basic ligands, the lutetium ion is effectively a stronger Lewis acid, and the interaction between lutetium and THF should be stronger; the corresponding rate of exchange of THF molecules should then be slower. Such an effect is not observed experimentally.

If the steric effect plays a central role, and if the exchange process follows a dissociation pathway, namely, that the rate-determining step is the dissociation of THF from the organolutetium complex, one would expect that the more bulky the system is, the more readily the THF molecule can leave. Thus, the rate of exchange of $(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF})$ with THF should be faster than that of $(\text{TMS}_2\text{Cp})_2\text{LuCl}(\text{THF})$ and $(\text{MeCp})_2\text{LuCl}(\text{THF})$ with THF. This prediction is also not observed experimentally. The order of the bulkiness of the ligands is $\text{C}_5\text{Me}_5 > \text{TMS}_2\text{Cp} > \text{MeCp}$. Although one TMS group is bigger than one methyl group, the TMS_2Cp groups in the lutetium complex can orient in such way that two bulky TMS groups are away from the environment surrounding the coordinated THF molecule.

The exchange process can occur in a way that a free THF molecule has to diffuse in and coordinate to lutetium while the coordinated THF moves out of the coordination sphere, the so-called concerted associative pathway. If this mechanism is operative, the rate of exchange will be faster when the metal center is less crowded since it is easier for a free THF molecule to access the metal ion coordination sphere. It is indeed found in Table 1.7 that the activation energy for

(MeCp)₂LuCl(THF) with THF is the lowest whereas that of (C₅Me₅)₂LuCl(THF) with THF is the highest.

This associative mechanism could be demonstrated more thoroughly if the entropy of activation were obtained since a value near zero would be predicted. In contrast, a positive value would be expected if the dissociative pathway were invoked. Unfortunately, as is discussed before, the complex splitting pattern of THF makes it impracticable to use computer line-shape simulation, and therefore, a conclusive analysis is prevented.

An analogous example of a dominant role of steric effects on reactivities of complexes is the phosphorus ligand exchange equilibria on Ni(0) [36]. A quantitative measure of steric effects in these ligand exchange systems proposes that steric effects are much more important than electronic effects in determining the exchange equilibria among phosphorus ligands on Ni(0), as well as in determining the degree of substitution of CO from Ni(CO)₄ by these ligands. For instance, P(CH₃)₃, a good electron donor, gave a remarkably stable Ni(0) complex while P(C₆F₅)₃, one of the best electron acceptors expected to form a strong back-bonding with Ni, failed to bond to Ni(0) in competition with P(CH₃)₃ or even P(O-o-C₆H₄CH₃)₃. In addition, a rather good correlation between ligand binding ability and the ligand cone angles for the ligands of the type PZ₃ has been found.

1.3 Summary

The reaction of LuCl_3 and $2\text{NaC}_5\text{Me}_5$ in tetrahydrofuran (THF) affords crystals of $(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF})$. An X-ray structure determination shows the Lu atom to be in a distorted tetrahedral array in which the Lu-Cl bond length is 2.53 Å, and the ring-Lu-ring angle is 137° . All methyl groups on the cyclopentadienyl rings are bent out of the planes of the rings, away from the lutetium atom. This bending phenomenon is, perhaps, caused by intramolecular steric repulsion as well as by an electronic effect in which the cyclopentadienyl rings put more negative charge on the face towards the highly positive charged lutetium atom.

Variable temperature ^1H NMR spectroscopy shows a dynamic equilibrium between coordinated and free THF in these three systems: $(\text{C}_5\text{Me}_5)_2\text{LuCl}(\text{THF}) + \text{THF}$, $(\text{TMS}_2\text{Cp})_2\text{LuCl}(\text{THF}) + \text{THF}$, and $(\text{MeCp})_2\text{LuCl}(\text{THF}) + \text{THF}$ with barriers to exchange, $\Delta G^\ddagger$, of 13.0 ± 0.3 Kcal/mol, 11.1 ± 0.1 Kcal/mol, and < 11 Kcal/mol at 0°C , respectively. A concerted associative pathway is, perhaps, a possible mechanism for these exchange processes since the activation energy increases with increase in steric crowdedness.

1.4 Experimental

General. Unless otherwise indicated, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone and were degassed before use. Toluene was distilled from sodium, and hexane was distilled from CaH_2 after refluxing overnight. Both of these solvents were degassed thoroughly before use. All air and moisture sensitive compounds were handled either in an argon atmosphere glovebox, or by standard Schlenk techniques. ^1H NMR spectra were recorded on the UCB-200 (200 MHz, FT) or UCB-250 (250 MHz, FT) spectrometers. Chemical shifts are reported in δ values, being referenced to tetramethylsilane (TMS) either directly with TMS as an internal standard or indirectly by the residual proton resonances of solvents referenced to TMS. Significant ^1H NMR data are tabulated in order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), and coupling constants in Hertz. Infrared spectra were determined on a Perkin-Elmer Model 297 Spectrometer. Visible spectra of THF solutions of the organometallic compounds were determined on a UV/Visible 9420/9430 IBM spectrophotometer. Low voltage mass spectral data are expressed as m/e (intensity expressed as percent of total ion current). Crystals were sealed inside thin walled quartz capillaries under argon and mounted on a modified Picker FACS-I Automatic diffractometer equipped with a Mo-K α X-ray tube and graphite monochromator. All weights, unless otherwise specified, are ± 0.01 g.

Measurement of the Rate of THF Exchange: Approximately 2 to 15 mg of the substituted cyclopentadienyl lutetium complex was loaded into 5mm NMR tubes and dissolved in about 0.4 to 0.7 mL of degassed toluene- d_6 solvent. Approximately 0.2 μL to 5 μL of THF was added to the above solutions. The ^1H NMR spectra were run on the UCB Berkeley FT-NMR 200 MHz spectrometer. The system employs a superconducting magnet, a deuterium lock system, and Nicolet software. Temperature was monitored by a Doric Trendicator 410A.

Chemical shifts were determined at five to ten degree intervals from -70°C to $+40^\circ\text{C}$. At fast exchange above the coalescence temperature, the chemical shifts were determined by extrapolating from the slow exchange limit.

Calculation of $\Delta G^\ddagger$ for the barrier to THF exchange was made by extrapolating values to the estimated coalescence temperature, then substituting into the formulas, $k=2^{-0.5}\pi\Delta\nu$, and $\Delta G^\ddagger=RT\ln(kh/Kk_B T)$, where $K=1$.

1,2,3,4,5-Pentamethylcyclopentadiene ($\text{Me}_5\text{C}_5\text{H}$) [32]: To a well-stirred mixture of 9.00 g (1.29 mol) of cut-up lithium wire in 1 L of dry diethyl ether was added a small portion of 85.70 g (0.63 mol) of 2-bromo-2-butene. After the reaction began, the remainder of the 2-bromo-2-butene was added at a rate sufficient to maintain gentle reflux. Following this addition, stirring was continued for an additional hour. Ethyl acetate (28.29 g, 0.32 mol), diluted with an equal volume of diethyl ether, was then added dropwise. The resulting milky white mixture was poured into 850 mL of saturated aqueous ammonium chloride. The ether layer was separated, and the pH of the aqueous layer was adjusted to ca. 9 with HCl. The water solution was then extracted three times with diethyl ether. The combined ether layers were dried over Na_2SO_4 , and concentrated to

100 mL or less by rotary evaporation. The concentrated solution was quickly added to a mixture of 5.57 g of p-toluenesulfonic acid monohydrate and 130 mL of diethyl ether in a 1 L 3-neck flask equipped with a reflux condenser and an addition funnel. Vigorous reflux began almost immediately, and water separated. The mixture was stirred 5 additional minutes after the reflux ended, then was poured into a solution of 3.00 g of Na_2CO_3 in a saturated solution of NaHCO_3 (340 mL). The ether layer was separated, and the aqueous layer was extracted three times with diethyl ether. The combined ether layers were dried over Na_2SO_4 . Ether was removed by rotary evaporation. Vacuum distillation afforded 24.86 g (58%) of light yellow liquid, bp 44–46 °C/1 torr.: ^1H NMR (200 MHz, CDCl_3) δ 0.95 (d, 3), 1.73 (s, 6), 1.78 (s, 6), 2.43 (q, 1) [Lit.[32]: bp 58.3°C/13.5 torr. ^1H NMR δ 1.08 (d, 3), 1.84 (br., 12), 2.5 (q, 1)].

1,2,3,4,5-Pentamethylcyclopentadienylsodium ($\text{Me}_5\text{C}_5\text{Na}$): Anhydrous ammonia was vacuum transferred to a $-78\text{ }^\circ\text{C}$ flask immediately prior to use. Ferric nitrate (0.10 g) was dissolved in 250 mL of ammonia. After a homogeneous brown solution was obtained, sodium (3.65 g, 0.16 mol) was added. A blue solution was formed, and started to boil at $-33\text{ }^\circ\text{C}$. After 1 h, the blue color disappeared and a grey precipitate of NaNH_2 formed. Liquid ammonia was allowed to boil off completely to give a dry grey precipitate, to which was added $\text{Me}_5\text{C}_5\text{H}$ (0.96 g, 7.1 mmol) in 250 mL of THF, and the resulting solution was stirred for 3h. After filtration, the solvent was removed under vacuum. The residue was washed with 2x50 mL of ether. A white powder (0.71 g) was obtained (64%). ^1H NMR (250 MHz, $\text{THF}-d_6$) δ 2.00 (s). [Lit.[37]].

Bis(1,2,3,4,5-Pentamethylcyclopentadienyl)Lutetium Chloride THF Complex: To 50 mL of a THF solution containing 1.37 g of LuCl_3 (Alfa) (4.9 mmol) was added 1.88 g of NaC_5Me_5 (11.9 mmol) in 40 mL of THF at -78°C . After the resulting mixture was stirred for 5 h at room temperature, the solvent was removed under vacuum. The residue was extracted by 2x50mL of toluene. The toluene solution was then concentrated to 70 mL, and cooled to -15°C overnight. Some transparent needle crystals formed. After the crystals were separated from the solution, the remaining solution was cooled again. White crystalline powder was collected (1.22 g). The overall yield was 37 %, mp. $160-162^\circ\text{C}$ (decomp.). ^1H NMR (250 MHz, toluene- d_6) δ 1.23 (m, 4), 1.99 (s, 30), 3.58 (m, 4). IR (cm^{-1}): 1600 (br.w), 1260 (m), 1065 (s), 1015 (s), 860 (w), 720 (w). mass spectrum, M/Z 480 (100%) for Cp^*_2LuCl , M+1 481 (calc: 25%, found: 26%), M+2 482 (calc: 33%, found: 34%).

Trimethylsilylcyclopentadiene [33]: To a suspension of NaH (39.00 g, 50% oil dispersion, 0.81 mol) in 150 mL of THF, freshly distilled C_5H_6 (67.0 mL, 0.81 mol) was added dropwise at 0°C . After the addition was completed, the solution was stirred for another 0.5 h and then filtered. To the filtrate, 102.9 mL of Me_3SiCl (0.81 mol) was added dropwise over 10 min. The reaction mixture was allowed to warm to room temperature, during which time precipitation of NaCl was clearly in evidence. The solution was separated from the precipitate by filtration. The solvent THF was then removed by rotary evaporation. Distillation gave 51.00 g of the product (38%); bp. $136-140^\circ\text{C}$; ^1H NMR (250 MHz, CDCl_3) δ 6.4 (m, 4), 3.2 (br. 1), -0.4 (s, 9) [Lit.[33] bp $138-140^\circ\text{C}$].

Bis(trimethylsilyl)cyclopentadiene: A solution of *n*-butyllithium (2.3 M, 53 mL, 0.12 mol) in hexane was added dropwise under an argon atmosphere to a stirred solution of freshly distilled trimethylsilylcyclopentadiene (17.00 g, 0.12 mol) in 20 mL of hexane. The mixture was stirred for an hour at room temperature. Trimethylchlorosilane (13.40 g, 0.12 mol) was then added, and the resulting mixture was heated for 3 h at 40 °C. The solution was filtered, the solvent was evaporated, and the residue was distilled in vacuum to give 16.30 g of the product; bp 43–45 °C/0.1 mmHg (63%); ^1H NMR (250 Hz, CDCl_3) δ -0.5 (s, 18), 6.42 (m, 2), 6.62 (m, 2) [Lit.[34]: bp. 40 °C/0.1 mm Hg.]

Bis[1,3-bis(trimethylsilyl)cyclopentadienyl]magnesium: At 0 °C, 7.33 mL of dibutylmagnesium (Alfa) (0.65 M in heptane) was added dropwise to a solution of 2.00 g of TMS_2CpH in 50 mL of hexane. After the solution was stirred for 24 h, hexane was removed under vacuum. A white solid was obtained in 84% yield. ^1H NMR showed 95% of the product. ^1H NMR (250 MHz, CD_2Cl_2) δ 6.46 (d, 2), 6.41 (t, 1), 0.28 (s, 18); IR (cm^{-1}): 2900 (s), 1460 (s), 1380 (w), 1250 (s); mp. 86–88 °C; [Lit.[38]].

Bis[bis(trimethylsilyl)cyclopentadienyl]lutetium Chloride THF Complex: To a suspension of 0.67 g (4.76 mmol) of LuCl_3 in 30 mL of THF was added 2.10 g of $(\text{TMS}_2\text{Cp})_2\text{Mg}$ (4.67 mmol) in 25 mL of THF dropwise at 0 °C. The mixture was stirred for 2 d, followed by filtration. After the removal of the solvent, a white solid was obtained. Recrystallization from hexane gave 0.91 g of the product (27%); mp. 170–172 °C (decomp.); ^1H NMR (250 MHz, toluene- d_6):

δ 6.50 (m, 6), 3.52 (m, 4), 1.41 (m, 4), 0.43 (s, 18); mass spectrum, M/Z 628 fr $(TMS_2Cp)_2LuCl$.

Bis(methylcyclopentadienyl)lutetium Chloride Dimer: To a suspension of KH (1.35 g, 0.034 mol) in 40 mL of THF was added freshly distilled methylcyclopentadiene (2.70 g, 0.035 mol). H_2 was evolved, and the suspension was stirred for 2 h until KH had reacted completely. $KMcCp$ precipitated when hexane was slowly added to the THF solution. The white crystalline material was collected, and 0.84 g (7.2 mmol) in 30 mL of THF was added to a stirred suspension of $LuCl_3$ (1.00 g, 3.6 mmol) in 10 mL of THF. After the resulting suspension was stirred overnight, some insoluble material was filtered. Removal of solvent from the filtrate afforded white solid, which was then extracted with toluene. After toluene was removed under vacuum, 0.54 g of white solid was obtained (20%). The product could be further purified by sublimation; mp. 120–125 °C; mass spectrum: M/Z 736 (100%), $M+1$ 737 (calc.: 29%, found: 32%), $M+2$ 739 (calc.: 65%, found: 68%); 1H NMR (250 MHz, toluene- d_6): 2.07 (s, 3), 6.06 (m, 4).

Bis(methylcyclopentadienyl)lutetium Chloride THF Complex: In a NMR tube, 15.5 μL of THF (0.19 mmol) was added to a solution of 0.035 g of $[(McCp)_2LuCl]_2$ (0.048 mmol) in 0.68 mL of toluene- d_6 . $(McCp)_2LuCl \cdot THF$ was formed in the above solution; 1H NMR (250 MHz, toluene- d_6): δ 5.89 (s, 4), 3.46 (m, 4), 2.24 (s, 3), 1.33 (m, 4).

1.5 Appendix A: X-ray Analysis:

The crystal structure of the bis(pentamethylcyclopentadienyl)lutetium chloride THF complex reported in this chapter was solved by Dr. Allan Zalkin at the Lawrence Berkeley Laboratory.

Structure of $[(CH_3)_5C_5]_2LuCl \cdot OC_4H_8$: A rectangular, transparent single crystal of $[(CH_3)_5]_2LuCl \cdot THF$ was sealed inside a quartz capillary, 0.3 mm in diameter in an argon atmosphere and examined with a modified Picker FACS-1 diffractometer equipped with a graphite monochro (MoKa). Unit cell parameters, $a=17.125$ Å, $b=18.246$ Å, $c=8.512$ Å, $\alpha=91.39^\circ$, $\beta=87.97^\circ$, $\gamma=116.87^\circ$ and $V=2370.9$ Å³, were derived by a least-squares fit to the setting angles of the unresolved MoKa components of 27 reflections ($20^\circ < 2\theta < 35^\circ$) at 23 °C.

The crystal system is triclinic, and the space group is $P\bar{1}$. There are two molecules, which are crystallographically independent but chemically equivalent, in the unit cell, so that the calculated density is 1.549 g/cm³.

The structure was solved by the heavy atom Patterson method, and was refined by full-matrix least-squares on F using anisotropic thermal parameters; hydrogen atoms were not included. Refinement converged to give $R=0.031$, $R_w=0.040$ for 6746 [$F^2 > 1 \sigma(F^2)$] data.

Following are the atomic coordinates, bond lengths and angles, thermal parameters, experimental details, least-squares planes, and drawings of the molecules.

Supplemental Table 1. Positional and Isotropically Equivalent Thermal Parameters with Standard Deviations for $[(CH_3)_5C_5]_2LuCl \cdot OC_4H_8$

Molecule 1				
atom	x	y	z	$B_{eq} \frac{\text{\AA}^2}{\text{atom}}$
Lu(1)	0.24457(1)	0.01077(1)	0.12313(3)	2.580(8)
Cl(1)	0.14118(12)	-0.05268(12)	-0.10109(22)	5.07(7)
O(1)	0.13977(28)	-0.08539(25)	0.2926(5)	4.0(1)
C(1)	0.1902(4)	0.1228(4)	0.0804(8)	4.0(2)
C(2)	0.2791(4)	0.1621(4)	0.0635(8)	3.9(2)
C(3)	0.3162(4)	0.1655(4)	0.2120(9)	4.2(2)
C(4)	0.2464(5)	0.1244(4)	0.3195(8)	4.0(2)
C(5)	0.1680(4)	0.0985(4)	0.2372(9)	4.0(2)
C(6)	0.3003(5)	-0.0963(5)	0.0350(11)	5.2(3)
C(7)	0.3218(5)	-0.0801(5)	0.1935(11)	5.3(3)
C(8)	0.3837(4)	-0.0011(5)	0.2106(8)	4.1(3)
C(9)	0.4043(4)	0.0345(4)	0.0606(10)	4.7(2)
C(10)	0.3514(5)	-0.0245(6)	-0.0490(8)	5.3(3)
C(11)	0.1258(6)	0.1194(6)	-0.0425(10)	6.3(4)
C(12)	0.3328(6)	0.2076(5)	-0.0821(10)	6.2(3)
C(13)	0.4131(5)	0.2229(5)	0.2575(13)	7.0(3)
C(14)	0.2552(7)	0.1253(5)	0.4994(9)	6.4(4)
C(15)	0.0739(5)	0.0610(6)	0.3057(12)	6.9(4)
C(16)	0.2386(7)	-0.1815(7)	-0.0350(17)	10.4(6)
C(17)	0.2898(8)	-0.1483(7)	0.3197(15)	9.1(5)
C(18)	0.4327(7)	0.0391(7)	0.3608(11)	7.7(5)
C(19)	0.4861(6)	0.1166(6)	0.0170(14)	8.1(4)
C(20)	0.3588(8)	-0.0135(10)	-0.2266(11)	10.9(8)
C(21)	0.1399(6)	-0.0845(5)	0.4655(8)	5.4(3)
C(22)	0.0778(6)	-0.1713(5)	0.5153(10)	6.5(3)
C(23)	0.0132(6)	-0.1989(6)	0.3844(11)	7.7(4)
C(24)	0.0636(5)	-0.1573(5)	0.2381(10)	6.8(3)

Supplemental Table 1 (continued)

atom	Molecule2			
	x	y	z	B _{eq}
Lu(2)	0.25076(1)	0.51689(1)	0.37975(3)	2.574(8)
Cl(2)	0.14505(13)	0.46942(13)	0.61155(23)	5.35(7)
O(2)	0.14292(26)	0.42300(26)	0.2175(5)	4.0(1)
C(25)	0.3025(5)	0.6451(4)	0.1971(9)	4.8(3)
C(26)	0.2153(5)	0.6156(4)	0.2022(11)	5.3(3)
C(27)	0.1890(5)	0.6243(5)	0.3559(13)	5.7(3)
C(28)	0.2655(7)	0.6615(4)	0.4447(9)	5.5(3)
C(29)	0.3359(4)	0.6758(4)	0.3437(9)	4.0(2)
C(30)	0.4057(4)	0.5220(5)	0.3634(10)	4.8(3)
C(31)	0.3528(5)	0.4532(5)	0.2738(8)	4.8(3)
C(32)	0.2928(4)	0.3941(4)	0.3777(10)	4.3(2)
C(33)	0.3091(5)	0.4277(4)	0.5282(9)	4.3(3)
C(34)	0.3771(5)	0.5067(5)	0.5217(10)	4.8(3)
C(35)	0.3553(9)	0.6535(7)	0.0401(12)	9.8(6)
C(36)	0.1568(8)	0.5879(7)	0.0577(15)	10.0(5)
C(37)	0.0969(8)	0.6052(8)	0.4107(22)	14.4(8)
C(38)	0.2733(13)	0.6946(8)	0.6140(12)	14.6(10)
C(39)	0.4341(6)	0.7358(5)	0.3827(15)	8.8(4)
C(40)	0.4950(6)	0.5909(6)	0.3102(17)	9.7(5)
C(41)	0.3713(8)	0.4386(8)	0.1010(11)	8.8(5)
C(42)	0.2257(7)	0.3051(5)	0.3416(13)	7.5(4)
C(43)	0.2664(7)	0.3813(7)	0.6798(11)	7.3(4)
C(44)	0.4189(7)	0.5630(6)	0.6629(13)	8.0(5)
C(45)	0.0529(5)	0.3783(6)	0.2710(11)	7.4(3)
C(46)	0.0060(7)	0.3251(8)	0.1293(13)	11.3(5)
C(47)	0.0672(7)	0.3481(8)	-0.0063(13)	10.5(5)
C(48)	0.1548(6)	0.4038(6)	0.0537(9)	6.5(3)

$$\bar{a} = B_{eq} = 1/3 \sum_{ij} a_i^* a_j^* a_i a_j$$

Supplemental Table 2. Anisotropic Thermal Parameters ($\text{\AA}^2$)^b with Estimated Standard Deviations for $[(\text{CH}_3)_5\text{C}_5]_2\text{LuCl}_2 \cdot \text{OC}_4\text{H}_8$

Molecule 1						
Atom	B ₁₁	B ₂₂	B ₃₃	B ₁₂	B ₁₃	B ₂₃
Lu(1)	2.777(11)	2.504(11)	2.471(11)	1.201(8)	-0.314(8)	-0.312(8)
Cl(1)	5.19(8)	6.06(9)	4.05(8)	2.59(7)	-1.95(7)	-1.79(7)
O(1)	3.91(19)	3.27(18)	3.99(22)	0.87(15)	0.37(16)	0.08(16)
C(1)	4.7(3)	3.85(29)	4.0(3)	2.41(25)	-1.05(26)	-0.36(24)
C(2)	4.9(3)	3.72(28)	3.5(3)	2.12(25)	-0.31(25)	-0.02(23)
C(3)	4.02(29)	2.73(25)	6.0(4)	1.54(22)	-1.88(28)	-1.19(26)
C(4)	6.7(4)	3.04(26)	2.89(28)	2.75(27)	-0.51(27)	-0.42(21)
C(5)	4.28(29)	3.07(26)	5.3(4)	2.36(23)	-0.09(27)	-0.69(25)
C(6)	4.9(3)	4.6(3)	6.9(5)	3.0(3)	0.0(3)	-1.9(3)
C(7)	5.9(4)	4.9(4)	6.6(5)	3.9(3)	1.4(4)	1.9(3)
C(8)	4.4(3)	5.4(4)	3.9(3)	3.44(29)	-0.12(26)	0.16(27)
C(9)	3.36(27)	4.6(3)	6.5(4)	2.19(25)	0.89(28)	1.2(3)
C(10)	6.4(4)	9.4(6)	2.8(3)	6.0(4)	0.07(29)	-0.3(3)
C(11)	6.7(4)	8.2(5)	5.4(4)	4.4(4)	-2.4(4)	-0.6(4)
C(12)	8.0(5)	6.2(4)	4.4(4)	3.1(4)	1.2(4)	1.8(3)
C(13)	4.8(4)	4.4(4)	10.6(7)	0.9(3)	-3.2(4)	-2.1(4)
C(14)	11.3(7)	5.9(4)	3.1(3)	4.7(4)	-1.5(4)	-1.3(3)
C(15)	4.8(4)	7.3(5)	9.4(6)	3.5(4)	2.7(4)	1.7(5)
C(16)	8.5(6)	7.3(6)	15.8(11)	4.2(5)	-3.4(7)	-7.3(7)
C(17)	10.5(7)	8.8(6)	11.1(8)	7.1(6)	4.4(5)	6.2(6)
C(18)	8.4(6)	12.0(8)	5.5(5)	6.8(6)	-3.5(4)	-2.0(5)
C(19)	5.0(4)	6.8(5)	12.3(8)	2.6(4)	3.8(5)	3.4(5)
C(20)	12.3(8)	22.2(14)	3.4(4)	12.4(10)	1.1(5)	1.6(6)
C(21)	7.3(5)	4.4(3)	3.0(3)	1.3(3)	0.3(3)	0.51(25)
C(22)	7.3(5)	4.7(4)	4.7(4)	0.4(3)	0.9(4)	0.5(3)
C(23)	6.7(5)	5.8(5)	6.3(5)	-0.7(4)	1.8(4)	0.5(4)
C(24)	4.9(4)	5.9(4)	5.6(4)	-1.2(3)	-0.0(3)	-0.8(3)

Supplemental Table 2 (continued)

Molecule 2						
Atom	B ₁₁	B ₂₂	B ₃₃	B ₁₂	B ₁₃	B ₂₃
Lu(2)	2.643(11)	2.531(11)	2.582(12)	1.204(8)	0.067(8)	0.071(8)
Cl(2)	5.54(9)	6.98(11)	4.18(9)	3.48(8)	1.93(7)	1.48(8)
O(2)	3.13(18)	3.92(20)	4.11(22)	0.81(15)	-0.52(16)	-0.41(17)
C(25)	6.7(4)	3.36(29)	4.5(4)	2.32(29)	0.5(3)	1.00(26)
C(26)	5.8(4)	3.11(29)	7.0(5)	1.81(28)	-2.1(4)	0.8(3)
C(27)	3.9(3)	3.8(3)	9.9(7)	2.29(27)	2.0(4)	2.4(4)
C(28)	10.1(6)	3.3(3)	3.7(3)	3.7(4)	0.6(4)	0.06(25)
C(29)	4.17(29)	3.20(27)	4.6(3)	1.50(23)	-0.20(26)	0.53(24)
C(30)	3.59(28)	4.7(3)	6.8(5)	2.48(26)	0.5(3)	2.0(3)
C(31)	5.8(4)	7.4(5)	3.1(3)	4.8(4)	0.32(28)	0.1(3)
C(32)	4.2(3)	3.40(28)	6.2(4)	2.43(24)	-0.94(29)	-1.13(28)
C(33)	4.7(3)	5.1(3)	4.1(3)	3.14(29)	0.62(27)	1.18(28)
C(34)	4.9(3)	4.9(3)	5.4(4)	2.86(29)	-2.1(3)	-1.1(3)
C(35)	16.0(10)	7.5(6)	5.4(5)	5.0(6)	6.0(6)	2.8(4)
C(36)	10.9(8)	7.2(6)	10.6(8)	2.4(5)	-6.8(7)	0.6(5)
C(37)	9.3(7)	10.6(8)	26.8(17)	8.1(7)	10.7(9)	9.4(10)
C(38)	34.4(21)	8.9(7)	3.9(5)	13.0(11)	2.3(8)	-0.4(5)
C(39)	6.1(5)	4.5(4)	14.3(9)	0.8(3)	-4.4(5)	0.9(5)
C(40)	4.0(4)	7.9(6)	17.4(11)	2.8(4)	3.3(5)	6.0(7)
C(41)	10.8(7)	14.9(10)	3.8(4)	8.7(7)	1.4(4)	-0.1(5)
C(42)	9.0(6)	3.3(3)	10.5(7)	2.9(4)	-3.7(5)	-1.9(4)
C(43)	8.8(6)	9.8(6)	5.3(5)	5.8(5)	2.4(4)	4.3(4)
C(44)	10.0(7)	7.6(5)	7.6(6)	4.7(5)	-5.0(5)	-2.8(5)
C(45)	3.1(3)	8.4(5)	6.7(5)	-0.8(3)	0.7(3)	-0.2(4)
C(46)	6.5(6)	13.0(9)	6.4(5)	-3.0(6)	-2.7(5)	0.7(6)
C(47)	6.8(6)	11.8(8)	6.1(6)	-1.8(5)	-2.2(5)	-2.1(5)
C(48)	5.7(4)	8.3(5)	3.6(4)	1.5(4)	-0.7(3)	-2.2(3)

^b Temperature factor has the form: $-0.25\exp(h^2a^{*2}B_{11} + 2hka^*b^*B_{12} + \dots)$.

Supplemental Table 3. Selected Interatomic Distances in

Molecule 1		Molecule 2	
Lu(1) - O(1)	2.340(04)	Lu(2) - O(2)	2.336(04)
Lu(1) - Cl(1)	2.529(02)	Lu(2) - Cl(2)	2.517(02)
Lu(1) - C(1)	2.637(07)	Lu(2) - C(25)	2.624(07)
Lu(1) - C(2)	2.608(07)	Lu(2) - C(26)	2.661(07)
Lu(1) - C(3)	2.623(06)	Lu(2) - C(27)	2.629(07)
Lu(1) - C(4)	2.621(06)	Lu(2) - C(28)	2.582(07)
Lu(1) - C(5)	2.638(06)	Lu(2) - C(29)	2.610(06)
Lu(1) - C(6)	2.619(07)	Lu(2) - C(30)	2.612(07)
Lu(1) - C(7)	2.635(07)	Lu(2) - C(31)	2.624(07)
Lu(1) - C(8)	2.622(06)	Lu(2) - C(32)	2.646(06)
Lu(1) - C(9)	2.605(06)	Lu(2) - C(33)	2.628(07)
Lu(1) - C(10)	2.595(07)	Lu(2) - C(34)	2.595(07)
O(1) - C(21)	1.472(08)	O(2) - C(45)	1.443(08)
O(1) - C(24)	1.451(08)	O(2) - C(48)	1.460(09)
C(1) - C(2)	1.362(09)	C(25) - C(26)	1.338(11)
C(1) - C(5)	1.401(10)	C(25) - C(29)	1.388(10)
C(2) - C(3)	1.422(09)	C(26) - C(27)	1.397(12)
C(3) - C(4)	1.405(10)	C(27) - C(28)	1.412(12)
C(4) - C(5)	1.411(09)	C(28) - C(29)	1.383(11)
C(6) - C(7)	1.400(12)	C(30) - C(31)	1.397(11)
C(6) - C(10)	1.400(11)	C(30) - C(34)	1.407(11)
C(7) - C(8)	1.357(10)	C(31) - C(32)	1.408(10)
C(8) - C(9)	1.406(10)	C(32) - C(33)	1.389(10)
C(1) - C(11)	1.527(09)	C(33) - C(34)	1.385(10)
C(2) - C(12)	1.533(10)	C(25) - C(35)	1.558(12)
C(3) - C(13)	1.567(09)	C(26) - C(36)	1.540(12)
C(4) - C(14)	1.543(09)	C(27) - C(37)	1.510(11)
C(5) - C(15)	1.536(10)	C(28) - C(38)	1.537(12)
C(6) - C(16)	1.550(11)	C(29) - C(39)	1.579(10)
C(7) - C(17)	1.551(11)	C(30) - C(40)	1.537(10)
C(8) - C(18)	1.534(10)	C(31) - C(41)	1.536(11)
C(9) - C(10)	1.407(11)	C(32) - C(42)	1.537(10)
C(9) - C(19)	1.560(10)	C(33) - C(43)	1.531(10)
C(10) - C(20)	1.523(11)	C(34) - C(44)	1.533(11)
C(21) - C(22)	1.516(10)	C(45) - C(46)	1.533(13)
C(22) - C(23)	1.510(13)	C(46) - C(47)	1.465(15)
C(23) - C(24)	1.499(12)	C(47) - C(48)	1.482(11)
Cp(1) - Lu(1)	2.340	Cp(4) - Lu(2)	2.336
Cp(2) - Lu(1)	2.331	Cp(3) - Lu(2)	2.342

^aCp(1)-Cp(4) are the centroids of atoms C(1)-C(5), C(6)-C(10), C(25)-C(29) & C(30)-C(34) respectively.

Supplemental Table 4. Selected Interatomic Angles (°) in

Molecule 1		Molecule 2	
Cl(1)-Lu(1)-O(1)	89.0(12)	Cl(2)-Lu(2)-O(2)	90.10(13)
Lu(1)-O(1)-C(21)	127.1(4)	Lu(2)-O(2)-C(45)	121.8(5)
Lu(1)-O(1)-C(24)	123.3(4)	Lu(2)-O(2)-C(48)	126.5(4)
C(21)-O(1)-C(24)	109.6(5)	C(45)-O(2)-C(48)	111.7(6)
C(2)-C(1)-C(5)	108.7(6)	C(26)-C(25)-C(29)	110.0(8)
C(2)-C(1)-C(11)	125.4(7)	C(26)-C(25)-C(35)	122.3(9)
C(5)-C(1)-C(11)	125.1(7)	C(29)-C(25)-C(35)	127.1(8)
C(1)-C(2)-C(3)	108.8(6)	C(25)-C(26)-C(27)	108.4(7)
C(1)-C(2)-C(12)	127.0(7)	C(25)-C(26)-C(36)	124.8(10)
C(3)-C(2)-C(12)	123.6(7)	C(27)-C(26)-C(36)	126.3(9)
C(2)-C(3)-C(4)	107.2(6)	C(26)-C(27)-C(28)	106.9(7)
C(2)-C(3)-C(13)	126.1(7)	C(26)-C(27)-C(37)	125.9(11)
C(4)-C(3)-C(13)	125.1(7)	C(28)-C(27)-C(37)	127.0(17)
C(3)-C(4)-C(5)	107.4(6)	C(27)-C(28)-C(29)	107.5(7)
C(3)-C(4)-C(14)	124.8(7)	C(27)-C(28)-C(38)	127.2(11)
C(5)-C(4)-C(14)	126.6(7)	C(29)-C(28)-C(38)	124.6(11)
C(1)-C(5)-C(4)	108.0(6)	C(25)-C(29)-C(28)	107.2(7)
C(1)-C(5)-C(15)	123.8(7)	C(25)-C(29)-C(39)	127.2(8)
C(4)-C(5)-C(15)	127.7(7)	C(28)-C(29)-C(39)	123.8(8)
C(7)-C(6)-C(10)	107.7(7)	C(31)-C(30)-C(34)	108.4(6)
C(7)-C(6)-C(16)	125.4(10)	C(31)-C(30)-C(40)	125.7(9)
C(10)-C(6)-C(16)	126.6(10)	C(34)-C(30)-C(40)	123.8(9)
C(6)-C(7)-C(8)	109.5(7)	C(30)-C(31)-C(32)	107.6(7)
C(6)-C(7)-C(17)	122.7(9)	C(30)-C(31)-C(41)	124.9(3)
C(8)-C(7)-C(17)	127.1(9)	C(32)-C(31)-C(41)	126.2(8)
C(7)-C(8)-C(9)	107.7(7)	C(31)-C(32)-C(33)	107.5(6)
C(7)-C(8)-C(18)	126.5(8)	C(31)-C(32)-C(42)	128.6(9)
C(9)-C(8)-C(18)	125.2(8)	C(33)-C(32)-C(42)	123.8(8)
C(8)-C(9)-C(10)	108.3(7)	C(32)-C(33)-C(34)	109.5(6)
C(8)-C(9)-C(19)	125.5(8)	C(32)-C(33)-C(43)	125.2(8)
C(10)-C(9)-C(19)	124.7(8)	C(34)-C(33)-C(43)	124.9(8)
C(6)-C(10)-C(9)	106.8(7)	C(30)-C(34)-C(33)	107.1(7)
C(6)-C(10)-C(20)	127.6(10)	C(30)-C(34)-C(44)	126.7(8)
C(9)-C(10)-C(20)	125.2(10)	C(33)-C(34)-C(44)	126.0(3)
O(1)-C(21)-C(22)	105.8(6)	O(2)-C(45)-C(46)	104.3(8)
C(21)-C(22)-C(23)	101.4(7)	C(45)-C(46)-C(47)	109.0(7)
C(22)-C(23)-C(24)	106.6(7)	C(46)-C(47)-C(48)	106.7(8)
O(1)-C(24)-C(23)	105.3(7)	O(2)-C(48)-C(47)	107.5(7)
Cp(1)-Lu(1)-Cp(2)	136.66	Cp(4)-Lu(2)-Cp(3)	136.50
Cp(1)-Lu(1)-Cl(1)	105.51	Cp(4)-Lu(2)-Cl(2)	105.71
Cp(2)-Lu(1)-Cl(1)	106.05	Cp(3)-Lu(2)-Cl(2)	106.17
Cp(1)-Lu(1)-O(1)	105.02	Cp(4)-Lu(2)-O(2)	104.75
Cp(2)-Lu(1)-O(1)	104.47	Cp(3)-Lu(2)-O(2)	104.92

Supplemental Table 5. Crystallographic Summary and Data Processing for

a, Å	17.125(6)
b, Å	18.246(6)
c, Å	8.512(3)
α, °	91.39(3)
β, °	87.97(3)
γ, °	116.87(3)
cryst syst	triclinic
space group	$P\bar{1}$
volume, Å ³	2370.9
d(calcd), g/cm ⁻³	1.549
Z	4
temp (°C)	23.0
empirical formula	C ₂₄ H ₃₈ O ₁ Cl ₁ Lu ₁
f(000), e	1112
fw	552.99
color	yellow
reflection rules	None.
x-ray	MoKα (graphite monochromated)
wave-length (Kα ₁ , Kα ₂), Å	0.70930, 0.71359
crystal size (mm)	0.18 x 0.27 x 0.50
abs coeff, cm ⁻¹	42.94
abs corr range	1.94-3.11
cryst decay corr range	0.92-1.03
diffractometer	modified Picker FACS-1
sinθ/λ, min,max	0.054, 0.596
hkl limits	h -20,20; k -21,21; l -10,2
scan type & 2θ limits, °	θ-2θ, 4.4-50.1
scan width, °2θ	1.50 + 0.693 × tanθ
no. of standards, frequency	3, 200
variation of standards (%)	5.41, 2.57, 3.69
no. scan data	11370
no. unique reflections	8382

Supplemental Table 5. (continued)

R_{int}^b	0.022
no. non-zero weighted data	6746 ($F^2 > 1\sigma$)
p^c	0.050
extinction k^d	9.25×10^{-8}
max % extinction corr	9.1
no. parameters	487
R (non-zero wtd dat) ^e	0.031
R_w^f	0.040
R (all data)	0.047
Goodness of fit ^g	1.20
max shift/esd in least-square	0.0375
max/min in diff map ($e/\text{\AA}^3$)	0.87, -0.61

^a Unit cell parameters were derived by a least-squares fit to the setting angles of the unresolved MoKa components of 27 reflections ($20^\circ < 2\theta < 35^\circ$).

^b R_{int} = agreement factor between equivalent or multiply measured reflections = $\sum [I_{hkl} - \langle I_{hkl} \rangle] / \sum \langle I_{hkl} \rangle$

^c In the least-squares, the assigned weights to the data are $1.0/[\sigma(F)]^2$ were derived from $\sigma(F^2) = [S^2 + (pF^2)^2]$, where S^2 is the variance due to counting statistics and p is assigned a value that adjusts the weighted residuals of the strong reflections to be comparable to the weak ones.

^d Simple extinction correction, $(F_{obs})_{corr} = (1 + kI)F_{obs}$, where I is the uncorrected intensity and F_{obs} is the observed scattering amplitude.

^e $R = \sum (|F_{obs}| - |F_{cal}|) / \sum |F_{obs}|$

^f $R_w = \sqrt{[\sum w(|F_{obs}| - |F_{cal}|)^2] / \sum w F_{obs}^2}$

^g σ_1 = error in observation of unit weight =

$\sqrt{[\sum w(|F_{obs}| - |F_{cal}|)^2] / (n_o - n_v)}$, where n_o is the number of observations and n_v is the number of variables.

Supplemental Table 6. Least Squares Planes in $[(CH_3)_5C_5]_2LuCl \cdot OC_4H_8$

Plane No. 1

$$-7.71626 x + 17.81169 y + 1.63871 z = 0.84603$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
C(1)	0.0048(96)	Lu(1)	-2.340(4)
C(2)	-0.0086(96)	C(11)	0.240(16)
C(3)	0.0099(100)	C(12)	0.149(16)
C(4)	-0.0081(106)	C(13)	0.359(16)
C(5)	0.0012(096)	C(14)	0.234(17)
		C(15)	0.171(16)

Plane No. 2

$$16.17839 x - 12.62953 y - 0.86778 z = 6.04486$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
C(6)	0.0005(119)	Lu(1)	-2.331(41)
C(7)	0.0050(115)	C(16)	0.138(20)
C(8)	-0.0069(106)	C(17)	0.223(19)
C(9)	0.0071(108)	C(18)	0.149(19)
C(10)	-0.0079(133)	C(19)	0.332(18)
		C(20)	0.127(24)

Plane No. 3

$$-6.34195 x + 17.71217 y - 2.11809 z = 9.10308$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
C(25)	-0.0118(118)	Lu(2)	-2.342(4)
C(26)	0.0064(120)	C(35)	0.133(21)
C(27)	0.0022(138)	C(36)	0.193(20)
C(28)	-0.0125(139)	C(37)	0.131(24)
C(29)	0.0077(98)	C(38)	0.167(28)
		C(39)	0.366(18)

Plane No. 4

$$15.74269 x - 13.64237 y + 1.39017 z = -0.24036$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
C(30)	0.0118(111)	Lu(2)	-2.336(04)
C(31)	-0.0087(119)	C(40)	0.403(19)
C(32)	-0.0003(105)	C(41)	0.242(20)
C(33)	0.0066(103)	C(42)	0.106(17)
C(34)	-0.0110(106)	C(43)	0.178(18)
		C(44)	0.075(18)

Supplemental Table 6. (continued)

Plane No.5

$$-8.02733 x + 17.85119 y + 1.53269 z = 0.98749$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
C(11)	0.069(14)	Lu(1)	-2.570(5)
C(12)	-0.079(13)		
C(13)	0.071(14)		
C(14)	-0.034(15)		
C(15)	-0.024(14)		

Plane No. 6

$$16.06306 x - 12.91549 y - 0.86085 z = 6.22043$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
C(16)	-0.013(18)	Lu(1)	-2.537(6)
C(17)	0.058(17)		
C(18)	-0.085(17)		
C(19)	0.067(16)		
C(20)	-0.088(23)		

Plane No. 7

$$-6.79783 x + 17.68671 y - 2.24216 z = 9.14713$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
C(35)	-0.094(19)	Lu(2)	-2.561(7)
C(36)	0.056(18)		
C(37)	-0.023(24)		
C(38)	-0.095(27)		
C(39)	0.058(17)		

Plane No. 8

$$15.45402 x - 13.90270 y + 1.72828 z = -0.10911$$

C(40)	0.080(19)	Lu(2)	-2.545(7)
C(41)	()		
C(42)	-0.054(16)		
C(43)	0.100(16)		
C(44)	-0.100(16)		

Supplemental Table 6. (continued)

Plane No. 9

$$14.55992 x - 15.26391 y - 0.90825 z = 3.05704$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
O(1)	0.016(6)	Lu(1)	0.228(12)
C(21)	-0.154(12)		
C(22)	0.223(13)		
C(23)	-0.180(13)		
C(24)	0.054(12)		
Lu(1)	0.228(12)		

Plane NO.10

$$-10.20524 x + 17.19673 y - 2.57496 z = 5.25368$$

Distance to the Plane (Å)

Atoms in the Plane		Atoms not in the Plane	
O(2)	0.002(7)	Lu(2)	0.098(14)
C(45)	0.014(14)		
C(46)	-0.057(18)		
C(47)	0.063(17)		
C(48)	-0.028(13)		

Supplemental Figure 1. ORTEP drawing of molecule 1 in the same configuration as Figure 2 in the main text; 50% probability ellipsoids.

Supplemental Figure 2. ORTEP view of molecule 1 as seen down the
Lu(1)-C1(1) bond; 50% probability ellipsoids.

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Chapter 2

Utilization of Organolanthanide Reagents in Mukaiyama Reactions

2.1 Introduction

One of the important contemporary problems in modern synthetic organic chemistry is the control of stereochemistry in C-C bond forming reactions. The aldol addition reaction, one of the oldest organic reactions, has emerged as a powerful tool for use in achieving such stereocontrol.

This method is highly recommended due to several desirable features. First, a new carbon-carbon bond is formed, which is especially important since it allows the building up of large molecules from small building blocks. Second, two useful functional groups are present in a product to serve as reaction sites for further synthetic transformations. Finally, two new chiral centers are created. In addition, it is a reaction of fundamental importance in the biosynthesis of a broad range of biologically significant natural products [7].

The general aldol reaction is shown in Scheme 2.1:

Scheme 2.1

RCH_2COX = aldehydes, ketones, esters, amides.

$\text{R}'\text{COR}''$ = aldehydes, ketones.

When simple ketones and esters react with aldehydes, for example, two diastereomeric aldols, syn and anti, may be formed.

Fig.2.1 Syn and anti diastereomers

These two isomers are produced in an unequal but usually comparable amounts [11].

What controls the formation of two diastereoisomers? There are two models which have been used to predict the product stereochemistry. They are cyclic and acyclic. Of these two, the cyclic model gives the more satisfactory prediction.

2.1.1 Cyclic Model In 1957, Zimmerman and Traxler accounted for the observed aldol diastereoselection by advancing the hypothesis that the reaction proceeded via a preferred six-member chairlike transition state [25]: this is referred to as the cyclic model. Subsequent investigations by Dubios [3,5], Heathcock [9], Musamune [61] and Evans [7,8] have unambiguously shown that aldol diastereoselection is consistent with the elaborated cyclic model (Scheme 2.2).

Scheme 2.2

In the cyclic model, two important factors determine the ratio of the two diastereomers in an aldol addition reaction: first, the enolate geometry and second, the size of the substituents attached to the carbonyl group. For example,

In equation 2.2, cyclopentanone, which must be trans (E) in the enolate form, gives mainly the anti aldol whereas ethyl t-butyl ketone, which affords a cis (Z) enolate, gives the syn aldol upon reacting with an aldehyde, [4]. These results suggest the general relationship: E enolate $\longrightarrow$ anti aldol and Z enolate $\longrightarrow$ syn aldol. However, to predict the stereochemistry of the aldol products correctly, a second factor must be taken into consideration. When the substituent is a bulky one, for example t-butyl in ethyl t-butyl ketone as shown in equation 2.1, excellent syn selectivity was obtained. In contrast, Z-enolate derived from propionaldehyde reacts with benzaldehyde as shown in eq. 2.3 to produce an equal amount of syn and anti aldols [9].

These results can be easily interpreted by the cyclic model (Scheme 2.2). When R' is a bulky group, and the enolate form is Z, the transition state 2 is destabilized relative to 1, in which both $R' \longleftrightarrow R''$ and $R'' \longleftrightarrow L$ interactions are maximized. As a result, Z enolates prefer to give syn aldols.

Heathcock and co-workers have demonstrated that for specific lithium enolates (either E or Z) with R', a sterically demanding group, diastereoselection could be completely achieved; however, when R' is C₂H₅, i-C₃H₉, OMe, C₆H₅, which are less bulky substituents, the diastereoselectivity is diminished greatly, [1,3-5]. Some lithium enolate results are listed in Table 2.1.

Table 2.1

Reaction of Lithium Enolates with Benzaldehyde [1,4]

Entry	R	Base	Z:E	Syn:Anti
1	MeO	LDA	5:95	62:38
2	i-Bu	LDA	5:95	49:51
3	Et	LDA	30:70	64:36
4	i-Bu	LDA	>98:2	>98:2
5	1-adamantyl	LDA	>98:2	>98:2
6	Ph	LDA	>98:2	88:12
7	Mesityl	LDA	5:95	8:92

Subsequently, Evans and co-workers studied the steric effects conferred by the metal center [7,8]. By maximizing the bulk of the metal ligands on boron, the pseudo-1,3-diaxial $R'' \longleftrightarrow L$ interaction in the transition state 2, 3 confers enhanced diastereoselectivity, despite the less important interaction between R'

and R" due to the smaller group (R'). This study demonstrates the generality of employing boron enolates in stereoselective aldol condensations and the utility of boron triflates (R_2BOTf) in the selective enolization of ketones. The representative aldol condensations summarized in Table 2.2 were carried out according to the general procedure as described in the following equation (eq. 2.5).

Table 2.2
Reaction of Dialkylboron Enolates with Benzaldehyde [7,8]

Entry	R	L	Z:E	Syn:Anti
1	Et	n-Bu	>99:1	>97:3
2	Ph	n-Bu	99:1	97:3
3	i-Pr	n-Bu	45:55	44:56
4	t-Bu	n-Bu	99:1	97:3
5	Cyclohexyl	n-Bu	0:100	33:67

From these data, it is clear that the resultant aldol diastereoselection observed with benzaldehyde is excellent when the illustrated dialkylboron enolates of defined structure are given, namely, the stereostructure of the aldol products is correlated with the stereostructure of the enolates. In addition, the size of R' can be varied without loss of aldol diastereoselection. The comparative observations between boron and lithium enolates support the hypothesis that aldol condensation reactions proceed via cyclic transition states involving cooperative metal ion ligation of the enolate and carbonyl substrates. The limitation of the utilization of boron enolates in aldol condensation reactions is that only ketones and t-butyl

thiopropionate can be readily enolized.

2.1.2 Acyclic Model. In 1974, Mukaiyama [18] introduced a new method in which silyl enol ethers are condensed with carbonyl compounds activated by titanium tetrachloride. This method is often superior to the use of lithium enolates or metal salts in the aldol condensation reaction because it prevents di-, poly- or self-condensation products.

The Mukaiyama reaction was described [18] as follows: A silyl enol ether (5) could readily attack a carbonyl compound 6 activated by titanium tetrachloride in a nucleophilic fashion to form trimethylsilyl chloride and an intermediate chelate (7). Hydrolysis of 7 should then afford aldol 8 as shown in eq. 2.6.

What kind of role does a Lewis acid play in this reaction? Mukaiyama [18] found that the carbonyl absorption of dibenzyl ketone in methylene chloride is 1720 cm^{-1} , but was shifted to 1640 cm^{-1} when one equivalent of $TiCl_4$ was added. Thus, the role that the Lewis acid plays is to pull electron density away from the carbonyl carbon so that a nucleophile such as a silyl enol ether can easily attack

the carbonyl carbon. In other words, the primary function of the Lewis acid is to activate the carbonyl carbon.

This can be further confirmed by the two following facts [18]: first, the solvent effects; second, the relative effect of the amount of the Lewis acid upon the yield of aldols.

Mukaiyama treated the silyl enol ether with equimolar amounts of dibenzyl ketone and titanium tetrachloride as shown in eq.2.7 in various solvents at room temperature.

Table 2.3
Solvent Effects [18]

Solvent	Isolated Yield
Dichloromethane	64
Benzene	24
n-Hexane	24
Tetrahydrofuran	0
Diethyl Ether	0

The results in Table 2.3 give one an immediate recognition of the fact that methylene chloride is significantly favored in this reaction to give the highest yield; the aldol product was not obtained at all in diethyl ether or tetrahydrofuran. This indicates that the complex of the Lewis acid with carbonyl group of the ketone in this case is not formed at all probably due to the better competing Lewis bases such as diethyl ether or tetrahydrofuran.

The yield of the aldol as affected by the relative amount of titanium tetrachloride was investigated for the reaction in eq. 2.8.

eq. 2.8

Mukaiyama found that the aldol was obtained in the highest yield when an equimolar amount of titanium tetrachloride was applied (Table 2.4).

Table 2.4 [18]

Molar ratio of the acid	Yield
0	0
0.13	80
0.25	81
1	94
2	71

The stereochemistry of the reaction of various preformed metal enolates with aldehydes has been well studied. Much less is known about simple diastereoselection in the related reaction of enol ethers with aldehyde under conditions of Lewis acid activation [13]. Several mechanisms have been proposed to account for the observed stereochemistry, yet these studies reveal no consistent pattern.

Mukaiyama initially proposed that the reaction occurs via an 8-membered cyclic transition state to form the chelated 6-membered ring intermediate as shown in eq.2.6, but this transition state model could not be used to predict the observed stereochemistry.

Modifying Mukaiyama's initial proposal and combining with the Zimmerman-Traxler model (cyclic model) discussed before, Chan [2] worked out the hypothesis that the transition states 9 and 10 shown in chart 2.1 with chair-

like structures may account for the stereoselection of the reaction.

Fig. 2.2 Proposed transition state structures

All R groups being equatorial, the transition state 9 has a lower energy than the transition state 10. Therefore, the anti isomer is the major product. Their results are shown below in Table 2.5.

Table 2.5 [2]

Silyl Enol Ether	Aldehyde	Z/E	Syn:Anti
	Ph	15:85	25:75
	Bu	15:85	6:94
	Ph	100:0	33:67
	Bu	100:0	47:53
	iso-Bu	100:0	48:52
	iso-Bu	100:0	39:61
	Ph	100:0	33:67

Based on the same model, one could draw transition state structures 11 and 12 in Fig. 2.3 for the Z silyl enol ether.

Fig. 2.3 Proposed transition state structures

Accordingly, 12 has lower energy than 11, and the anti aldol is the predominant stereoisomer.

The stereoselectivity predicted by Chan's model is consistent with his experimental results. However, the ratio of two isomers is independent of the geometry of the silyl enol ethers. In a further examination, Heathcock and his coworkers carried out a systematic investigation on the reactions of various enol-silanes with benzaldehyde and isobutyraldehyde [13]. Some of their results are presented in Table 2.6.

Table 2.6
Reaction of Enolsilanes with Benzaldehyde [13]

Entry	R	R'	Lewis Acid	Z:E	Syn:Anti
1	i-Pr	Ph	SnCl_4	100:0	37:63
2	Et	Ph	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	100:0	60:40
3	i-Pr	Ph	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	97:3	56:44
4	i-Pr	i-Pr	$\text{TiCl}_4 \cdot \text{Et}_2\text{O}$	97:3	46:54
5	i-OPr	Ph	SnCl_4	11:89	30:70
6	t-Bu	Ph	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	100:0	>5:95

From these results, they concluded that there is essentially no stereoselectivity with any of the enolsilanes they studied, except the *t*-butyl derivative (entry 6). However, the syn/anti ratio in entry 6 is totally different from that of the corresponding Li-enolate reaction with benzaldehyde. In the latter case, it is quite probable that the reactions proceed via cyclic transition states as discussed above. Consequently, they believe that these product ratios are in best accord with an open transition state. There are two reasons for that argument. First, there is no effect of the specific acid (TiCl_4 , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, SnCl_4) on stereoselectivity, which implies that the Lewis acid is not intimately associated in the transition state for the reaction. Second, the enolsilane double bond geometry does not significantly affect the ratio of products whereas it does in the Li-enolate reaction.

The open transition state or acyclic model is as follows:

Fig. 2.4 Open Transition State Model

This model is based on the assumption that a Lewis acid is coordinated with the aldehyde oxygen on the hydrogen side [24, 12]. Among these four transition states, 13 and 16 are destabilized because of the gauche interaction between BF_3 and the methyl group. On the other hand, the 13 and 15 transition states are not very stable due to the R-R' interaction especially when a bulky R is employed. Overall, there is no clear cut indication of which transition state is the most stable leading to a predominant product stereochemistry. Nevertheless, the exceptional example (entry 6) can be accounted for with this model. Namely, Z-5,5-dimethyl-3-trimethylsilyloxy-2-pentene proceeds via the transition state 14 since the transition state 13 has higher energy due to the severe R' and R interac-

tion ($R=t$ -butyl in this case). As a result, a high anti ratio is observed.

2.1.3 Catalytic Mukaiyama Reaction A number of simple Mukaiyama aldol condensations catalyzed by a variety of salts have also been reported.

The reactions of silyl enol ethers and acetals catalyzed by trityl perchlorate ($\text{Ph}_3\text{C}^+\text{ClO}_4^-$) led to the discovery of utilizing this salt to activate the carbonyl groups of aldehydes in the aldol reaction with silyl enol ethers [19]. In the first place, a trimethylsilyl enol ether was chosen as an enolate component and was treated with benzaldehyde in the presence of a catalytic amount of trityl perchlorate (5% mol) in dichloromethane. The aldol reaction proceeded smoothly at -78°C to give the corresponding β -hydroxy ketone in good yield (80%). However, it was noted that the diastereoselectivity of the reaction was low. Later, it was found that anti aldol was obtained preferentially by using the tert-butyltrimethylsilyl enol ether.

The results are shown in Table 2.7.

Table 2.7 [19]

Entry	Silyl Enol Ether	Z:E	Aldehyde	Yield	Syn:Anti
1		11:89	PhCHO	74	51:49
2		24:76	PhCHO	89	16:84
3		94:6	PhCHO	80	27:73
4		99:1	PhCHO	89	58:42
5		0:100	PhCHO	77	64:36
6		0:100	PhCHO	92	26:74

While the precise reaction mechanism is not yet known, open transition states similar to those shown in Fig. 2.4 account for the observed stereochemistry.

The Mukaiyama reactions were also found to be catalyzed by tris(diethylamino)sulfonium (TAS) difluorotrimethylsilicate [23], which serves as a fluoride ion source to generate the TAS enolate shown in Fig. 2.5.

Fig. 2.5 TAS enolate

The anionic moiety of the enolate in THF solvent possesses negligible bonding interaction with the TAS counter cation and acts as a highly nucleophilic species.

The reaction scheme is as follows (Scheme 2.3).

Scheme 2.3

The problems with this type of reaction are that the equilibrium (2) lies so far to the left [22,15] that the aldol reaction of the TAS enolate and aldehyde substrate does not take place smoothly. In addition, the aldol anion 18 reacts with other aldehyde molecules to give higher polymers. However, an excess of 19 can be used to trap the 20 effectively.

The aldol reaction catalyzed by $\text{TAS}^+\text{Me}_3\text{SiF}_2^-$ gives an syn aldol as the major isomer independent of the configuration of a silyl enol ether. Some examples are given below:

Table 2.8

Aldol Reaction via TAS Enolates [15,22]

Entry	Enol Silyl Ether	Aldehyde	Z/E	Syn:Anti
1		PhCHO	100:0	86:14
2		PhCHO	100:0	84:16
3		PhCHO	30:70	63:37
4		PhCHO	9:91	94:6

Another similar catalytic reagent [21,20] is tetraalkylammonium fluoride (eq.2.10). Among different tetraalkylammonium fluoride reagents, such as tetrabutylammonium fluoride (TBAF), benzyltrimethylammonium fluoride (BTAF) and tetraethylammonium fluoride (TEAF), TBAF serves as the most effective catalyst, affording aldol adducts in high yield.

The sparingly solubility of metal fluorides in organic solvents makes it necessary to use a large amount of salts and a higher temperature in order to obtain a reasonable rate.

In the presence of TBAF, the diastereoisomer ratio of the reaction shown in

eq.2.10 proved to be time dependent. The ratio of anti to syn changed gradually from 65:35 (5 min, 45% yield) to a final equilibrium of 54:46 (8 h, 86%). The ready reversibility of the present aldol reaction suggests that the time dependency of the diastereoisomer ratio is caused by a retroaldol process.

Recently, it was reported that rhodium (I)-diphosphine complexes catalyze the aldol addition of enolsilanes to aldehydes, an enantioselective version being possible if chiral phosphines are used [65].

2.1.4 Synthesis of Silyl Enol Ether The initial stage of a program to study any kind of aldol reaction is to generate the enolate.

The general procedure to make an enolate is outlined in scheme 2.4:

Scheme 2.4

Various cations can be introduced into an enolate structure with different bases.

The common bases associated with a lithium cation are amides, for example, lithium diisopropylamide (LDA), lithium cyclohexylisopropylamide (LCPA), lithium 2,2,6,6-tetramethylpiperidide (LTMP) [26], etc.

Metal hydrides such as sodium hydride and potassium hydride have been found to be useful only to generate enolates from ketones [29].

A DME solution containing a zinc enolate can be obtained by treatment of 1 molar equiv of lithium enolate with 0.5 molar equiv of anhydrous zinc chloride.

A solution of the corresponding magnesium enolate can either be obtained by an analogous reaction of 1 molar equiv of lithium enolate with 0.5 molar equiv of anhydrous magnesium bromide or be obtained from a reaction of an enol acetate with dimethylmagnesium [28].

House and Kramar [27] have discussed detailed generalizations regarding the composition and reactions of enolate mixtures derived from unsymmetrical ketones, namely, the regiochemical aspect. The stereochemical aspects of enolate chemistry, however, will be summarized below.

The question arises as to whether two isomers (Z and E) can be interconverted readily? It is appropriate to consider stereoisomeric enolates (Z and E) as separate entities since the energy barrier separating the two stereoisomers must be appreciable [27]. Equation 2.11 below illustrates the fact that during this interconversion the carbonyl π -orbital and carbanion p-orbital lie at right angles (as shown in 23) and electron delocalization is no longer possible [33].

Therefore, Z and E enolates are derived from two separated courses, which can be depicted in scheme 2.5:

Scheme 2.5

It has been reported that conformer 25 is more stable than conformer 26 by about 0.8 kcal/mol in propionaldehyde [31], and the energy difference is presumable even greater for ketones and esters, where R is larger than hydrogen. When $\text{R}=\text{C}_2\text{H}_5$, the estimated energy difference between 25 and 26 is 1.68 Kcal/mol, which corresponds to a Z/E ratio of 51 to 1 at -70°C [26].

According to the argument above, one would anticipate that Z enolate will be more favored as R becomes bulkier. However, in reality, the Z/E ratio is affected not only by the structure of the enolate, but by bases and reaction medium as well. It was found that the similar bases LDA and LCPA give almost identical Z/E ratios while the more bulky LTMP gives more E enolate than LDA [26]. In addition, the nature of solvent medium has a substantial effect on the Z/E ratios. The results [30] recorded in Table 2.9 point to a smooth change of the isomer ratio.

Table 2.9

Entry	Equiv HMPA*	Solvent	Cis/Trans
1	0	100% THF	9:91
2	0.5	3% HMPA-THF	11:89
3	1.0	6% HMPA-THF	47:53
4	2.0	11% HMPA-THF	77:23
5	4.7	23% HMPA-THF	84:16

The composition of two metal enolate isomers can be analyzed by derivatization with TMSCl as illustrated in eq.1.12.

It has proved to be difficult to synthesize a specific configuration of silyl enol ethers, especially when esters are involved. The complications are C vs O silylation and sensitivity of products towards water, acid and heat. These make the products hard to isolate and purify.

By adjusting parameters such as the structure of a substrate and a silylating reagent, however, one should be able to overcome these difficulties. For example [32], addition of trimethylsilyl chloride to methyl lithioacetate in tetrahydrofuran solution at -78°C , followed by warming to room temperature, produces a mixture of O-silylated (65%) and C-silylated (35%) products as shown in eq.2.13.

while ethyl lithioacetate gives slightly greater amounts of the C-silylated ester (40%), and *tert*-butyl lithioacetate gives almost exclusively (98%) the C-silylated ester. Rathke's experimental results reveal a pattern that substitution on the α -carbon favors O-silylation while the substitution on the alcohol portion of the ester favors C-silylation.

The employment of *tert*-butyldimethylchlorosilane (TBSCl) in trapping lithium ester enolates makes the ketene acetals easier to isolate [32]. Tetrahydrofuran solutions of lithium ester enolates are inert to TBS at -78°C . A sluggish reaction occurs on warming to room temperature but is accompanied by appreciable amount of ester condensation. Satisfactory results can be obtained with solvent mixtures containing HMPA. In addition to giving a more stable silyl enol ether, TBSCl has a greater tendency than trimethylsilyl chloride to furnish O-silylated products as shown in eq.2.14.

In summary, a desirable enolate can be obtained by proper choices of substrate structure, solvent, base and a trapping reagent.

2.1.5 The Use of Organolanthanides in Organic Synthesis. Organolanthanide chemistry and structural investigations of its molecular species are in rapid evolution and it allows for increasing understanding of organic reactions induced by

lanthanides. For about the past decade there has been an increasing interest by organic chemists in the lanthanides. Organic chemistry first benefited from the wide use of NMR shift reagents, but catalysts and reagents based on lanthanide derivatives are being investigated more and more. Several review articles are available [34-37].

Various oxidation states of lanthanides are widely used in organic synthesis: metals, Ln(II), Ln(III), Ln(IV). The main oxidation state is +3, hence, Ln(IV) compounds are powerful oxidants [38], while divalent lanthanides are one-electron donors [39].

One characteristic of the lanthanides is the hardness of the metal center. Therefore, Ln(IV), Ln(III) and Ln(II) derivatives are Lewis acids, as deduced from their chemical behavior, but their properties are closely dependent on the nature of the ligands around the metal center. Another characteristic feature of lanthanides is their strong affinity for oxygen. This oxophilicity is a property useful for the activation of oxygenated organic functions.

The following are some examples of the applications of lanthanide derivatives in organic reactions.

Lanthanide metals, such as cerium, were investigated by Imamoto and his co-workers [40] in Barbier-type and Reformatsky-type reactions. These types of reactions are of prime importance since they provide ways to make new C-C bonds. In most of their experiments, cerium amalgam or cerium turnings were used in the presence of a catalytic amount of mercury(II) chloride. Table 2.10 below shows that many allyl or propargyl halides and carbonyl compounds smoothly lead to homallylic alcohols while Table 2.11 gives evidence that β -hydroxyesters could be obtained in good yields from α -bromo and β -iodo esters.

Table 2.10

Cerium Amalgam Mediated Synthesis of Homoallylic Alcohol[7]

Entry	Halide	Carbonyl Comp.	Product*	Yield(%)
1	$\text{CH}_2=\text{CH}-\text{CH}_2\text{I}$	$p\text{-BrC}_6\text{H}_4\text{COCH}_3$	$p\text{-BrC}_6\text{H}_4\text{C}(\text{OH})(\text{CH}_2)_2\text{CH}_2\text{CH}=\text{CH}_2$	95
2	$\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{I}$	$p\text{-NCC}_6\text{H}_4\text{CHO}$	$p\text{-NCC}_6\text{H}_4\text{CH}(\text{OH})(\text{CH}_2)_2\text{C}(\text{CH}_3)=\text{CH}_2$	69
3	$\text{HC}\equiv\text{C}-\text{CH}_2\text{I}$	$p\text{-ClC}_6\text{H}_4\text{CHO}$	$p\text{-ClC}_6\text{H}_4\text{CH}(\text{OH})-\text{CH}_2\text{C}\equiv\text{CH}$	65
4	$\text{C}_6\text{H}_5\text{CH}_2\text{I}$			59
5	$\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2\text{I}$			79

* Reactions were performed in THF from 0 °C to room temperature for iodides, and at room temperature for bromides.

Table 2.11

Reformatsky Reaction Using Cerium Metal[7]

Entry	Halo ester	Carbonyl Comp.	T (°C)	Hydroxy ester(yield(%))
1	ICH_2COOEt	$n\text{-C}_7\text{H}_{15}\text{CHO}$	0	63
2	ICH_2COOEt	$\text{C}_6\text{H}_5\text{CHO}$	0	81
3	ICH_2COOEt	$p\text{-NO}_2\text{C}_6\text{H}_4\text{COCH}_3$	-40	74
4	$\text{BrCH}_2\text{COOEt}$	$\text{C}_6\text{H}_5\text{COCH}_3$	r.t.	60

The use of cerium metal to mediate the Barbier-type and Reformatsky-type reactions has several characteristic features [40]: (1) The reaction proceeds in the

presence of carbonyl compounds giving homoallylic alcohols in satisfactory yields. (2) The reaction is chemoselective; ketones react smoothly, while other functional groups such as vinylic bromo (entry 1), alkoxycarbonyl (entry 5), and cyano (entry 2) remain unaffected under the conditions employed. (3) Propargyl iodide, whose organometallic derivatives are not easily available, also reacts with carbonyl compounds to afford the addition products in 60-70 % yields.

The dipositive oxidation state is unusual for the lanthanides. The divalent lanthanide species are sufficiently stable only when certain electronic configurations $\text{Eu}^{2+} = 4f^7$, $\text{Sm}^{2+} = 4f^6$ and $\text{Yb}^{2+} = 4f^{14}$ are achieved. The electrode potential values ($\text{Ln}^{3+}/\text{Ln}^{2+}$) [6] in aqueous solution are -0.35V (europium), -1.15V (ytterbium) and -1.55V (samarium). These values indicate the reactivity sequence as follows: $\text{Sm(II)} > \text{Yb(II)} > \text{Eu(II)}$. Indeed, the most interesting reactions arise from Sm^{2+} derivatives.

D.F.Evans and his co-workers were the first to prepare and study Grignard analogues based on Eu(II) , Yb(II) and Sm(II) [41,42]. These organometallic species react as typical Grignard reagents:

Namy, Grignard and Kagan [43] first used Ln(II) species such as SmI_2 as a soluble electron-donor in Barbier-like reaction (eq.2.18).

This reaction was found to be of wide generality; hence its scope and mechanism were studied [44,45]. Electron transfer with radical intermediates are likely to be involved in the mechanism [41].

Some representative results are listed in Table 2.12.

Table 2.12
SmI₂ in Barbier-like Reaction [44,45]

Entry	Carbonyl Comp.	RX	Conditions	Product	Yield(%)
1	2-octanone	CH_3I	25 C, 1h	$n\text{-C}_7\text{H}_{15}\text{-C(OH)(CH}_3)_2$	95
2	2-octanone	$n\text{-BuOTf}$	65 C, 12h	5-methylundecan-5-ol	49
3	cyclohexanone	allyl bromide	25 C, 20min	1-allylcyclohexanol	69
4	pivaldehyde	allyl iodide	25 C, 5min	$\text{t-BuCH(OH)-CH}_2\text{-CH=CH}_2$	78

The divalent lanthanides are also powerful reducing agents. As was indicated by the electrode potential values, samarium(II) has much stronger reducing power than ytterbium(II) and europium(II). For example, SmI_2 converts aldehydes to alcohols quantitatively at room temperature while YbI_2 is quite inefficient [20].

Several types of organic molecules can be reduced regioselectively by the

divalent lanthanide species: (1) Cinnamic acid and its ethyl ester are reduced at room temperature in excellent yields [46]:

R=H, Et.

Ln=Yb, Sm.

eq.2.19

(2) Selective removal of ortho halogens in halogenobenzoic acids was obtained by using an excess of $(\text{C}_6\text{F}_5)_2\text{Yb}$ in THF [47].

(3) Recently it was found that SmI_2 is the reagent of choice for the reduction of α -hetero substituted ketones to ketones [48,49]:

X=Cl, SPh, SO_2Ph , HgCl .

Many of the applications of lanthanides to organic chemistry deal with trivalent lanthanides, the +3 oxidation state being the most common state. By transmetallation between organolithium compounds and anhydrous CeI_3 , organocerium reagents can be made, which then can be used in Grignard-like reactions.

Table 2.13 gives some examples of this type of reaction involving organocerium reagents [50].

Table 2.13

Addition of organocerium reagents to aldehydes and ketones [17]

Entry	Reagent	Carbonyl Comp.	Product	Yield(%)
1	$n\text{-BuLi}-\text{CeCl}_3$	PhCOCH_3	$\text{PhC(OH)(CH}_3)_n\text{-Bu}$	98
2	$i\text{-BuLi}-\text{CeCl}_3$	PhCOCH_3	$\text{PhC(OH)(CH}_3)_n\text{-Bu}$	98
3	$n\text{-BuLi}-\text{CeCl}_3$	PhCH=CH-CHO	$\text{PhCH=CH-CH(OH)}_n\text{-Bu}$	96
4	$\text{HC}\equiv\text{CLi}-\text{CeCl}_3$			89
5	$i\text{-BuLi}-\text{CeCl}_3$	$(\text{PhCH}_2)_2\text{CO}$	$(\text{PhCH}_2)_2\text{C(OH)}_n\text{-Bu}$	65

As one can see, the organocerium(III) reagents react cleanly in THF at -78°C to -65°C with a variety of carbonyl compounds including those which are very prone to enolization [50] (see entry 4,5 in Table 2.12). This property is attributed to the low basicity of the organocerium reagents [50].

Another type of transmetallation between lithium reagents and lanthanide halides is that to produce a cerium enolate from a lithium enolate and anhydrous cerium(III) chloride at -78°C [51] as shown in eq.2.23.

This transmetallation product, when used in an aldol reaction as shown below, exploits the stronger chelation of the cerium ion (relative to lithium) in the six-membered intermediate. Therefore, retro-aldol and/or cross enolizations are suppressed, and higher yields are obtained than reactions with the corresponding lithium enolates.

However, there are no differences in stereoselectivities observed between the two enolate systems.

Fry reported that lanthanide ions such as LaBr_3 can assist electrochemically initiated aldol condensations as shown below:

These reactions are generally not diastereoselective [59].

Recently, Kagan and his co-workers [52] found that LaCl_3 can be used to catalyze the following reaction:

Since the reaction occurs at high temperature for long periods of time, it is not possible to obtain good stereoselectivity.

The tetravalent oxidation state of the lanthanides is also uncommon. The lanthanides with a +4 oxidation state are very powerful oxidation reagents. Unfortunately, only Ce^{4+} is readily accessible. The most widely used ceric salt as a strong oxidizing reagent is ceric ammonium nitrate (CAN). The following is a brief view of the synthetic aspects of CAN [5].

(1) Oxidation of RCH_2OH to $RCHO$. eq.2.27

In summary, with the increasing awareness of unique properties of lanthanides, organic chemists may benefit increasingly by using lanthanide elements. It can be anticipated that the near future will bring many new developments in this area.

2.2 Results and Discussion:

2.2.1 Catalytic Properties of $[(\text{TMS}_2\text{Cp})_2\text{YbCl}]_2$ and the scope of the Mukaiyama reactions. As stated earlier, the control of stereochemistry in C-C bond forming reactions is a rather challenging area to date in organic chemistry. The use of metal enolates provides a way to synthesize aldol products stereoselectively in some particular cases; however, in other cases, it fails. The Mukaiyama aldol condensation, on the other hand, provides mild reaction conditions to circumvent the di-, poly, or self-condensation products sometimes found in metal-enolate aldol condensations, but essentially no stereoselectivity is observed [13].

In order to achieve the control of stereoselectivity as well as to maintain mild reaction conditions in aldol condensations, the present study of using organolanthanide reagents in the aldol condensation was started. The use of organolanthanide reagents has several advantages. First, the bulky substituted cyclopentadienyl ligand may play an essential role in the control of stereochemistry. Second, the organic ligands provide organolanthanide complexes with suitable solubilities in organic solvents. Finally, the lanthanide (III) ions are Lewis acids, which might be able to activate and catalyze the aldol reactions.

The particular type of organolanthanide reagent explored is $[(\text{TMS}_2\text{Cp})_2\text{YbCl}]_2$. The TMS_2Cp ligand was chosen for it is bulky, and its anion is a weak base. Ytterbium (III) was studied because YbCl_3 is readily available, inexpensive, and Yb is the second smallest element in the lanthanide series. In addition, the dimer complex can be broken up by a Lewis base, such as benzal-

dehyde to form a Lewis acid-base complex, which would then be easily attacked by a nucleophile. The synthesis of this dimer complex was straightforward as illustrated by the following reactions.

27

It has been shown [52] that LaCl_3 could catalyze the Mukaiyama aldol condensation at reflux temperature in CH_2Cl_2 . However, such a high temperature would prevent the control of the stereochemistry of the reaction. In order to probe the specific reactivity of $(\text{TMS}_2\text{Cp})_2\text{YbCl}$ (27), the reaction of the trimethylsilyl enol ether of methyl isobutyrate with benzaldehyde was examined at various temperatures. This particular trimethylsilyl enol ether was used because it is easy to prepare. The reaction procedure is described as follows: to a methylene chloride solution of equimolar amounts of benzaldehyde and 27 was added one equiv of the trimethylsilyl enol ether of methyl isobutyrate. The reaction mixture was stirred at different temperatures for given periods of time. After hydrolysis, the resulting organic layer was extracted with pentane and washed with water. The aldol product, methyl 2,2-dimethyl-3-trimethylsilyloxy-3-phenylpropionate was obtained after the removal of solvents, and purification by column chromatography (silica gel).

The results are summarized in Table 2.14.

Table 2.14

Entry	T (°C)	Time (h)	% conversion of PhCHO
1	60	18	>99
2	25	12	>99
3	0	8	>99
4	-78	10	70

Table 2.14 demonstrates that 27 is an efficient reagent for the Mukaiyama aldol condensation even at -78°C . It is clear that the role of 27 is to complex the carbonyl groups on benzaldehydes as indicated by the fact that the carbonyl stretching band of benzaldehyde (1720 cm^{-1}) was shifted to 1660 cm^{-1} when an equivalent amount of 27 was added. As a consequence, carbonyl bonds may be lengthened and more easily attacked by nucleophiles, such as silyl enol ethers.

To investigate the effect of the amount of 27 upon the reaction, the following experiment was first carried out. After the reaction mixture of equal moles of trimethylsilyl enol ether of methyl isobutyrate, benzaldehyde and 27 in CH_2Cl_2 was stirred for 4h at 25°C , the volatile material was vacuum transferred to a flask immersed in a liquid nitrogen dewar flask. The analysis of this volatile material revealed that it contained solvent CH_2Cl_2 , TMSCl and trace amounts of the aldol product while the hydrolysis of the solid residue gave quantitative amounts of the hydroxy aldol product and the organic ligand from 27.

This finding suggests the following equilibrium:

If an excess amount of trimethylsilyl chloride, TMSCl, is used, it should be possible to drive the equilibrium far towards the formation of trimethylsilyl aldol product (29); therefore, the 27 would be liberated, and could then catalyze the next cycle of the reaction. Table 2.15 lists the yield and time of the aldol reaction in the presence of various amounts of 27. The reaction time was adjusted by the kinetic studies discussed in chapter 3.

Table 2.15

Entry	Cat A (mol ratio)	TMSCl (mol ratio)	Time (h)	% conversion of PhCHO
1	1	0	12	>99
2	0.10	1	11	>88
3	0.01	1	4	>99
4	0.005	1	6	74

The results in Table 2.15 show that 27 can be used as a catalyst in the Mukaiyama aldol reaction whereas, in the case of TiCl_4 or other Lewis acids, an equimolar amount has to be applied to obtain the highest yield.

The solvent effects on this reaction were studied by treating the silyl enol ether (28) with one equiv of benzaldehyde in the presence of 10% of 27 in different kinds of solvents at room temperature (Table 2.16).

Table 2.16
Solvent Effects

Entry	Solvent	% conversion of PhCHO
1	Methylene Chloride	>99
2	Diethyl Ether	>95
3	THF	82
4	Hexane	50

The results reveal that the reaction goes almost to completion when polar solvents such as CH_2Cl_2 , THF, and diethyl ether are used; however, in the case of non-polar solvents such as hexane, the yield is poor probably due to the low solubility of the benzaldehyde-27 complex. In a comparison, aldol products were not obtained at all in diethyl ether or tetrahydrofuran when common Lewis acids such as TiCl_4 or BF_3 were used. In the later case, diethyl ether and tetrahydrofuran compete with benzaldehyde to complex the Lewis acids. As a result, the complexation of TiCl_4 with benzaldehyde does not occur to a great extent. On the contrary, Yb(III) is a weaker Lewis acid, and different bases compete more effectively for it so that the Mukaiyama aldol reaction catalyzed by 27 can take place even in THF or ether. In another words, the following equilibrium is established rapidly.

To examine the versatility of the Mukaiyama reaction catalyzed by the Yb(III) complex, various kinds of substrates were used in the presence of a 0.01 molar equiv of 27 in CH_2Cl_2 at room temperature for 4-5 h. Results are summarized in Table 2.17.

Table 2.17

Entry	Silyl Enol Ether	Aldehyde	Isolated Yield
1			82
2			85
3			86
4			57
5			51
6			NR.
7			51
8			56
9			85
10			NR.
11			NR.
12			NR.
13			NR.
14			NR.

Careful scrutiny of the results listed in Table 2.17 leads to the fact that silyl enol ethers derived from esters can react with various kinds of aldehydes,

aromatic as well as aliphatic, whereas the trimethylsilyl enolates derived from ketones in entry 12, 13 or cyclopropane derivative in entry 14 fail to react with benzaldehyde. In addition, an aldol product cannot be obtained when the silyl enol ether is mixed with ketones such as acetophenone and cyclohexanone. This reaction pattern shows a certain chemoselectivity.

As far as regioselectivity is concerned, the silyl enol ether gave only the 1,2 addition products when α, β unsaturated aldehydes were used as shown in entry 7, 8. This kind of product is almost impossible to obtain when a metal enolate is used.

2.2.2 Stereoselectivity and Possible Transition States. The important aspect of this study was to investigate the simple diastereoselectivity of the Mukaiyama aldol reaction. The first task was to synthesize silyl enol ethers. As discussed before, this is not a simple task. However, with proper choices of the silylating reagent and ester, the following sets of silyl enol ethers were prepared successfully.

Cy = Cyclohexyl

* TMSCl = Trimethylsilyl Chloride

* TBDMSCl = t-Butyldimethylsilyl Chloride

With these different silyl enol ethers in hand, the Mukaiyama aldol reactions were carried out with 10-20% of 27 in CH_2Cl_2 at -78°C . The results are tabulated in Table 2.18.

Table 2.18

Entry	Silyl Enol Ether(Z:E)	Aldehyde	Syn/Anti	Yield (%)
1	(97:3)	PhCHO	78:22	60
2			70:30	63
3	(15:85)	PhCHO	19:81	58
4			18:82	65
5	(99:1)	PhCHO	90:10	51
6	(26:74)	PhCHO	25:75	55
7	(82:18)	PhCHO	74:26	52
8	(100:0)	PhCHO	82:18	70

Based on the results in Table 2.18, several generalizations can be made. First, the double bond geometry is the major controlling factor in determining the syn/anti product ratio; namely, the *E* silyl enol ethers give the anti aldol products whereas the *Z* silyl enol ethers afford the syn aldol products. Second, the data show that changing the size of the group attached to silyl enol ether from OCH_3 to OEt , OiPr has little effect on the product isomer ratios. Finally, the *E* silyl enol ethers seem to be more selective giving a high ratio of anti product than the *Z* silyl enol ethers.

These generalizations allow us to postulate a reaction scheme for the Mukaiyama reaction catalyzed by the Yb(III) complex. The fact that the double bond geometry strongly correlates with the ratio of the product isomers suggests

that the reaction proceeds through a cyclic transition state rather than the acyclic transition state with which the product isomer ratio is independent of the geometry of the silyl enol ether as discussed in the case of Mukaiyama reactions activated by TiCl_4 . The formulated reaction scheme 2.6 is shown below:

scheme 2.6

Notice that the silyl group has to be syn to the chlorine atom in the Yb(III) complex in order to form the partial Si-Cl bond in the cyclic transition states.

This scheme can then be used to interpret the following facts. First, the size of OR can be varied without the loss of aldol diastereoselection. This implies that the bulkiness of the ligand on the Yb(III) dominates the determination of the product isomer ratio, and the interaction between the ligand on the Yb(III) and the Ph group is more important than that between the OR group and Ph. As a result, transition states 31, 32 have higher energy than transition states 30, 33, and the enolates proceed through transition states 30, 33 to give selective aldol products. Second, in the transition state 33 derived from the Z silyl enol ether, the methyl group is in an axial position whereas in the 30 transition state derived from the E silyl enol ether the methyl group is in an equatorial position. An energy difference of 1.7 Kcal/mol has been found between axial methylcyclohexane and equatorial methylcyclohexane [53]. The difference in energy might be important in the higher selectivity of E silyl enol ether since 30 has lower energy than 33.

In summary, the product isomer ratio of the Mukaiyama reaction catalyzed by the Yb(III) complex can be predicted by the double bond geometry of silyl enol ether. In contrast, such a correlation is not observed when the Mukaiyama reaction is activated by TiCl_4 or other common Lewis acids.

2.2.3 Assignment of Stereochemistry: Problems in assigning stereochemistry to diastereoisomeric aldol products have been examined by several research groups [14, 25 57, 58]. The following criteria are helpful to achieve such assignments.

In nonpolar aprotic solvents: (1) the two diastereoisomers exist as intramolecularly hydrogen bonded compounds as shown in the following structures 34 and 35 with the six-membered ring containing the hydrogen bond in a

chair conformation and with the maximum number of substituents R equatorial;

Fig. 2.6 Chair Conformation

(2) the anti isomer 34, with fewer nonbonding steric interactions, forms a stronger hydrogen bond with the result that the ir frequency difference, $\delta_{\text{free OH}} - \delta_{\text{assoc. OH}}$ is larger for (34) than for (35) [57];

(3) the NMR coupling constant J_{ab} is typically 6-9 Hz for the anti isomer 34 (with trans diaxial protons H_a and H_b) while J_{ab} is typically 2-5 Hz for the syn isomer 35. This can be best illustrated by the following Newman projections:

Fig. 2.7 Newman Projection

It is known that the coupling constant is a function of the angle between the two protons. The angle between H_a and H_b is 180° in the anti conformation, and 60° in the syn conformation, provided that there is hydrogen bonding in both conformations. As a result, the coupling constant (J_{ab}) in the anti product is larger than that in the syn product. In addition, the coupling constant difference is reduced when the hydrogen bond is disrupted by acetylating or silylating the hydroxyl group or measuring the NMR spectrum in a protic solvent;

(4) the chemical shifts for H_b in the anti and syn compounds are different with anti upfield and syn downfield.

The application of these criteria led to the assigned stereochemistry.

2.3 Summary

An organoytterbium (III) complex, $[(\text{TMS}_2\text{Cp})_2\text{YbCl}]$, has been found to be an effective catalyst for Mukaiyama aldol condensations. At room temperature, the reaction of a silyl enol ether with benzaldehyde goes smoothly in the presence of 0.01 molar percent of the catalyst to give >99% of the product after 3h. At -78°C , the reaction gives kinetically controlled diastereoselectivity; namely, E silyl enol ethers give anti aldol products while Z silyl enol ethers afford syn aldol products predominately. Based on the above experiments, a cyclic reaction scheme is proposed to predict the product isomer ratios. Moreover, this cross aldol reaction exhibits a certain reaction pattern. For example, both aromatic and aliphatic aldehydes are usable substrates. Ketones such as acetophenone and cyclohexanone, or cyclopropane derivative, on the other hand, do not react with silyl enol ethers. Similarly, the silyl enol ethers derived from ketones do not react with benzaldehyde, either. When α , β -unsaturated aldehydes are used, only 1,2-addition products are formed.

2.4 Experimental

General. Unless otherwise indicated, materials were obtained from commercial suppliers and distilled before use. Tetrahydrofuran (THF), diethyl ether and toluene were distilled from sodium/benzophenone, and degassed three times before use. Hexane was distilled from CaH_2 after refluxing overnight. Dichloromethane was vacuum transferred from solutions of dichloromethane and lithium tetrahydridoaluminate (LiAlH_4) after the solution was stirred overnight, and degassed before use. All operations involving air-sensitive compounds were carried out with either an argon atmosphere glovebox, or standard Schlenk techniques. ^1H NMR spectra were recorded on the UCB-200 (200 MHz, FT), or UCB-250 (250 MHz, FT), or UCB-500 (500 MHz, FT) spectrometers. Significant ^1H NMR data are tabulated in order: multiplicity (s, singlet; d, doublet; m, multiplet), number of protons, coupling constant in Hertz. Significant ^{13}C NMR data are also recorded. Both ^1H NMR and ^{13}C NMR chemical shifts are referenced to tetramethylsilane (TMS) proton and carbon resonances either directly with TMS as an internal standard or indirectly by resonance of solvents referenced to TMS. Elemental analyses were performed by the Microanalytical Laboratory operated by the College of Chemistry, University of California, Berkeley. Infrared spectra were determined on a Perkin-Elmer Model 297 spectrometer. Visible spectra were determined on a UV/Visible IBM/9430 spectrophotometer. Low voltage mass spectral data are expressed as m/z (intensity expressed as percent of total ion current). All weights, unless otherwise specified, are ± 0.01 g.

Lithium Diisopropylamide (LDA). To a stirring solution of 0.56 g (5.5 mmol) of diisopropylamine in 15 mL of dry ethereal solvent (THF or ether) at 0 °C was added dropwise 5.5 mmol of a solution of n-BuLi in hexane. Following the addition, the mixture was stirred for an additional 10 min.

General Procedure for the Preparation of Silyl Ketene Acetals of Simple Esters [30]. A. Enolization in THF. A solution of 5.5 mmol of LDA in 15 mL of dry THF was cooled to -78 °C. To this rapidly stirred solution was added 5.0 mmol of an ester over 4 min. Following the addition, the reaction mixture was stirred at -78 °C for 2.5 min, and then treated with 3.59 mL (5.5 mmol) of t-BuMe₂SiCl in HMPA. After an additional 2 min at -78 °C, the reaction mixture was warmed to room temperature over 30 min. Pentane extraction gave the crude product, which was further purified by distillation under vacuum.

B. Enolization in 23 vol % HMPA-THF. A solution of 5.5 mmol of LDA in 15 mL of dry THF was cooled to -78 °C and 4.5 mL of HMPA was added. To this rapidly stirred solution was added 5.0 mmol of an ester over 4 min. The reaction mixture was stirred at -78 °C for 2.5 min, and then treated with 1.59 mL of t-BuMe₂SiCl (5.5 mmol) in hexane. The resulting mixture was stirred for an additional 2 min, and was then allowed to warm to room temperature over 30 min. Pentane extraction afforded a crude product, which was further purified by vacuum distillation.

Pentane extraction was to dilute the reaction mixture with 30 mL of ice-cold pentane, to wash the mixture quickly 3 times with ice-cold water. The organic

layer was separated, washed with saturated brine, and dried over Na_2SO_4 . The solvent was then removed by rotary evaporation.

The products obtained in A and B were subjected to ^1H NMR analysis. Z/E isomer ratios were determined by integration of two different peaks corresponding to two isomers.

1-Methoxy-2-methyl-1-trimethylprop-1-ene (28). In a 50 mL flask containing 14 mmol of LDA and 30 mL of ether, 1.37 mL of methyl isobutyrate (12 mmol) was added dropwise at 0 °C. After the resulting mixture was stirred for 30 min at that temperature, chlorotrimethylsilane (1.88 mL, 15 mmol) was added at once. The solution was then allowed to warm to room temperature over 1 h. A white solid formed, which was filtered. The removal of solvent afforded 1.60 g of crude product (84%). Vacuum distillation gave 1.00 g of product (53%), b.p. 58–60 °C/20 mmHg; IR: 1710 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.13 (s,9), 1.44 (s,3), 1.49 (s,3), 3.42 (s,3). [Lit.(54) b.p. 35 °C/15 mmHg; IR: 1708 cm^{-1} ; ^1H NMR (CCl_4): δ 0.18, 1.48, 1.54, 3.48.]

(Z)-1-Ethoxy-1-(t-butyldimethylsilyloxy)prop-1-ene: The tert-butyldimethylsilyl enol ether of ethyl propionate was prepared by method B as described above. Distillation gave 0.68 g (yield: 63%) of the product, Z/E ratio=97:3; b.p. 43–44 °C/0.1 mmHg; ^1H NMR (CDCl_3): δ (Z-isomer) 0.10 (s, 6), 0.88 (s, 9), 1.19 (t, 3, $J=6.9$), 1.45 (d, 3, $J=6.4$), 3.37 (q, 1, $J=6.4$), 3.61 (q, 2, $J=7.0$); ^{13}C NMR (500 Hz, CDCl_3): δ (Z isomer) -4.2, 9.6, 14.5, 18.1, 25.7, 62.7, 70.1, 155.9. [Lit[2]: ^1H NMR (CCl_4): δ (Z-isomer) 0.12, (s, 6), 0.93 (s, 9), 1.25

(t, 3), 1.45 (d, 3), 3.29 (q, 1), 3.65 (q, 2).]

(E)-1-Ethoxy-1-(trimethylsilyloxy)prop-1-ene: To a 100 mL flask containing 50 mL of THF and 8 mL of $\text{HN}(\text{i-Pr})_2$, was added 0.26 mL of $n\text{-BuLi}$ (2.2 M) dropwise at 0 °C. The resulting mixture was stirred for 15 min and cooled to -78 °C. To this solution 5.52 mL of ethyl propionate was added dropwise over 8 min. After an additional 5 min, the solution was treated with 7.60 mL of chlorotrimethylsilane (TMSCl). The reaction mixture was stirred for another 5 min period, and allowed to warm to room temperature over 30 min. White solid (LiCl) was precipitated. After 40 mL of cold pentane was introduced into the solution, the white solid was filtered. The solvent was removed by rotary evaporation. Distillation at reduced pressure gave 4.52 g of the desired product (yield, 54%), b.p. 42–45 °C/20 mmHg; Z/E ratio=15:85; ^1H NMR (CDCl_3): δ (E isomer) 0.15 (s, 9), 1.16 (t, 3, $J=7.1$ Hz), 1.44 (d, 3, $J=6.6$ Hz), 3.67 (q, 1, $J=6.6$ Hz), 3.77 (q, 2, $J=7.0$ Hz); ^{13}C NMR (CDCl_3): δ (E isomer) -0.29, 9.6, 14.8, 62.9, 80.3, 152.9; IR: 1700 cm^{-1} . [Lit.[2]: ^1H NMR (CCl_4) δ 0.19 (s, 9), 1.18 (t, 3), 1.43 (d, 3), 3.25 (q, 2), 3.58 (q, 1).]

Isopropyl propionate: To a mixture of 26.1 mL of propionic acid and 10.6 mL of isopropanol was added 4 mL of concentrated sulfuric acid. After the mixture was heated under reflux for 1 h, it was diluted with 55 mL of cold water. An organic layer separated and washed with 5% aqueous NaHCO_3 twice (2×25 mL) until no more CO_2 was evolved. If the separated aqueous layer was not basic, the above procedure was repeated. The organic layer was once again washed with 25

mL of water and separated with the aid of NaCl. The dried (Na_2SO_4) organic layer was distilled giving 8.02 g (50% yield) of product, b.p. 112–113 °C; ^1H NMR (CDCl_3): δ 4.93 (q, 2), 2.21 (q, 2, $J=7.6$), 1.15 (d, 6, $J=6.3$), 1.05 (t, 3, $J=7.6$); [Lit.[64]: 109–110 °C].

(Z)-1-(t-Butyldimethylsilyloxy)-1-isopropoxyprop-1-ene: This compound was prepared by the procedure B. Distillation afforded 0.60 g of the desired product (52%), Z/E ratio=99/1; b.p. 40–42 °C/1mmHg; ^1H NMR (CDCl_3): δ (Z isomer) 0.20 (s, 6), 0.98 (s, 9), 1.21 (d, 6), 1.55 (d, 3), 3.50 (q, 1), 4.12 (m, 1); δ (Z isomer) -4.3, 9.7, 18.0, 21.6, 25.6, 69.0, 72.3, 154.0. [Lit.[13] ^1H NMR (CDCl_3): δ 1.48 (d, 3), 3.48 (q, 2), 4.12 (m, 1)].

(E)-1-(t-Butyldimethylsilyloxy)-1-isopropoxyprop-1-ene: This compound was synthesized by the procedure A. Distillation gave 0.80 g of the product (70%) with Z/E ratio of 26/74, b.p. 50–52 °C/1mmHg; ^1H NMR (CDCl_3): δ 0.19 (s, 6), 1.09 (s, 9), 1.20 (d, 6), 1.52 (d, 3), 3.81 (t, 1), 4.32 (m, 1). [Lit.[13]: ^1H NMR (CDCl_3): δ 1.46 (d, 3), 3.78 (q, 1), 4.34 (m, 1).]

(Z)-1-(t-Butyldimethylsilyloxy)-1-methoxy-2-phenyl-ethene: This compound was made by procedure B; b.p. 95–97 °C/0.1mmHg; yield: 81%; Z/E ratio=100:0; ^1H NMR (CDCl_3): δ 0.26 (s, 6), 1.00 (s, 9), 3.69 (s, 3), 4.61 (s, 1), 7.45 (m, 5); ^{13}C NMR (CDCl_3): δ -3.9, 18.1, 25.8, 55.0, 78.4, 123.4, 126.5, 127.9, 137.0, 157.9; IR: 1640 cm^{-1} . Anal. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_2\text{Si}$: C, 68.18; H,

9.09; Found: C, 68.49, H, 8.91.

Cyclohexyl propionate: This compound was prepared by the method described for isopropyl propionate. Distillation provided the desired product in 45% yield; b.p. 45–48 °C/1mmHg; ^1H NMR (CDCl_3): δ 1.11 (t, 3), 1.20–1.80 (m, 10), 2.27 (q, 2), 4.73 (m, 1); ^{13}C NMR (CDCl_3): δ 9.1, 23.7, 25.3, 27.9, 31.6, 72.2, 173.9. [Lit. [63]: b.p. 93 °C/35 mmHg].

(Z)-1-(t-Butyldimethylsilyloxy)-1-(cyclohexyl)prop-1-ene: Procedure A gave 0.86 g of product (64%); b.p. 104–106 °C/1mmHg; ^1H NMR (CDCl_3): δ (Z isomer) 0.17 (s, 6), 0.95 (s, 9), 1.3–1.4 (m, 6), 1.52 (d, 3, $J=6.5$), 1.6–1.8 (m, 2), 1.8–2.0 (m, 2), 3.51 (q, 1, $J=6.5$), 3.85 (m, 1); ^{13}C NMR (CDCl_3): δ (Z isomer) –4.3, 9.7, 17.9, 23.2, 25.1, 25.3, 27.8, 31.5, 71.9, 74.4, 153.8; Z/E ratio=82/18; IR: 1660 cm^{-1} ; Anal. Calcd. for $\text{C}_{15}\text{H}_{30}\text{O}_2\text{Si}$: C, 66.67; H, 11.11; Found: C, 66.78; H, 11.38; Mass spectrum: m/z , 270.

2,2-Dimethyl-3-hexanol [55]: A solution of 5.30 mL (4.30 g, 57.2 mmol) of butanal in 20 mL of ether was cooled to –78 °C, and 38.2 mL (65.0 mmol) of a 1.7 M solution of t-BuLi in pentane was added over a 30 min period. The solution was stirred at –78 °C for 1 hr and allowed to warm to room temperature. After an additional 2.5 h at room temperature, 150 mL of saturated aqueous NH_4Cl was poured into the solution. The layers were separated, and the aqueous phase was extracted twice with ether. The combined organic layers were washed

with 10% aqueous NaHSO_3 , water, and then dried over MgSO_4 . Rotary evaporation of the solvent provided 6.85 g of crude product (95% pure by GC). IR: 3400 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3): δ 0.9 (s), 0.95 (t), 1.0-1.8 (br.), 3.2 (m).

2,2-Dimethyl-3-hexanone: A solution of 3.41 g (26.1 mmol) of 2,2-dimethyl-3-hexanol in 50 mL of CH_2Cl_2 was added to a rapidly stirring suspension of pyridium chlorochromate (8.4 g, 39.2 mmol) in 50 mL of CH_2Cl_2 . The mixture was stirred for 11 h, after which the solvent was decanted from the mixture, and the residue was extracted 3 times with ether. The combined organic extracts were passed through a pad of Florisil. The solvents were removed by rotary evaporation. The residue was distilled to give 1.48 g (44%) of colorless liquid. b.p. $124\text{--}126\text{ }^\circ\text{C}$; $^1\text{H NMR}$ (CDCl_3): δ 0.80 (t, 3, $J=7.3$), 1.04 (s, 9), 1.47 (sextet, 2, $J=7.3$, $J=7.0$), 2.36 (t, 2, $J=7.0$); IR: 1750 cm^{-1} . [Lit.[55]: b.p. $125\text{--}125.8\text{ }^\circ\text{C}$.]

2,2-Dimethyl-3-trimethylsilyloxy-3-hexene: To an ether solution of LDA (16.5 mmol) was added 2,2-dimethyl-3-hexanone (15 mmol, 1.92 g) dropwise at $-78\text{ }^\circ\text{C}$ over 5 min. After 2 h, chlorotrimethylsilane (2.10 mL, 16.5 mmol) was added, and the solution was allowed to warm to room temperature over approximately 30 min. When the solution mixture reached $0\text{--}10\text{ }^\circ\text{C}$, a white solid began to precipitate from the reaction mixture. After another 0.5-1 h, the reaction mixture was partitioned between pentane and saturated aqueous NaHCO_3 solution, and the pentane layer was separated and dried over Na_2SO_4 . Upon removal of the solvent, a pale yellow liquid was left. Distillation afforded 2.00 g of the product

(67%), b.p. 36–38 °C/0.1mmHg; ^1H NMR (CDCl_3): δ 0.22 (s, 9), 0.94 (t, 3, $J=7.5$), 1.04 (s, 9), 1.98 (dq, 2, $J=6.8$, $J=7.5$), 4.48 (t, 1, $J=6.8$); IR: 1660 cm^{-1} ; ^{13}C NMR (CDCl_3): δ 1.0, 14.5, 19.4, 28.6, 38.1, 106.1, 157.5; Mass spectrum: m/Z , 200; Anal. Calcd. for $\text{C}_{11}\text{H}_{24}\text{OSi}$: C, 65.93; H, 12.07; Found: C, 66.01; H, 12.32.

Bis[bis(trimethylsilyl)cyclopentadienyl]ytterbium Chloride Dimer (27): To a 50 mL of THF suspension of 2.28 g of YbCl_3 (8.1 mmol) was added 3.60 g of $(\text{TMS}_2\text{Cp})_2\text{Mg}$ in 20 mL of THF dropwise at room temperature. After the resulting red solution was stirred for 48 h at room temperature, the solvent was removed under vacuum. The red solid was then extracted by ether to remove insoluble material (MgCl_2). After the ether solvent was removed under vacuum, the residue was extracted by toluene. The removal of toluene gave 3.96 g of red solid (78%), which sublimed at 160–170 °C/ 10^{-5} – 10^{-6} torr. ^1H NMR (200 MHz, CDCl_3): δ 22.4 (s) ($w_{1/2} = 74$ Hz), ring protons are too broad to be observed; UV: $\lambda_{\text{max}}=418.4$ nm (in CH_2Cl_2); mp. 288–292 °C; Mass spectrum: m/Z , 1252 (dimer), 626 (monomer). Due to the air and moisture sensitivities of this compound, satisfactory elemental analysis was not obtained; [Lit. [60]].

General Procedures for The Reaction of Silyl Enol Ethers with Aldehydes: To a solution of 3 mmol of aldehyde and a catalytic amount of $(\text{TMS}_2\text{Cp})_2\text{YbCl}$ (27) (0.03–0.30 mmol) in 20 mL of CH_2Cl_2 was added 3 mmol of silyl enol ether and 3 mmol of chlorotrimethylsilane (TMSCl) at room temperature or at –78 °C. After certain periods of time, the reaction mixture was

quenched with 10 mL of aqueous NH_4Cl solution, and diluted with 20 mL of pentane. The organic layer was separated, washed, and dried over Na_2SO_4 . The solvent was removed by rotary evaporation. The crude product was examined by ^1H NMR to determine the yield of conversion of aldehydes and the ratio of isomers. The pure aldol adducts were isolated by flash or gravity column chromatography on silica gel.

In some cases, the ^1H NMR spectrum of the crude product revealed it to be a mixture of the β -hydroxy and β -silyloxy esters. In these cases, the crude mixture was desilylated by $\text{HF}-\text{CH}_3\text{CN}$ to give β -hydroxy esters.

Methyl 2,2-Dimethyl-3-trimethylsilyloxy-3-phenylpropionate (29):

^1H NMR (CDCl_3): δ -0.11 (s, 9), 1.02 (s, 3), 1.15 (s, 3), 3.70 (s, 3), 5.00 (s, 1), 7.30 (s, 5); ^{13}C NMR (500 MHz, CDCl_3): δ 0.067, 19.0, 21.6, 48.9, 51.5, 79.1, 127.3, 127.5, 140.7, 177.2; IR: 1700 cm^{-1} ; mass spectrum: 265 ($\text{M}-\text{CH}_3$); Anal. Calcd. for $\text{C}_{15}\text{H}_{24}\text{O}_3\text{Si}$: C, 64.27; H, 8.57; Found: C, 64.05; H, 8.47. (Lit.[52])

This compound was formed by the reaction of the trimethylsilyl enol ether of methyl isobutyraldehyde with benzaldehyde under different reaction conditions, and purified by gravity column chromatography.

(i) The silyl enol ether of methyl isobutyrate (1 mmol) was added to 30 mL of CH_2Cl_2 solution of benzaldehyde (1 mmol) and 27 (1 mmol). The reaction mixture was refluxed for 20 h, and was quenched with aqueous NH_4Cl solution. The work-up procedure described above gave >99% conversion of benzaldehyde to the desired product.

(ii) The reaction mixture of silyl enol ether and benzaldehyde with equivalent moles of 27 was stirred both at room temperature and at 0 °C overnight. After work-up, ^1H NMR showed >99% conversion of benzaldehyde to the product in both cases.

(iii) The above reaction mixture was also stirred at -78 °C for 10 h; 70% of benzaldehyde was converted.

(iv) To a CH_2Cl_2 solution of 9 mmol of benzaldehyde and 0.9 mmol of 27 were added 9 mmol of trimethylsilyl enol ether of methyl isobutyrate and 9 mmol of chlorotrimethylsilane (TMSCl). The reaction mixture was stirred for 11 h at room temperature. After work-up, ^1H NMR showed 88% conversion of benzaldehyde.

(v) The reaction with 0.1 equiv of 27 carried out in ether gave 82 percent conversion.

(vi) The reaction of 0.1 equiv of 27 was carried out in hexane but gave only 50% conversion of benzaldehyde.

(vii) When the reaction with 0.01 molar ratio of 27 was carried out in THF, the percentage conversion was 95%.

(viii) The percentage conversion is 74% when a 0.005 molar ratio of 27 was used.

Methyl 2,2-Dimethyl-3-trimethylsilyloxy-3-(4-biphenyl)-propanoate: To a solution of 4-phenylbenzaldehyde (1.05 g, 5.75 mmol) and 27 (0.036 g, 0.0575 mmol) in 10 mL of CH_2Cl_2 was added the trimethylsilyl enol ether of methyl isobutyrate (1.00 g, 5.75 mmol) and 0.63 g of TMSCl (5.75 mmol). The reaction mixture was stirred at room temperature for 2.5 h. After work-up described above, 1.8 g of crude product was obtained (pale yellow solid). ^1H NMR shows that >98% of 4-phenylbenzaldehyde was converted to the product. Sublimation under vacuum yielded pure white solid (85%), m.p. 74–75 °C; ^1H NMR (CDCl_3): δ 0.01 (s, 9), 1.01 (s, 3), 1.15 (s, 3), 3.70 (s, 3), 5.01 (s, 1), 7.26–7.62 (m, 9); mass spectrum: m/z , 356; Anal. Calcd. for $\text{C}_{21}\text{H}_{28}\text{O}_3\text{Si}$: C, 70.76; H, 7.92; Found: C, 70.92; H, 7.78.

(E) Methyl 2,2-Dimethyl-5-phenyl-3-trimethylsilyloxypent-4-enoate: This compound was obtained from the reaction of 0.38 g of trans-cinnamaldehyde (2.8 mmol), 0.50 g of trimethylsilyl enol ether of methyl isobutyrate (2.8 mmol), 0.018 g of 27 (0.028 mmol), and 0.31 g of TMSCl (2.8 mmol) in 30 mL of CH_2Cl_2 for 3h. After quenching, washing, extracting and drying as described before, 0.75 g of crude product was obtained. Flash chromatography gave 0.45 g of pure product (56%); ^1H NMR (CDCl_3 , 250 MHz): δ 0.09 (s, 9), 1.11 (s, 3), 1.19 (s, 3), 3.67 (s, 3), 4.48 (d, 1, $J=7.2$), 6.15 (dd, 1, $J=16.0$, $J=7.2$), 6.50 (d, 1, $J=16$), 7.35 (m, 5); ^{13}C NMR (500 MHz, CDCl_3): δ 177.0, 136.7, 131.9, 128.7, 128.5, 127.5, 126.4, 78.4, 60.2, 48.4, 21.2, 19.8, 0.23; IR: 1725, 1650 cm^{-1} ; mass spectrum: m/z , 306 (0.27), 291 (13.77), 205 (88.89). Anal. Calcd. for $\text{C}_{17}\text{H}_{26}\text{O}_3\text{Si}$: C, 66.67; H, 8.50; Found: C, 66.55; H, 8.60.

Methyl (E) 2,2-Dimethyl-3-trimethylsilyloxyhex-4-enoate: This compound was prepared by the reaction of 0.20 g of crotonaldehyde (2.9 mmol), 0.50 g of trimethylsilyl enol ether (2.9 mmol), 0.018 g of 27 (0.028 mmol), and 0.31 g of TMSCl (2.8 mmol) in CH_2Cl_2 for 3 h. After work-up and flash column chromatography, 0.35 g of product was obtained (51%). ^1H NMR (CDCl_3): δ 5.56 (d, q, 1, $J=14.5$, $J=5.3$), 5.41 (d, d, 1, $J=14.5$, $J=7.5$), 4.23 (d, 1, $J=7.5$), 3.64 (s, 3), 1.68 (d, 3, $J=5.3$), 1.11 (s, 3), 1.03 (s, 3), 0.04 (s, 9); IR: 1730, 1620 cm^{-1} ; ^{13}C NMR (500 MHz, CDCl_3): δ 177.4, 130.2, 128.2, 78.5, 51.5, 48.2, 21.2, 19.7, 17.7, 0.29; mass spectrum: m/z 244 (0.17), 229 (14.03), 143 (85.76). This compound is not stable upon standing; therefore, a satisfactory elemental analysis was not obtained.

Methyl 3-(2-Furyl)-2,2-dimethyl-3-trimethylsilyloxypropanoate: This product was synthesized from the reaction of 2-furaldehyde (0.28 g, 2.9 mmol), methyl silyl enol ether of methyl isobutyrate (0.50 g, 2.9 mmol), 27 (0.018 g, 0.029 mmol), and TMSCl (0.31 g, 2.8 mmol) in 15 mL of CH_2Cl_2 at room temperature for 5.5 h. After work-up and flash column chromatography, 0.67 g of the product was obtained (85%). ^1H NMR (CDCl_3): δ 7.25 (m, 1), 6.28 (m, 1), 6.13 (m, 1), 4.93 (s, 1), 1.16 (s, 3), 1.14 (s, 3), -0.07 (s, 9); ^{13}C NMR (CDCl_3): δ 177.78, 176.75, 154.32, 141.42, 109.83, 107.84, 73.37, 51.65, 21.11, 19.44, -0.47; IR: 2940, 1720, 1665 cm^{-1} ; mass spectrum: m/z , 270. Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_4\text{Si}$: C, 57.78; H, 8.15; Found: C, 57.63; H, 8.26.

Methyl 2,2-Dimethyl-3-trimethylsilyloxyhexanoate: This product was

made by the following reaction: 0.072 g of butanal (1 mmol) and 0.06 g of 27 (0.1 mmol) with 0.17 g of trimethylsilyl enol ether of methyl isobutyrate (1 mmol) and 0.10 g of TMSCl (1 mmol) in 10 mL of CH_2Cl_2 at room temperature for 1.5 h. Usual work-up procedures and gravity column purification gave 0.14 g of product (57%). Only spectroscopic characterization was obtained. ^1H NMR (CDCl_3 , 250 MHz): δ 0.10 (s, 9), 0.84 (t, 3), 1.01 (s, 3), 1.08 (s, 3), 1.2-1.5 (m, 4), 3.60 (s, 3), 4.78 (d, d, 1).

Ethyl (2SR, 3SR)-2-Methyl-3-hydroxy-3-phenylpropanoate: The reaction of 0.20 g of (Z) t-butyldimethylsilyl enol ether of ethyl propionate (0.94 mmol) with 0.10 g of benzaldehyde (0.94 g) in the presence of 0.06 g of 27 (0.09 mmol) and 0.12 g of TMSCl (1 mmol) in CH_2Cl_2 at -78°C for 8 h gave 0.17 g of the product. ^1H NMR spectrum revealed the ratio of syn/anti=78/22. (title isomer) ^1H NMR (CDCl_3): δ 1.10 (d, 3), 1.21 (t, 3), 2.80 (dq, 1), 4.19 (q, 2), 5.12 (d, 1, $J=4.3$), 7.40 (m, 5); IR: 3400, 1720 cm^{-1} . [Lit[2]: ^1H NMR (CCl_4): δ 4.90 (d, $J=4.0$)].

Ethyl (2SR, 3RS)-2-Methyl-3-hydroxy-3-phenylpropanoate: This product was synthesized by the following reaction: 0.17 g of (E)-trimethylsilyl enol ether of ethyl propionate with 0.10 g of benzaldehyde (1 mmol) in the presence of 0.06 g of 27 and 0.10 g of TMSCl (1 mmol) in CH_2Cl_2 at -78°C for 8 h. After work-up, 67% conversion of benzaldehyde was found by ^1H NMR, isomer ratio (syn/anti)=30/70; (title isomer) ^1H NMR (CDCl_3): δ 7.38 (m, 5), 4.78 (d, 1, $J=8.4$), 4.20 (q, 2), 2.85 (dq, 1), 1.25 (t, 3), 1.08 (d, 3). [Lit.[2]: ^1H NMR (CCl_4):

δ 4.55 (d, $J=8.0$)).

Isopropyl (2SR, 3SR)-2-Methyl-3-hydroxy-3-phenylpropanoate: This compound was produced by the reaction of 0.20 g (0.87 mmol) of (Z) *t*-butyldimethyl enol silyl ether of isopropyl propionate with 0.09 g of benzaldehyde in 20 mL of CH_2Cl_2 solution of 0.05 g of 27 (0.087 mmol) and 0.094 g of TMSCl (0.87 mmol). ^1H NMR spectrum shows that the isomer ratio of syn/anti is 90/10. ^1H NMR (CDCl_3): δ 1.12 (d, 6), 1.21 (d, 3), 2.78 (dq, 1), 4.95 (qq, 1), 5.06 (d, 1, $J=4.7$), 7.30 (m, 5). [Lit.[56]: ^1H NMR (CDCl_3): δ 1.10 (d, 3), 1.13 (d, 3), 1.18 (d, 3), 2.71 (dq, 1), 4.97 (qq, 1), 5.03 (d, 1, $J=4.0$), 7.28 (m, 5)].

Isopropyl (2SR, 3RS)-2-Methyl-3-hydroxy-3-phenylpropanoate: This substance was synthesized from the reaction of (E) *t*-butyldimethylsilyl enol ether of isopropyl propionate (0.20 g, 0.87 mmol) with 0.16 g of benzaldehyde (0.87 mmol) in a CH_2Cl_2 solution containing 0.15 g of 27 and 0.094 g of TMSCl at -78°C for 8 h. After work-up, the ^1H NMR spectrum showed the ratio of syn/anti=25/75. ^1H NMR (CDCl_3): δ 7.40 (m, 5), 5.03 (qq, 1), 4.78 (d, 1, $J=7.8$), 2.75 (m, 1), 1.25 (d, 3), 1.14 (d, 3), 0.95 (d, 3). [Lit.[56]: ^1H NMR (CDCl_3): δ 7.31 (br, 5), 5.02 (qq, 1), 4.70 (d, 1, $J=7.4$), 2.74 (dq, 1), 1.23 (d, 3), 1.18 (d, 3), 0.99 (d, 3).]

Cyclohexyl (2SR, 3SR)-2-Methyl-3-hydroxy-3-phenylpropanoate: Isomer ratio of syn/anti is 74/26. Only spectroscopic characterization was obtained. ^1H NMR (CDCl_3): δ 1.10 (d, 3), 1.2-2.0 (m, 10), 2.80 (dq, 1), 4.75 (m, 1), 5.03

(d, 1, $J(\text{syn})=4.4$ Hz), 7.35 (s, 5).

Methyl (2SR, 3SR)-3-Hydroxy-2,3-diphenylpropanoate: The reaction of (Z) *t*-butyldimethylsilyl enol ether of methyl phenylacetate with benzaldehyde in 0.05 eq. of 27 at -78 °C for 8 h. After work-up, the ^1H NMR spectrum showed the ratio of syn/anti=82/18. These two isomers can be separated by flash chromatography. Syn isomer: ^1H NMR (CDCl_3) δ 2.63 (br, s, 1), 3.53 (s, 3), 3.88 (d, 1, $J=7.5$), 5.30 (d, 1, $J=7.5$), 7.31 (m, 10); ^{13}C NMR (500 MHz, CDCl_3): δ 172.8, 140.8, 129.1, 128.6, 128.2, 128.0, 127.9, 126.6, 75.0, 59.6, 52.0; mp. 93.0–94.5 °C. Anti isomer: ^1H NMR (CDCl_3) δ 3.27 (d, 1, $J=3.9$), 3.71 (s, 3), 3.88 (d, 1, $J=9.4$), 5.17 (dd, 1, $J=9.4$, $J=3.92$), 7.15 (m, 10); ^{13}C NMR (500 MHz, CDCl_3): δ 173.9, 140.7, 135.1, 128.5, 128.4, 128.1, 127.8, 127.5, 126.6, 76.6, 59.8, 52.3; mp. 102.0–104.0 °C; Anal Calcd. for $\text{C}_{16}\text{H}_{16}\text{O}_3$: C, 74.98; H, 6.29; Found: C, 74.88; H, 6.32. mass spectrum: 238 ($\text{M}-\text{H}_2\text{O}$).

Attempted Preparation of 4-Ethyl-2,2-dimethyl-5-phenyl-5-trimethylsilyloxy-3-pentanone: To a solution of 0.10 g of benzaldehyde (0.94 mmol) and 0.06 g of 27 (0.094 mmol) in 20 mL of CH_2Cl_2 were added 0.19 g of 2,2-dimethyl-3-trimethylsilyloxy-3-hexene (0.94 mmol) and 0.10 g of TMSCl . The reaction mixture was stirred overnight at room temperature. After work-up, the ^1H NMR spectrum showed that there were no NMR peaks associated with the desired product. The peaks observed were those of benzaldehyde and 2,2-dimethyl-3-hexanone. ^1H NMR (CDCl_3): δ 9.90 (s, 1), 7.70–7.40 (m, 3), 7.85 (d, 2), 2.40 (t, 3), 1.55 (m, 2), 1.08 (s, 9), 0.85 (t, 3).

Attempted Preparation of Methyl 2,2-Dimethyl-3-trimethylsilyloxy-3-phenylbutanoate: In a 100 mL of flask, 0.34 g of acetophenone, 0.5 g of trimethylsilyl enol ether of methyl isobutyrate, 0.018 g of 27 and 0.31 g of TMSCl in 20 mL of CH_2Cl_2 were stirred at room temperature overnight. After work-up, ^1H NMR spectrum showed only peaks for starting material.

Methyl 2,2,4-Trimethyl-3-trimethylsilyloxypentanoate: To 20 mL of a CH_2Cl_2 solution of 0.14 g of isobutanal (2 mmol) and 0.06 g of 27 were added 0.34 g of the trimethylsilyl enol ether of methyl isobutyrate and 0.21 g of TMSCl. After work-up and gravity column chromatography, 0.25 g of desired product was obtained (51%). ^1H NMR (CDCl_3 , 250 MHz): δ 0.00 (s, 9), 0.73 (d, 3), 0.84 (d, 3), 1.12 (s, 3), 1.21 (s, 3), 3.32 (d, 1, $J=3.6$), 3.62 (s, 3); ^{13}C NMR (500 MHz, CDCl_3): δ 176.0, 81.6, 51.8, 45.0, 29.8, 22.2, 21.6, 16.0, 12.4, 0.90; mass spectrum: 173 ($\text{M}^+ - \text{TMS}$).

Ethyl (2SR, 3RS) and (2SR, 3SR)-3-Hydroxy-2-methyl-5-phenyl-4-pentenoate: The ethyl (2SR, 3RS)-3-hydroxy-2-methyl-5-phenyl-4-pentenoate was obtained from the reaction of (E) trimethylsilyl enol ether of ethyl propionate and cinnamaldehyde at -78°C in CH_2Cl_2 . The reaction mixture was quenched after 8 h stirring. Work-up and flash column chromatography gave 0.85 g of the desired product (48%); isomer ratio (syn/anti) = 18/82. The ethyl (2SR, 3SR)-3-hydroxy-2-methyl-5-phenyl-4-pentenoate was obtained from the reaction of (Z) *t*-butyldimethylsilyl enol ether of ethyl propionate and cinnamaldehyde in CH_2Cl_2 at -78°C . After work-up and flash column chromatography, the yield was 59%.

The isomer ratio of syn/anti is 70/30. From these mixtures, the following assignments were made: Anti isomer: ^1H NMR (250 MHz, CDCl_3) δ 1.17 (d, 3), 1.20 (t, 3), 2.57 (dq, 1), 2.92 (d, 1), 4.11 (q, 2), 4.36 (q, 1, $J=6.9$, $J=10.6$), 6.10 (dd, 1, $J=6.9$, $J=15.9$), 6.55 (d, 1, $J=15.9$), 7.14-7.40 (m, 5); ^{13}C NMR (500 MHz, CDCl_3): δ 14.1, 20.9, 45.6, 60.3, 74.5, 126.5, 127.7, 128.5, 132.0, 136.4, 175.4; Syn isomer: ^1H NMR (250 MHz, CDCl_3): 1.18 (d, 3), 1.21 (t, 3), 2.70 (dq, 1), 2.80 (d, 1), 4.15 (q, 2), 4.55 (q, 1, $J=7.0$, $J=5.0$), 6.13 (dd, 1, $J=15.6$, $J=7.0$), 6.60 (d, 1, $J=15.6$), 7.15-7.40 (m, 5); ^{13}C NMR (500 MHz, CDCl_3): δ 14.2, 21.0, 45.3, 60.6, 73.0, 126.4, 127.6, 128.8, 129.0, 131.4, 136.5, 175.2; mass spectrum: m/z , 234 (100%), $M+1$ 235 (Calc.: 15.5%; Found: 17.7%).

Attempted Preparation of Methyl 2-Methyl-2-(1-trimethylsilyloxycyclohexyl)propionate. The solution of trimethylsilyl enol ether of methyl isobutyrate (0.10 g, 0.57 mmol), cyclohexanone (0.056 g, 0.57 mmol), 27 (4 mg, 0.0057 mmol) and TMSCl (0.062 g, 0.57 mmol) in 20 mL of CH_2Cl_2 was stirred overnight at room temperature. After work-up, ^1H NMR spectrum indicated only peaks of starting material.

1-Ethoxy-1-trimethylsilyloxycyclopropane. To a suspension of 1.27 g of Na metal (55 mmol) in 30 mL of ethyl ether and 3.50 mL of TMSCl (27.6 mmol) was added 3.55 mL of ethyl 3-bromopropionate dropwise. During the addition, the solution was stirred rapidly at such a speed as to keep the ether boiling. The mixture was stirred for another 30 min, filtered and distilled under vacuum to

give 2.1 g of the product (44%). b.p. 48–49 °C/14 torr; ^1H NMR (CDCl_3): δ 0.12 (s, 9), 0.78 (m, 4), 1.10 (t, 3, $J=7.12$), 3.59 (q, 2, $J=7.12$); ^{13}C NMR (CDCl_3): δ 0.63, 13.86, 15.19, 61.57, 86.39; [Lit. [62]: b.p. 43–45 °C/12 torr].

Reaction of 1-Ethoxy-1-trimethylsilyloxycyclopropane with benzaldehyde. In a 5 mL NMR tube, 1-ethoxy-1-trimethylsilyloxycyclopropane (0.22 M), benzaldehyde (0.25 M), 27 (0.026 M) and TMSCl (0.23 M) were dissolved in 0.75 mL of CD_2Cl_2 . ^1H NMR spectra were taken after 30 min, 40 min of mixing, and there were only peaks of starting material. The NMR sample was then heated at 38 °C overnight. ^1H NMR spectrum was taken again, and did not indicate any peaks of the desired product (ethyl 4-phenyl-4-trimethylsilyloxybutanoate).

1-Trimethylsilyloxy-1-cyclohexene. To 20 mL of an ether solution of LDA (27.6 mmol) was added cyclohexanone (2.85 mL, 27.5 mmol) dropwise at –78 °C over 5 min. After 2 h, TMSCl (3.49 mL, 27.6 mmol) was added, and the solution was allowed to warm to room temperature over 30 min. After another 0.5 h, the reaction mixture was diluted with 30 mL of pentane, washed with ice-cold water twice and dried over Na_2SO_4 . Upon removal of the solvents and distillation under vacuum, 1.9 g of the product was obtained (41%), b.p. 74–76 °C/20 mmHg; ^1H NMR (CDCl_3): δ 0.15 (s, 9), 1.40 (m, 2), 1.60 (m, 2), 1.90 (m, 4), 4.85 (t, 3); Mass spectrum: m/z , 170; [Lit.[18]: b.p. 73–74 °C/20 mmHg].

Attempted Preparation of 2-(1-Trimethylsilyloxybenzyl)-1-cyclohexanone. To a solution of 0.10 g of benzaldehyde (1.0 mmol), 0.63 g of 27 (1.0 mmol) in 20 mL of CH_2Cl_2 was added 0.16 g of 1-trimethylsilyloxy-1-cyclohexene. The mixture was stirred at room temperature for 48 h. After work-up, ^1H NMR was taken and showed peaks of starting material.

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Chapter 3

Kinetic Study of a Mukaiyama Reaction

3.1 introduction

The sequence of steps of a Mukaiyama reaction has been proposed as described in Ch.2. However, there has been no mechanistic study of this type of reaction. To gain some insight into the mechanism of the Mukaiyama reaction as well as electronic effects on the rates of the reaction, a detailed kinetic study was undertaken.

3.2 Results and Discussion

One convenient aspect of this kinetic study on the following Mukaiyama reaction is the ease of monitoring the growth of peaks from the product (29) and the disappearance of peaks from the reactants (28) by ^1H NMR since the protons from methyl group and methoxy group in 28 have different chemical shifts from that in 29.

By integration, the relative concentrations of 28 and 29 can be calculated. For example, if the proton peak area from the methoxy group in 28 is X_i at time i , and the proton peak area from methoxy group in 29 is Y_i , we have the following relationship:

$$X_i + Y_i = C_0 \quad \text{eq. 3.2}$$

C_0 = initial concentration of 28.

The first experiment was carried out with 1 equivalent of silyl enol ether 28, benzaldehyde, and TMSCl, and 0.05 equivalents of 27 in CD_2Cl_2 . A series of spectra were obtained at various time intervals. It was found that the reaction proceeded in first order with respect to the concentration of 28 after plotting $-\text{Ln}C_i$ vs. t .

Figure 3.1 Reaction of PhCHO with 28

The equations are derived as follows:

$$X_i \propto C_i \quad (C_i = \text{conc. of 28 at time } i)$$

$$X_i + Y_i \propto C_o$$

$$C_i = \frac{X_i}{X_i + Y_i} \times C_o$$

$$\text{Ln} \frac{C_i}{C_o} = \text{Ln} \frac{X_i}{X_i + Y_i} = -k't \quad \text{eq.3.3}$$

The second experiment was to examine the importance of excess amounts of TMSCl. When 1 equivalent of silyl enol ether (28) was mixed with 1 equivalent of benzaldehyde and 0.05 equivalents of 27 in the absence of excess TMSCl in CD_2Cl_2 , the reaction rate appeared much slower, and a poor correlation between $-\text{Ln}C_i$ and t_i was found. As the concentration of TMSCl was increased to 1.5 equivalents, the reaction rate was almost unchanged in comparison with the reaction under 1.0 equivalent of TMSCl. This phenomenon indicates that the reaction depends on the concentration of TMSCl when it is low; however, when the concentration increases to certain extent, the reaction is no longer dependent on the amount of TMSCl and proceeds in a first order kinetics in silyl enol ether. In addition, when one equiv of $t\text{-BuMe}_2\text{SiCl}$ was used instead of TMSCl, the reaction rate was essentially the same.

Next, the amount of catalyst 27 was varied. The analyses showed that the reaction proceeded two times as fast if the amount of 27 was doubled. However, when a double amount of benzaldehyde was employed, the reaction rate remained essentially the same. The results are summarized in Table 3.1.

Table 3.1
Rate Constants

entry	28 (a)	PhCHO(a)	27 (a)	TMSCl(a)	$k' \times 1000 (s^{-1})(b)$	$k (s^{-1}M^{-1})(b)$
1	0.40(1)	0.44(1.1)	0.023(0.058)	0.47(1.2)	4.1	0.18
2	0.41(1)	0.44(1.1)	0.046(0.11)	0.42(1.0)	7.9	0.17
3	0.39(1)	0.87(2.2)	0.083(0.21)	0.53(1.3)	16.5	0.20
4	0.39(1)	0.46(1.2)	0.02(0.051)	0	*	*
5	0.40(1)	0.43(1.1)	0.045(0.11)	0.59(1.5)	7.1	0.16
6	0.94(1)(c)	1.07(1.1)	0.058(0.062)	1.38(1.5)	4.8	0.08
7	0.41(1)	0.48(1.2)	0.035(0.086)	0.41(1.0)(d)	4.9	0.14

* rate is slower, and the correlation is poor.

a. the unit of concentration: M. and the numbers in the parenthesis are molar equiv.

b. the probable error in the rate constants is 10%.

c. silyl enol ether = Z-1-t-butyldimethylsilyloxy-1-ethoxy-1-propene

d. TMSCl was replaced by t-BuMe₂SiCl.

The information thus far allows several conclusions with respect to the mechanism of this reaction. The fact that the reaction kinetics is first order in silyl enol ether implies that the coupling between the benzaldehyde and the silyl enol ether is the rate-determining step, which is also supported by the evidence that the rate of the t-butyldimethylsilyl enol ether of ethyl propionate was slower than that of trimethylsilyl enol ether of methyl isobutyrate, and the bulk of the silyl group affects the rate of the reaction. The concentration of the benzaldehyde-27 complex is constant throughout the reaction. Furthermore, it is clearly confirmed that the role of TMSCl is to facilitate the equilibrium as discussed in chapter 2. Consequently, we can propose the following reaction

sequence consisting of three steps: (1) fast complexation; (2) slow addition reaction; (3) fast subsequent equilibrium as shown:

Scheme 3.1

Accordingly, the rate law for this reaction can be written as follows:

$$\text{rate} = -\frac{d[28]}{dt} = k[28][36] \quad \text{eq.3.4}$$

$$-\frac{d[28]}{dt} = k'[28], \text{ since (1) is fast; } [36] = \text{constant.} \quad \text{eq.3.5}$$

The derived equation is compatible with the experimental observation.

To confirm the mechanism just described, the following experiment was carried out, namely, the exchange process of free PhCHO and associated PhCHO. In a NMR tube, 1 equivalent of *para*-methylbenzaldehyde was mixed with 0.1

equivalent of $(\text{TMS}_2\text{Cp})_2\text{YbCl}$ in toluene- d_4 . Para-methylbenzaldehyde was chosen because Yb(III) is a paramagnetic element, which causes the broadening of ^1H NMR peaks of organic ligands associated with it. It is known that the paramagnetic effect decreases with the increase in distance between the metal center (Yb(III)) and ligand proton observed. Since the methyl group is relatively far from the coordinated oxygen in para-methylbenzaldehyde, it should be possible to see separate proton peaks from the coordinated and the free p-methylbenzaldehydes if the exchange process can be frozen out. When this NMR tube was examined at various temperatures, it was observed that the exchange process of the free MePhCHO and coordinated MePhCHO was fast at room temperature, showing average resonances for the methyl group as well as for the proton attached to the carbonyl group. However, at -20°C , the peak at 7-8 ppm broadened, and another new peak grew in at 10 ppm, which is the resonance of free MePhCHO. As the sample was cooled further to -40°C , the peaks narrowed as the exchange approached the slow exchange limit. Similar behavior was not observed for the methyl groups. Probably, they are so far away from the Yb(III) that there is not enough chemical shift difference to distinguish the methyl group of coordinated p-MePhCHO from that of free p-MePhCHO. This experiment clearly demonstrates that the exchange process of coordinated and free benzaldehydes to the ytterbium complex is fast at room temperature. In another words, the proposed fast complexation in the first step is verified.

Fig.3.2 ^1H NMR spectra of the exchange process of coord. and free $p\text{-MePhCHO}$

25 °C

-28.8 °C

-37.9 °C

-41.2 °C

To see if this complexation is complete, the following experiment was accomplished. The sample containing 1 molar equiv of benzaldehyde and 1 molar equiv of Yb-complex in CH_2Cl_2 was subjected to an IR study. A strong absorbance at 1660 cm^{-1} was found, which was assigned to the carbonyl group in the complex of PhCHO-27. The absence of a peak at 1720 cm^{-1} for free benzaldehyde shows that the complexation of benzaldehyde and 27 is complete. Similar shifts were also observed in other substituted benzaldehydes.

In order to get an assessment of the role of the electronic effect on this reaction, different substituted benzaldehydes were studied. Table 3.2 summarizes the results obtained (plots shown in Appendix A).

Table 3.2
Rate Constants of XPhCHO

entry	X	28 (a)	27 (a)	XPhCHO(a)	k ($\text{s}^{-1}\text{M}^{-1}$)(b)
1	OCH ₃	0.41	0.051	0.44	0.009
2	CH ₃	0.40	0.045	0.48	0.12
3	Ph	0.40	0.046	0.41	0.14
4	F	0.42	0.023	0.47	0.16
5	H	0.41	0.046	0.44	0.17
6	Cl	0.38	0.043	0.42	0.20

a. the unit of concentration: M.

b. the probable error in the rate constants is 10%.

Examining the results, one can clearly see that electron withdrawing groups assist

the reaction while electron releasing groups retard the reaction, but the effects are generally small. This finding indicates that the rate-determining step is electron-deficient in nature, which is also manifest in the ease with which the silyl enol ethers undergo nucleophilic attack at the carbonyl center.

To evaluate the importance of the electronic effect exerted by these substituents on the rate of this reaction, plots of $\log \frac{k}{k_0}$ vs. σ^+ and σ [1] were compared.

Figure 3.3 $\log \frac{k}{k_0}$ vs. σ^+

Figure 3.4 $\log \frac{k}{k_0}$ vs. σ_{para}

The Hammett equation shown below was used:

$$\log \frac{k}{k_0} = \rho \sigma \quad \text{eq.3.6}$$

Here k and k_0 are the corresponding rate constants with and without any substituents, ρ is a constant characteristic of the reaction and σ is a constant characteristic of the substituent.

As one can see, the correlations in both cases are not very good, in part perhaps because of the uncertainties of the rate constants. The precision is affected by errors in the integration as well as the uncertainty in determining the reaction time during the NMR pulses. Nevertheless, we can get some idea about the influence of the substituents on the reaction rates. The nature of the plots with σ and with σ^+ does not allow a clear distinction of which is better; however, the fact that the rate of the reaction of *p*-fluorobenzaldehyde with the silyl enol ether is slower than that of benzaldehyde indicates that σ^+ dominates, and that conjugation effects of the substituents are important.

It is known [2] that the reaction constant, ρ , measures the susceptibility of the reaction rate to the substituents. The magnitude of ρ reflects the distance between the reaction site and the substituent as well as the charge distribution at the reaction transition state [3]. The small ρ value of 0.36 in this case suggests that there is little charge change in the transition state, which can serve as evidence for the cyclic transition state model for this reaction as discussed in Ch.2.

Fig. 3.5

Another interpretation for the small value of ρ is that the electron donating groups might accelerated the loss of Cl as depicted below:

Fig. 3.6

However, this effect of electron donating groups would also retard the attack of the silyl enol ether. Conversely, electron withdrawing groups might enhance the rates by making the carbonyl group more electrophilic, resulting in a faster reaction of the silyl enol ether with the carbonyl group, but they might also lead to a reduction in the process of cleaving Cl from Yb center. These two opposite effects might coexist in both electron releasing and electron withdrawing groups, and a rather small value of ρ results. Accordingly, it further implies that the transition state involves the breaking of Yb-Cl bond and the forming of a C-C bond, and the cyclic transition state model is operative. The positive sign of ρ tells us that the electron withdrawing groups overall speed up the reaction though the effect is not highly significant, reflected by the small ρ .

As proposed earlier, the course of the reaction follows three steps as shown

in Scheme 3.1. An alternative mechanism can be depicted as follows:

Scheme 3.2

If (2) is the rate determining step, and (3) is fast, then the rate law can be written as:

$$\text{rate} = k_2[28][36] = k'[28] \quad \text{eq.3.7}$$

This is in agreement with the experimental observation.

The distinction between these two mechanisms is the formation of organoytterbium enolate (38) as a distinct intermediate in the second mechanism.

The ^1H NMR experiment below shows that there is no equilibrium between the trimethylsilyl enol ether of methyl isobutyrate and *t*-butyldimethylsilyl chloride in CD_2Cl_2 at room temperature in the presence of catalytic amount (10%) of 27 with trace acetophenone to break the dimer structure of 27.

Two possibilities therefore arise: the equilibrium may lie too far on the left side due to the bulk of t-butyl group on silicon that we were not able to detect or the intermediate (38) does not form at all.

To answer the questions, the reverse reaction was carried out.

The ^1H NMR spectra show that there is no equilibrium between these two over a period of time.

Therefore, it can be concluded that the intermediate (38) does not form for it is the necessary pathway for the exchange process on both directions as illustrated below:

As a consequence, the second alternative mechanism can be ruled out.

3.3 Summary

The mechanistic study of the Mukaiyama reaction of the silyl enol ether with benzaldehyde in the presence of 5%-10% of the catalyst, $(\text{TMS}_2\text{Cp})_2\text{YbCl}$, in dichloromethane- d_2 shows that the reaction proceeds with pseudo-first order kinetics in silyl enol ether, provided that an excess amount of TMSCl is present. The excess of TMSCl is essential to facilitate this reaction and to insure the first order kinetics. The kinetic study with a number of substituted benzaldehydes indicates that the reaction rates are only slightly affected by the nature of the substituents ($\rho = 0.36 \pm 0.05$) with electron-withdrawing groups increasing the rates. The experimental evidence demonstrates that the course of the reaction follows a three-step pathway as fast complexation, slow addition and fast subsequent equilibrium.

3.4 Experimental

Material. All of the aldehydes were obtained from commercial suppliers and used after distillation under argon and degassing three times. Dichloromethane was stirred over LiAlH_4 for 12 h, vacuum transferred, and degassed. The silyl enol ether of methyl isobutyrate was synthesized according to the procedure in chapter 2.

Kinetic Runs: The silyl enol ether of methyl isobutyrate (0.20-0.22 mmol), benzaldehyde (0.25-0.26 mmol), 20 (0.025-0.026 mmol) and TMSCl (0.23-0.24 mmol) were loaded into a NMR tube and dissolved in 0.56-0.60 mL of CD_2Cl_2 . The initial time was recorded upon mixing. The ^1H NMR spectra were run on the UC Berkeley FT-NMR 200 or 250 MHz spectrometers. The system employs a superconducting magnet, a deuterium lock system, and Nicolet Software. Temperature was monitored by a Doric Trendicator 410A. The temperature under which all the kinetics was run was around 19.8–23.0 °C. In each case, 0.2 °C variation was observed.

The integration of ^1H NMR peaks of the reactant and the product was converted into the concentration ratios, which were then used to correlate with time. Plots for the kinetic data were made by a least-squares fit, (k , $\pm 10\%$; T , ± 0.2 °C).

3.5 Appendix A

Fig.3.7---Fig.3.11 are the plots of $-\text{Ln}C_i$ vs. t for $p\text{-MeOPhCHO}$, $p\text{-MePhCHO}$, $p\text{-PhPhCHO}$, $p\text{-FPhCHO}$, $p\text{-ClPhCHO}$, respectively.

Fig.3.12 is the summary of Fig.3.1 and of Fig.3.7 to Fig.3.11.

Fig. 3.13 is the plot of the reaction of 28 with PhCHO in the presence of 1 equiv of $t\text{-BuMe}_2\text{SiCl}$.

Fig. 3.14 is the plot for the reaction of 28 with 2 equiv of PhCHO.

Figure 3.7 Reaction of p-MeOPhCHO with 28

Figure 3.8 Reaction of p-MePhCHO with 28

Figure 3.9 Reaction of p-PhPhCHO with 28

Figure 3.10 Reaction of p-FPhCHO with 28

Figure 3.11 Reaction of p-ClPhCHO with 28

Figure 3.12 Summary of Fig.3.1 and Fig.3.7-Fig.3.11

Figure 3.13 Reaction of 28 with PhCHO in the presence of 1 equiv of $t\text{-BuMe}_2\text{SiCl}$

Figure 3.14 Reaction of 28 with 2 equiv of PhCHO

3.6 References

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Chapter 4

Aldol Condensation of Organoytterbium (III) Enolate

4.1 Introduction

As stated earlier in chapter 2 (sec. 2.1.1), Heathcock and his coworkers [1] have demonstrated that for specific (Z) and (E) lithium enolates

Scheme 4.1

such as those with $R = t\text{-Bu}$, mesityl, etc. (sterically demanding groups), excellent diastereoselection could be obtained in the formation of syn and anti aldol products, respectively; however, for less bulky enolate substituents ($R = \text{Et}$, $i\text{-Pr}$, OMe , Ph), the diastereoselection is greatly diminished. In addition, the retroaldol condensation is another problem with regard to the syn-anti isomer ratios.

To determine if a metal enolate with some bulky ligands can give increased stereoselectivity, and if the equilibrium can be slowed down by a lanthanide cation (+3) known to be a strong Lewis acid, the utilization of organoytterbium (III) enolates in the aldol condensation was investigated.

4.2 Results and Discussion

The general procedure for employing organoytterbium complexes in the aldol condensation is shown below:

Scheme 4.2

The organoytterbium complex, $(\text{TMS}_2\text{Cp})_2\text{YbCl}\cdot\text{THF}$, was obtained by dissolving $[(\text{TMS}_2\text{Cp})_2\text{YbCl}]_2$ in THF, and the synthesis of the dimer was discussed in chapter 2. The full characterization of the organoytterbium enolates was not completed due to the difficulty of purification. The presence of LiCl, however, indicated the formation of Yb-enolates. The composition of E and Z enolates was determined by treating the enolate mixture with TMSCl and analyzing the resulting TMS enolate mixture by ^1H NMR since the chemical shift of the vinyl proton in Z enolate is different from that in E enolate.

To see if the Yb enolate can be used in the aldol condensation, the reaction shown below was first carried out.

Scheme 4.3

This particular ketone was chosen because it gives only the Z enolate due to the bulky t-butyl group. After the reaction mixture was quenched, ^1H NMR spectrum shows that there was only one isomer present, indicated by the peak at 4.75 ppm ($J=4.8$ Hz) for H_α in syn conformation. This result can serve as evidence for the reactivity of organoytterbium(III) enolates in the aldol condensation. The stereoselectivity observed here is consistent with the Li-enolate, and can be accounted for the fact that t-butyl is a bulky group, which causes the substantial energy difference between 1 and 2 transition states in the cyclic model (see scheme 2.2, chapter 2), and therefore only the syn isomer resulted.

To investigate the stereoselectivity of Yb-enolates, 3-pentanone was chosen. This is because the enolate derived from it has a sterically less demanding group ($\text{R} = \text{ethyl}$), with which Li-enolates gave very poor selectivity. The following reaction was therefore carried out.

Scheme 4.4

The result shows a 65:35 ratio of syn and anti isomers when the enolate composition (Z/E) is 75:25. This finding is different from what has been found in the case of Li-enolates. When Li-enolate of 3-pentanone with a Z/E ratio of 30:70 in THF was treated with benzaldehyde, 64:36 of syn/anti was observed.

The enolate compositions in both cases are different due to the difference in solvents in which the enolates were formed. It is known [12] that the solvent polarizability has a substantial influence on the Z/E composition of enolates as discussed in 2.1.4. In this case, Z enolate is the major configuration when ether is used as a solvent. It is also well established [2-4] that the vinyl proton in an E silyl enolate generally resonates downfield of the corresponding proton in the Z silyl enolate, so that the assignment of the Z/E enolates is quite clear.

Based on the above discussion, we can conclude that the result observed is consistent with the cyclic model; namely, Z $\Rightarrow$ syn and E $\Rightarrow$ anti despite the lack of steric bulk of the R group, and that metal center steric effects are important in conferring enhanced diastereoselection to the condensation processes.

That model could be tested more explicitly if an enolate with only Z or E configuration was used. This would involve the separation of the Z or E

trimethylsilyl enolate of 3-pentanone and conversion to a Li-enolate by treating with MeLi. However, it proved to be difficult to separate them both by spinning band column distillation due to their close boiling points or by a chromatography technique due to their unstability towards silica gel.

As mentioned before, the retroaldol condensation is another problem with respect to the syn/anti ratio, especially since, in some cases, the equilibrium is established rather rapidly to give a 50:50 mixture. For example, the condensation of the Li-enolate of propiophenone (Z/E = 99:1) with benzaldehyde gives syn/anti ratio of 88:12 if the reaction is quenched after 10 s at -78°C , but the ratio is only 80:20 after 5 min at this temperature [1].

In an effort to confer greater stereochemical control in thermodynamically controlled aldol processes, the following system was studied.

Scheme 4.5

This study confirms the postulate that Yb(III) is a better Lewis acid to coordinate the oxygen atoms in the aldolate so that the retroaldol equilibrium is retarded as shown below:

Scheme 4.6

The putative key intermediate shown above contains two metal-oxygen bonds. The unusually short length and associated high strength of the typical lanthanide-oxygen bond can be seen in X-ray data on metal oxides and hydroxides [5,6], and, in fact, much of the recent interest in the use of lanthanides in organic chemistry centers around their highly oxophilic character [7-9]. This study provides additional support for the strong oxygen chelation abilities of lanthanide ions (III).

4.3 Summary

The use of organoytterbium enolates shows a promising result with respect to increasing stereoselectivity. This can be served as evidence for the importance of the bulky ligands on the metal center. In addition, Yb(III) can retard the retroaldol equilibrium owing to its Lewis acidity.

4.4 Experimental

General . See chapter 2, section 2.4.

General Procedure for Aldol Condensations with Ytterbium Enolates. The following procedure for the preparation of (4SR, 5SR)-2,2-dimethyl-4-ethyl-5-hydroxy-5-phenyl-3-pentanone is illustrative. A solution of lithium diisopropylamide, prepared from 0.16 mL (0.11 g, 1.1 mmol) of diisopropylamine and 0.75 mL (1.1 mmol) of a 1.5 M hexane solution of n-butyllithium, in 5 mL of THF was cooled to -78°C . 2,2-Dimethyl-3-hexanone (0.16 mL, 0.13 g, 1.0 mmol) was added dropwise over a 30 s period. The mixture was stirred for 2 h at -78°C . The solvent was then removed under vacuum, leading an oily yellow substance. In the glovebox, the yellow substance was added to the solution of $[(\text{TMS}_2\text{Cp})_2\text{YbCl}]_2$ (0.5 g, 0.35 mmol) in 50 mL of THF. After the solution was stirred overnight, the solvent was removed under vacuum. The resulting solid was extracted with toluene to remove LiCl, and the extract was filtered and evaporated to dryness. The residue was dissolved in 30 mL of THF. To this solution, benzaldehyde (0.03 g, 0.7 mmol) was added at -78°C . After the mixture was stirred at that temperature for 1.5 h, saturated aqueous NH_4Cl was poured into the cold reaction mixture, which was then allowed to warm to room temperature and diluted with ether. The ether solution was washed and dried over MgSO_4 . Evaporation of the solvent afforded 0.70 g of the crude aldol product; ^1H NMR (250 MHz, CDCl_3): δ 0.75 (t, 3), 0.98 (s, 9), 1.40-1.60 (m, 2), 3.15-3.22 (m, 2), 4.80 (d, 1), 7.22 (s, 5); IR: 3500 (br.), 1700 (s). [Lit.(10): IR(film) 3450, 1680

cm^{-1} ; ^1H NMR (CDCl_3): δ 0.75 (t, 3, $J=8$), 1.00 (s, 9), 1.33-1.97 (m, 2), 3.07-3.40 (m, 2), 4.77 (d, 1, $J=5$), 7.22 (s, 5).]

The following aldols were also prepared by the foregoing general procedure.

(1RS, 3RS) and (1SR, 3RS)-1-Hydroxy-2-methyl-1-phenyl-3-pentanone

These two isomers were obtained as an oil in 95% conversion of benzaldehyde.

^1H NMR analysis of the crude product showed a 65:35 ratio of syn and anti.

^1H NMR (CDCl_3 , 250 MHz): δ 7.25 (s, 5), 5.01 (d, 1, $J=4.95$, syn), 4.75 (d, 1, $J=8.65$, anti), 2.60 (m, 1), 2.35 (q, 2), 1.20 (d, 3), 0.97 (t, 3). [Lit.(11):

^1H NMR (CCl_4): δ 7.17 (s, 5), 4.80 (d, 1, $J=3$, syn), 3.19 (s, 1, OH), 2.65 m, 1), 2.21 (m, 2), 0.98 (d, 3), 0.89 (t, 3). The anti isomer gave rise to an additional signal at δ 4.48 (d, $J=8$ Hz)].

(2RS,3RS) and (2RS,3SR)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-ones

The reaction mixture of the organoytterbium enolate of propiophenone and benzaldehyde in 20 mL of THF was stirred at -78°C , and 0.5 mL aliquots were removed at various time intervals. The aliquots were added to 15 mL of NH_4Cl (aq.), extracted with pentane, washed with H_2O and dried over Na_2SO_4 . The proportions of each diastereomer were determined from the ^1H NMR spectra.

^1H NMR (CDCl_3): δ 0.95 (d, 3), 3.60 (m, 1), 4.93 (d, 1, $J=8.2$, anti), 5.16 (d, 1, $J=3.4$, syn), 7.2-8.0 (m, 10). [Lit.(1): ^1H NMR (CCl_4): δ 0.90 (d, 3, $J=8$), 3.60 (quintet, 1, $J=8$), 4.72 (d, 1, $J=8$, anti), 5.07 (d, 1, $J=3$, syn), 6.97-7.97 (m, 10)].

4.5 References

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