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Catalysis of Homoaldol Reactions by Titanium (IV) Triflates

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A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of Master of Science

Department of Chemistry
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ABSTRACT

The introduction of enantioselectivity into zinc catalyzed homoaldol reactions is described. Coordinating ligands such as bis-oxazolines and β-amino alcohols inhibit the addition of zinc homoenolates to aldehydes while Lewis acids such as titanium (IV) isopropoxide and boron trifluoroetherate promote this reaction. Notably, the addition of zinc homoenolates to benzaldehyde mediated by chiral titanium (IV) alkoxides yields homoaldol adducts with moderate enantioselectivity.

The development of titanium catalysis of the homoaldol addition of silyloxyalkoxycyclopropanes to aldehydes is also described. The methodology features alkoxytitanium (IV) triflates as catalysts, which mediate homoenolate addition to a range of carbonyl substrates. The preparation of such titanium triflates by a new procedure, namely the treatment of titanium (IV) alkoxides with trimethylsilyltriflate, affords more reactive catalysts than those prepared by conventional methods. In addition, the catalyst system is stable at elevated temperatures for an extended period of time.

Titanium (IV) triflates derived from a variety of alkoxide ligands as well as ligands with sulfide linkages are effective catalysts for this reaction. Efforts directed towards extending this catalytic process to a highly enantioselective protocol are detailed. Moderate enantioselectivity is obtained in homoaldol reactions mediated by a tridentate alkoxide derived titanium tiflate.

Résumé

L'introduction du concept d'énantiosélectivité dans les réactions d'homoaldols catalysées par le zinc est décrite. Des ligands coordinants tels que des bis-oxazolines ou des alcools β-aminés inhibent l'addition d'homoénolates de zinc sur les aldéhydes, tandis que des acides de Lewis tels que l'isopropoxide de titane (IV) et le trifluoroéthérate de bore promeuvent cette reaction. Remarquablement, la médiation par des alkoxydes de titane (IV) chiraux de l'addition d'homoénolates de zinc sur la benzaldéhyde donne des produits homoaldols avec une énantiosélectivité modérée.

Le développement de la catalyse par le titane de l'addition homoaldol de silyloxyalkoxycyclopropanes sur des aldéhydes est aussi décrit. La méthodologie repose sur la catalyse par des triflates d'alkoxydes de titane (IV) qui sont effectifs pour des additions sur une variété de substrats carbonylés. La préparation de tels triflates de titane par le biais d'une nouvelle méthode, plus précisément le traitement d'alkoxydes de titane par le triflate de triméthylsilyle, produit des catalystes plus réactifs que par les techniques conventionnelles. De plus ce système de catalyse est stable à des temperatures élevées pendant de longues périodes de temps.

Les triflates de titane (IV) dérivés d'une variété de ligands alkoxydes ainsi que des ligands comportants des ponts soufrés catalysent cette réaction. La recherche sur l'extension de ce procédé catalytique vers un protocole hautement énantiosélectif est détaillée. Une énantiosélectivité modérée est obtenue dans les réactions d'homoaldols catalysées par un dérivé tridentate d'alkoxyde de triflate de titane.

ACKNOWLEDGEMENTS

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CHAPTER ONE

INTRODUCTION TO THE HOMOALDOL PROCESS

1.1 THE HOMOALDOL REACTION

The aldol reaction is prevalent in the biosynthesis of several natural products as enolate formation is both kinetically and thermodynamically accessible. The presence of a number of polyacetate and polypropionate derived natural products has led to the development of a number of asymmetric protocols to control the stereochemistry of the aldol process. Recent efforts in this area have focused on the use of chiral Lewis acids to effect enantioselective condensations.[1] However, the one carbon homologue, the homoaldol reaction, has not been developed to the extent of the aldol process because homoenolates are more difficult to prepare than enolates.

The homoaldol reaction is the addition of a homoenolate (a β-metallated carbonyl species) onto an aldehyde or ketone to yield γ-hydroxy-carboxylic acid derivatives (Figure 1). The products of this reaction are readily transformed into 1,4-diketones, tetrahydrofurans and γ-lactones. It is important to note that the formation of a metal alkyl bond prior to aldehyde addition makes the homoaldol reaction fundamentally different from the Mukaiyama aldol process, wherein the primary role of the Lewis acid is carbonyl activation.

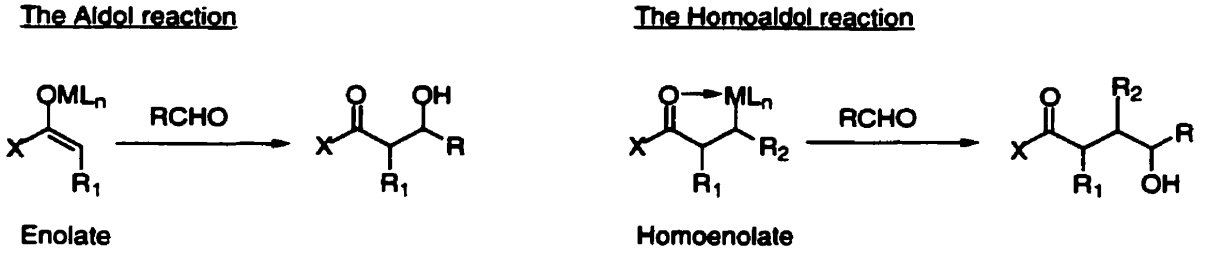
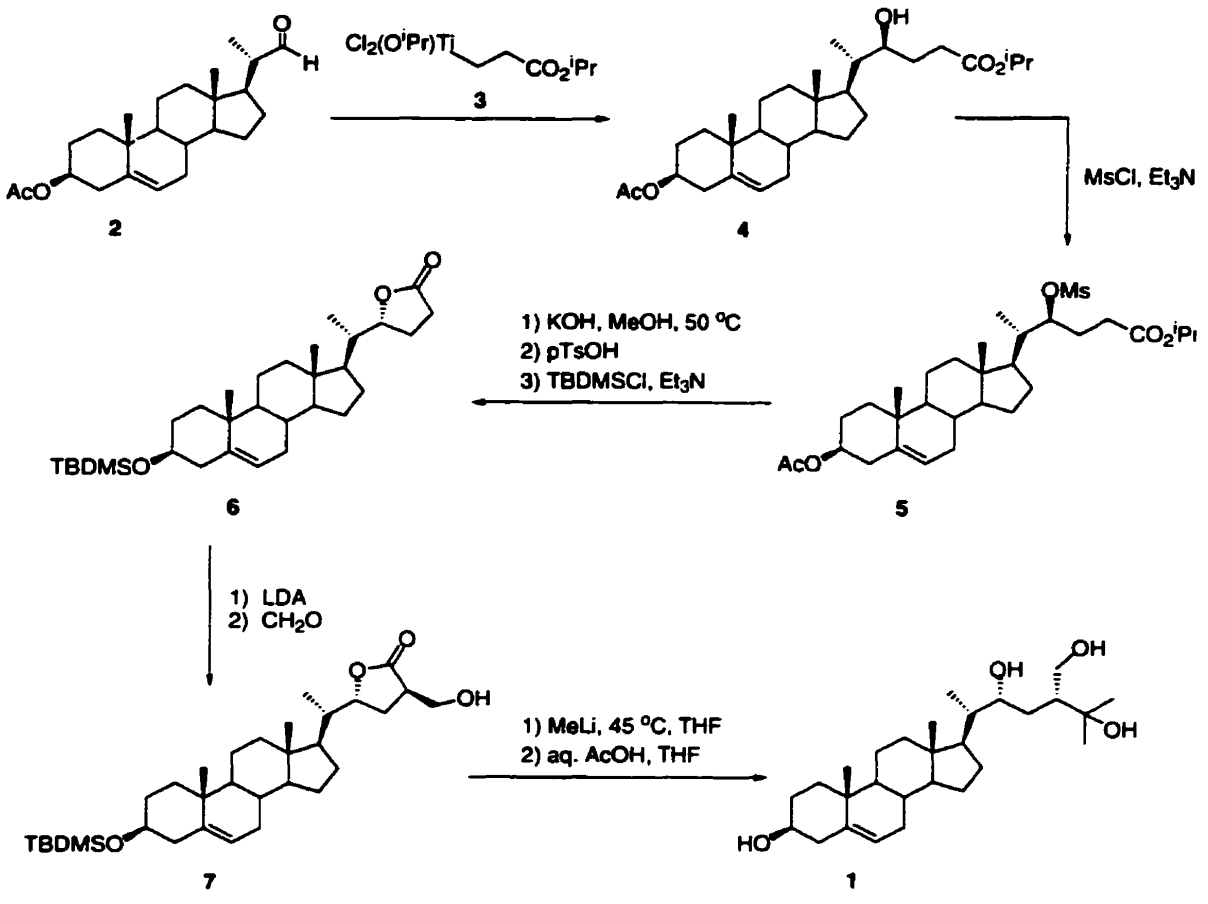


Figure 1. The aldol and homaldol reactions

Homoenolates are umpolung reagents that allow electrophilic reactions to take place at the β-position of a carbonyl compound, a site usually reserved for nucleophilic reagents. Since homoenolates are three-carbon building blocks, the homoaldol process can be used directly for the synthesis of natural products containing 1,4-oxygenated subunits which are not easily obtained through conventional aldol methodologies. An example is depresosterol **1**, a marine sterol with a highly oxygenated side chain.[2] A key feature in its synthesis is a homoaldol reaction between aldehyde **2** and homoenolate **3** to afford the γ-hydroxyester **4** as a 6 : 1 mixture of diastereomers (Scheme 1). Inversion of this stereocentre was accomplished via conversion to the mesylate **5**, followed by hydrolysis of the terminal ester group with potassium hydroxide in hot aqueous methanol. The resulting γ-hydroxyacid was lactonized with p-toluenesulfonic acid (pTsOH) to yield **6** as the sole product. Stereoselective hydroxymethylation of the lactone ring with lithium diisopropylamide and formaldehyde provided **7**. The lactone ring was opened with methyl lithium in hot tetrahydrofuran to yield depresosterol **1**, after removal of the silyl protecting group.



Scheme 1. Synthesis of depresosterol via homoenolate methodology

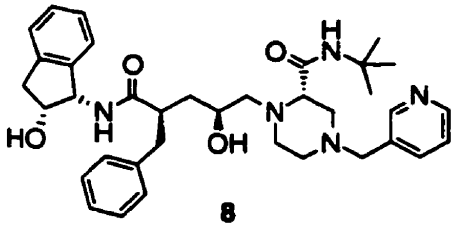
1.2 THE HOMOALDOL PROCESS IN PEPTIDOMIMETICS

Peptides and proteins such as haemoglobin, hormones, neurotransmitters and enzymes are naturally occurring polymers with vital biological functions. Their mechanisms of action are important in medicinal chemistry research for rational drug design. In this regard, the synthesis of peptide analogues (peptidomimetics) is a rapidly growing research area as it may lead to therapeutic applications which increase the effectiveness and selectivity of peptides or inhibit the function of an enzyme.[3]

In the desgin of peptidomimetics, the peptide backbone is often modified by replacing the labile amide bond of a peptide with other functional groups, such as a hydroxyethylene unit (Figure 2). The peptide analogue binds to the active site of an enzyme but is not cleaved under conditions of amide hydrolysis, thereby inhibiting the normal function of the enzyme.[4]

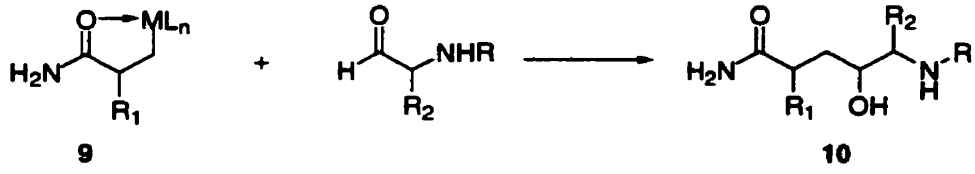
Figure 2. Design of peptidomimetics

The discovery that the aspartyl protease enzyme of the human immunodeficiency virus (HIV-1) is essential for its replication has led to intensive efforts towards the design of specific HIV-1 protease inhibitors.[5] Recently, a number of potent HIV-1 protease inhibitors have been reported, all of which contain a non-hydrolyzable hydroxyethylene dipeptide subunit.[6] An example is Crixivan™ **8**, currently marketed by Merck & Co.



8

The synthesis of the key subunit in **8** and other pharmaceutical agents which contain hydroxyethylene dipeptide isosteres can be envisioned using stereoselective homoenolate methodology. The addition of an amide-derived homoenolate such as **9** to an α-amino aldehyde yields a δ-amino-γ-hydroxy carbonyl derivative **10** which is the basic framework of a hydroxyethylene isostere (Equation 1).

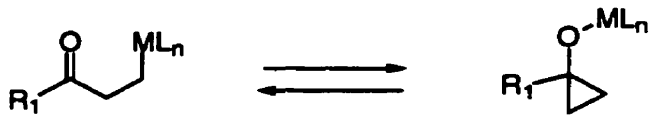


(1)

1.3 GENERATION OF HOMOENOLATES

The enolate required for the aldol process is easily obtained from aldehydes, ketones and esters by deprotonation α to the carbonyl group (pK_a 20 - 25) with mild bases such as lithium diisopropylamide, potassium or sodium hexamethyldisilazide. Homoenolates cannot be generated in a similar manner as deprotonation β to a carbonyl functionality is both kinetically and thermodynamically unfavourable.

The carbonyl group in enolates is protected against nucleophilic addition by resonance stabilization. However, homoenolates possess both nucleophilic and electrophilic sites which makes the tautomerism between oxyanionic and carbanionic isomers more problematic in homoenolate than in enolate chemistry. The carbanionic tautomer often undergoes rapid cyclization to the oxyanionic tautometer and thus rarely acts as a carbon nucleophile (Equation 2).[7] The difficulty in generating stable homoenolates has severely impeded the development of homoenolate chemistry.

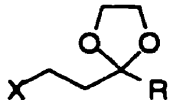


(2)

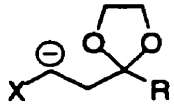
1.3.1 Homoenolate equivalents

The above problems can be overcome through the preparation of homoenolate equivalents. Here, the two main strategies are to protect the carbonyl group as an acetal or ketal or to mask it as a heteroallyl functionality.[7,8]

Homoenolate equivalents generated from carbonyl-protected compounds include Grignard and organolithium reagents such as **11a** and **11b** derived from β-haloacetals and β-haloketals (Figure 3). They can also be prepared by direct deprotonation at the β-position of acetals when this position is activated by groups such as phenylsulfonyl, nitro, phosphonium or phosphane oxides as in **12a - d**.



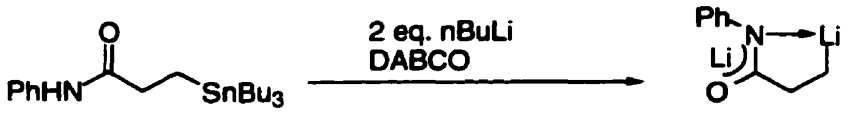
11a X = MgBr
11b X = Li



12a X = $PhSO_2$
12b X = NO_2
12c X = Ph_3P
12d X = $Ph_3P(O)$

Figure 3. Homoenolate equivalents derived from carbonyl-protected compounds

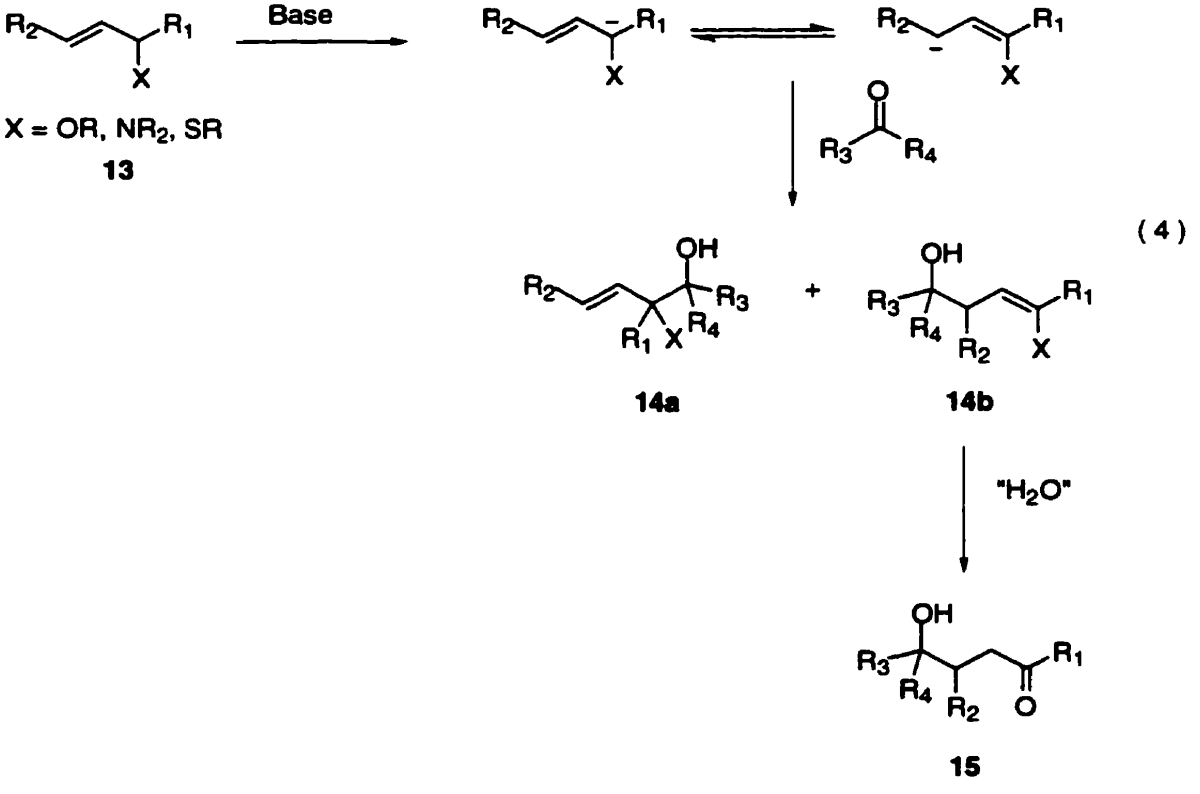
Other examples include the *in situ* protection of the carbonyl group through di-lithiation of tributylstannyl amides or bromo acids with two equivalents of base (Equations 3a, 3b).[9]



(3a)

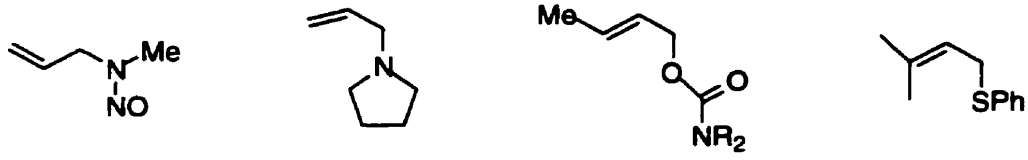
(3b)

An alternate method for the preparation of homoenolate equivalents is the deprotonation of heteroatom substituted allylic compounds such as **13**. These heteroallyl stabilized anions undergo addition to carbonyl compounds to yield the regioisomers **14a** and **14b.** Hydrolysis of **14b** (for X = OR, NR_2 or SR) provides the homoaldol adduct **15** (Equation 4).



(4)

The regioselectivity of the alkylation can be controlled by the nature and size of the groups attached to the heteroatom, the counter ion, the solvent and the reaction temperature. Examples of homoenolate equivalents prepared by this route include allyl methyl nitrosoamines **16a**, allylpyrolidines **16b**, O-allyl carbamates **16c** and allyl thioethers **16d** (Figure 4).

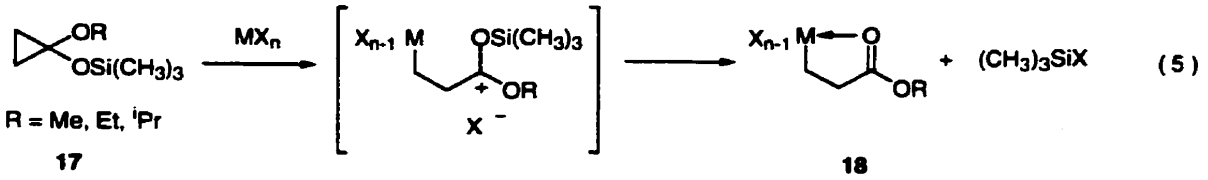


16a **16b** **16c** **16d**

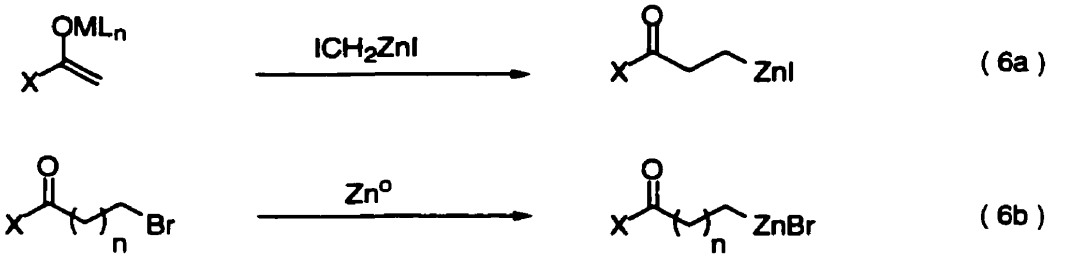
Figure 4. Heteroatom allyl precursors for homoenolate equivalents

1.3.2 Preparation of discrete homoenolates

Characterizable homoenolates have been prepared by Nakamura and Kuwajima through the ring opening of 1-alkoxy-1-(trimethylsilyloxy)cyclopropanes **17** with polyvalent metal salts such as titanium tetrachloride.[10] This method has been used to prepare several ester, ketone and aldehyde homoenolates of metals including tin, antimony, mercury, titanium and zinc. In cases where the mechanism of homoenolate formation has been studied, the reaction is believed to occur through initial σ-coordination of the metal to one of the carbon-carbon bonds of the cyclopropane **17**, followed by cleavage of this bond to form an oxygen-stabilized carbocation. Subsequent loss of trimethylsilyl halide generates the metal homoenolate **18** (Equation 5).



Discrete homoenolates can also be prepared through the homologation of enolates and the reduction of β-halo esters, nitriles and ketones with zinc metal. The latter method allows the preparation of higher enolate homologues (n >2) (Equations 6a, 6b).



A key stabilizing feature of distinct homoenolates is internal coordination of the carbonyl oxygen lone pair electrons to the metal centre. This chelation is evident in the mid-infra red absorption spectrum by a shifting of the carbonyl stretching frequency to lower wavenumbers (1600 - 1690 cm^{-1}) and in the ^{13}C NMR spectrum by a downfield shift of the carbonyl signal (170 - 200 ppm). In the case of tin and titanium homoenolates, this structural assignment has been confirmed by X-ray diffraction of the crystalline homoenolates (Figure 5). Tricholortitanium homoenolates are μ-dimers in the solid state where the titanium centre achieves octahedral geometry via bridging chlorine atoms.[11] On the other hand, trichlorotin homoenolates are five-coordinate monomeric species possessing distorted trigonal bipyramidal geometry while dichlorotin homoenolates are monomeric distorted

octahedral di-alkylated complexes.[12] In all three cases, the carbonyl group coordinates to the metal by its nonbonding electrons to form planar five-membered metallacycles.

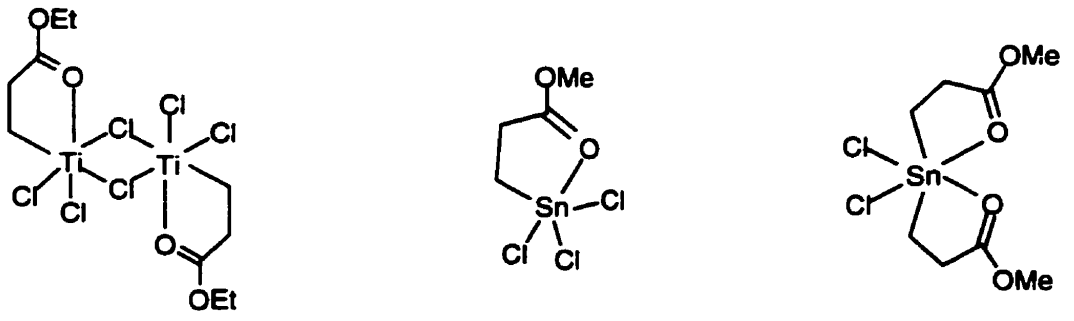


Figure 5. Schematic representation of crystal structures of trichlorotitanium, trichlorotin and dichlorotin homoenolates.

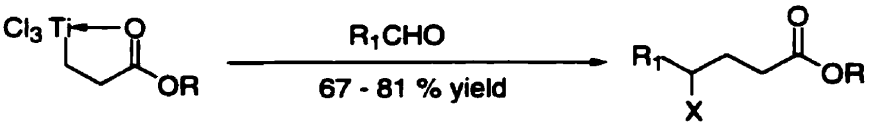
The presence of internal chelation accounts for the enhanced thermal stability of homoenolates prepared by this route.[10] For example, trichlorotitanium homoenolates have a half-life of four months in benzene at room temperature.[13] In comparison, uncoordinated alkyl titanium trihalides usually undergo rapid decomposition, primarily through β-hydride elimination.[14]

1.4 HOMOALDOL REACTIONS

Although homoenolates of several metals have been prepared via the ring opening of silyloxyalkoxycyclopropanes with metal halides, only zinc and titanium homoenolates are known to be reactive in the homoaldol process. Zinc homoenolates have also been used in conjugate additions, allylation, arylation, vinylation and acylation reactions.[15]

1.4.1 Homoaldol reactions with titanium (IV) homoenolates

Addition of titanium tetrachloride to a solution of a silyloxycylopropane in methylene chloride or deuteriochloroform ($CDCl_3$) rapidly generates a wine red solution of a trichlorotitanium (IV) homoenolate, which can be crystallized from hexanes. These homoenolates react readily with a range of aldehydes yielding the γ-hydroxyester **19a** with aliphatic aldehydes (Equation 7). In the case of conjugated aldehydes, *in situ* ionization and chlorination of the initially formed γ-hydroxyester occurs to yield the γ-chloroester **19b**.[13]

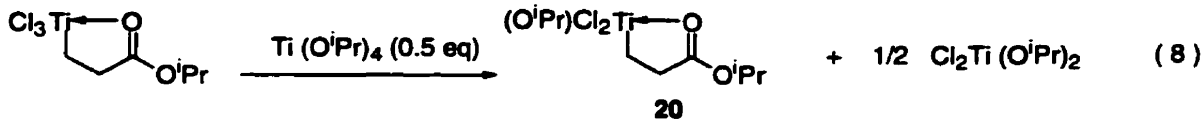


R = Me, Et, ^{i}Pr

19a X = OH
19b X = Cl

(7)

The low nucleophilicity of trichlorotitanium homoenolates towards ketones and their propensity to yield chlorinated products led to the development of alkoxide-modified titanium (IV) homoenolates. Ligand exchange of a trichlorotitanium homoenolate with 0.5 equivalents of titanium isopropoxide ($Ti(O^iPr)_4$) results in a monoalkoxydichlorotitanium homoenolate **20**, which reacts with conjugated aldehydes to give good yields of γ-hydroxyesters, with no formation of γ-chloroesters (Equation 8). The homoenolate **20** is also reactive towards ketones giving moderate yields of the corresponding γ-lactones. Further enhancement in the nucleophilicity can be obtained through the use of 0.5 equivalents of titanium tetra-t-butoxide, which provides higher yields of γ-lactones or γ-hydroxyesters with a range of aryl and aliphatic ketones.

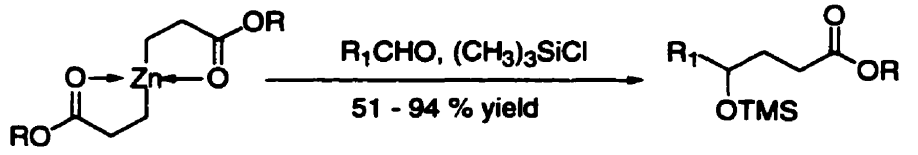


20

It is important to note that a stoichiometric amount of titanium tetrachloride is required for all homoaldol reactions carried out with titanium (IV) homoenolates.

1.4.2 Homoaldol reactions with zinc homoenolates

Zinc homoenolates are prepared by the addition of a silyloxyalkoxycyclopropane to freshly fused zinc chloride or zinc iodide in diethyl ether. The Schlenk equilibium favours the formation of two homoenolate units per zinc metal centre. In comparison to titanium homoenolates, zinc homoenolates are much less reactive towards electrophiles, exhibiting lower reactivities than Grignard or alkyl zinc species. They are inert towards aldehydes in a variety of solvents including methylene chloride, deuteriochloroform, carbon tetrachloride, benzene, diethyl ether and tetrahydrofuran. However, in the presence of one equivalent of trimethylsilylchloride (TMSCl), zinc homoenolates add rapidly to aliphatic and aryl aldehydes providing the γ-silyloxyester **19c** in good yields (Equation 9). In this instance, TMSCl is postulated to activate the aldehdye towards addition through silylation at the carbonyl oxygen.[15]

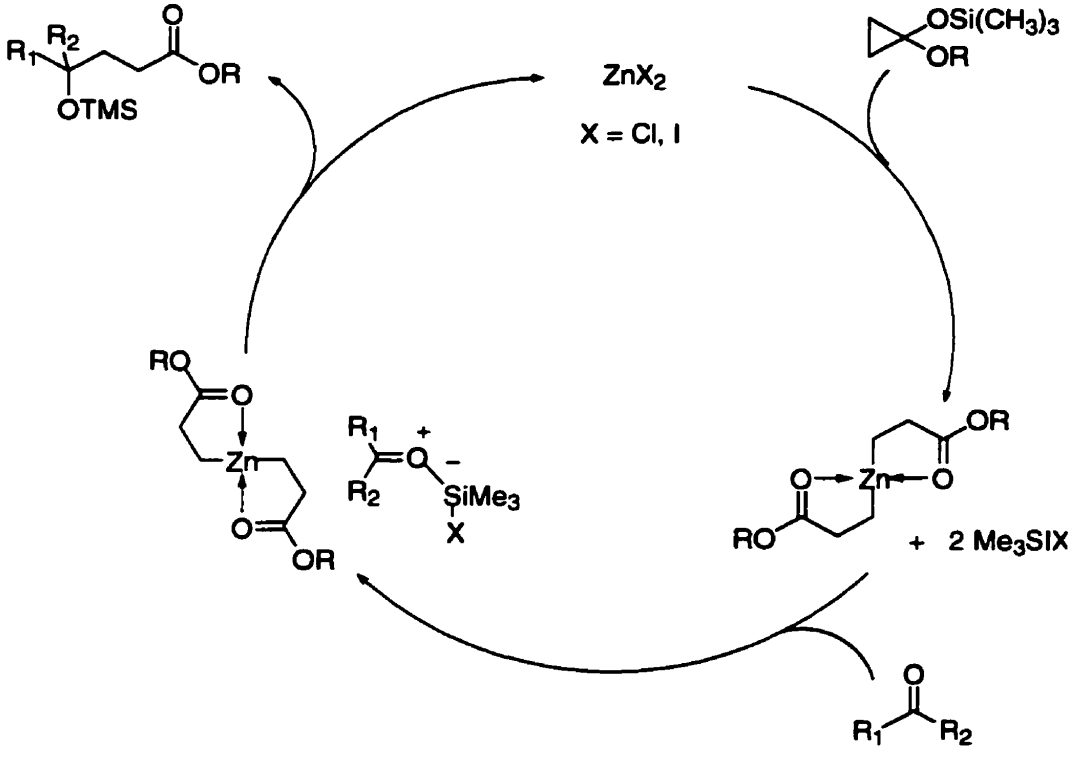


(9)

19c

R = Me, Et, ^{i}Pr

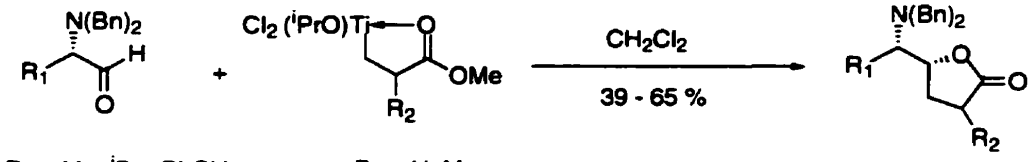
Another distinct difference between zinc and titanium homoenolates is that the addition of zinc homoenolates to aldehydes can be carried out using substoichiometric amounts of $ZnCl_2$ or ZnI_2 (3 - 5 mol %) and a silyloxyalkoxycyclopropane (Scheme 2). Furthermore, additions to less reactive substrates such as acetophenone and benzaldehyde dimethyl acetal can be accomplished with ZnI_2 catalysis.



Scheme 2. Catalysis of homoaldol reactions with $ZnCl_2$ and ZnI_2

1.4.3 Stereoselective homoaldol reactions

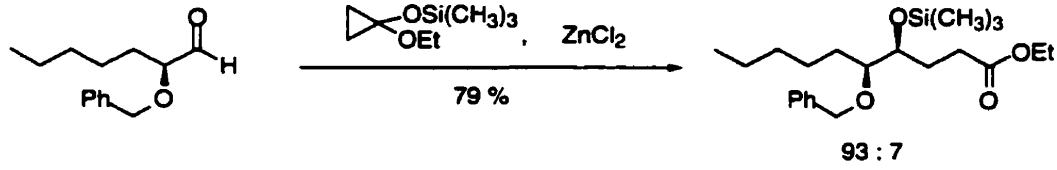
Since the pioneering work of Nakamura in the field of homoenolate chemistry, there have been only a few stereoselective homoaldol reactions reported in which discrete homoenolates are used.[i] For example, good Felkin-Anh selectivity has been reported in the addition of alkoxytitanium (IV) homoenolates to N,N-dibenzyl α-amino aldehydes (Equation 10).[16] The diastereomeric γ-lactones were obtained in *erythro* : *threo* ratios ranging from 10 : 1 to 13 : 1.



R_1 = Me, ^{i}Bu, $PhCH_2$ R_2 = H, Me

(10)

Chelation control has been observed in the addition of zinc homoenolates to α-alkoxy aldehydes providing the γ-silyloxyester with 93 : 7 *syn* diastereoselectivity (Equation 11).[15]

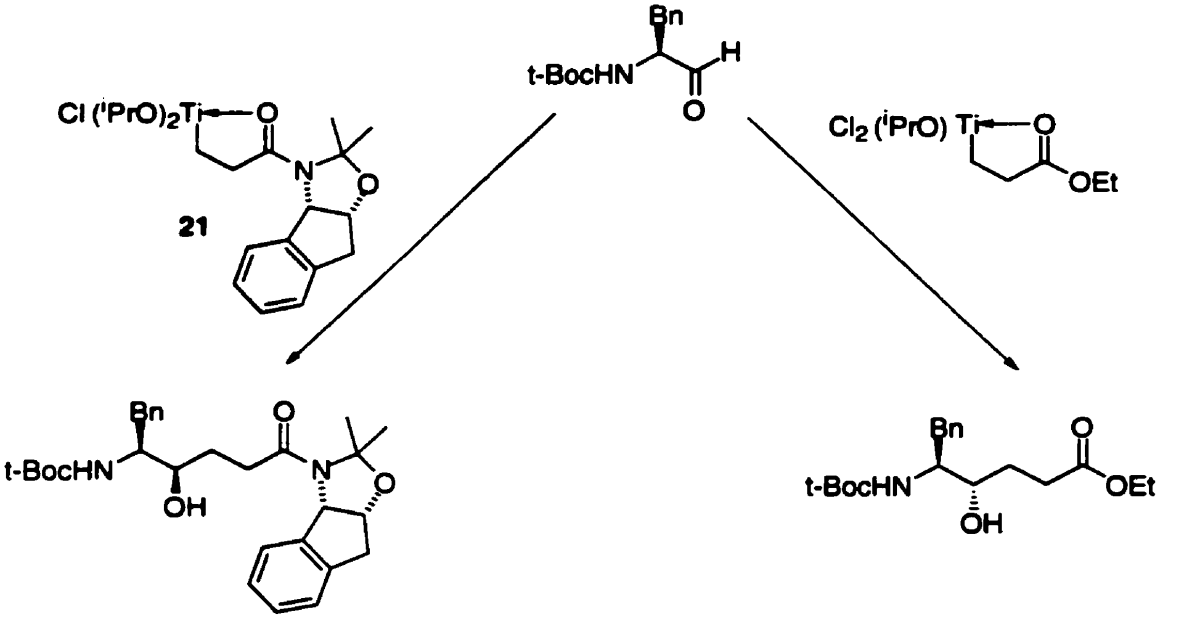


93 : 7

(11)

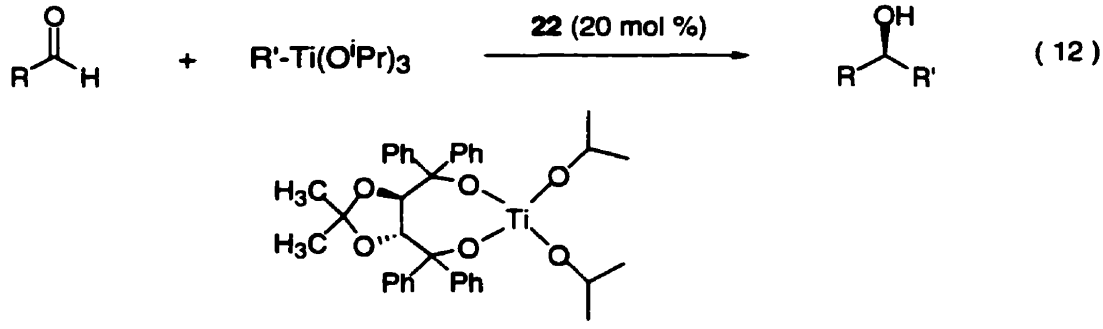
[i] For examples of stereoselective reactions using homoenolate equivalents, see: Ahlbrecht, H.; Beyer, U. *Synthesis*. **1999**, 365.

The sole account of reagent control in homoaldol reactions was reported by Armstrong, wherein a single diastereomer was obtained upon addition of an indanolamide titanium homoenolate **21** to t-Boc-(S)-phenylalaninal (Scheme 3).[17] The chiral auxiliary presuambly blocks one face of the homoenolate, allowing addition to occur only from the less hindered β-face. More importantly, the reaction proceeded with a complete override of the inherent chelation controlled addition between the aldehyde and a titanium ester homoenolate.



Scheme 3. Reagent control in homoaldol reactions

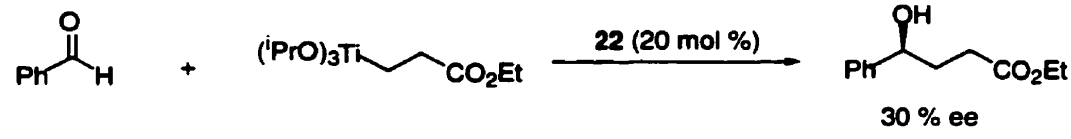
The only example of asymmetric catalysis using discrete homoenolates has been reported by Seebach in the addition of aryl and alkyl titanium derivatives to aldehydes in the presence of a catalytic amount of TADDOL-Ti(O^iPr)$_2$ **22** (Equation 12).[18, ii] The alkyl titanium species were prepared by treatment of alkyl or aryl lithium or Grignard reagents with $ClTi(O^iPr)_3$.



(12)

22

The enantiomeric excess of the products obtained was highly dependent on the nature of the transferred alkyl chain. Simple alkyl-Ti(O^iPr)$_3$ derivatives yielded products with excellent enantiomeric excess (*ca* 98 %) while the enantioselectivity decreased to 66 % with $PhCH_2$-Ti(O^iPr)$_3$. Furthermore, the presence of heteroatoms at positions closer than the δ-carbon significantly lowered the selectivity of the addition. For example, the homoaldol product of benzaldehyde was obtained with an enantiomeric excess of only 30 % (Equation 13).



(13)

[ii] TADDOL : α, α, α', α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol

1.5 OVERVIEW OF PROJECT

The potential of the homoaldol reaction in the stereoselective synthesis of peptidomimetics warrants the development of efficient asymmetric protocols for this process. As mentioned above, accounts of stereoselective homoaldol reactions using discrete homoenolates are scarce. There have been no reports of enantioselective additions of silyloxycyclopropanes to aldehydes. Furthermore, there are no examples of asymmetric catalysis in this particular class of homoaldol reactions.

We are interested in developing efficient, versatile systems for catalytic, enantioselective homoaldol reactions. Such a methodology would be a powerful contribution to the attempts that are being made to synthesize hydroxyethylene dipeptide isosteres and natural products containing 1,4-oxygenated subunits.

We began this study, as described in Chapter Two, with chiral auxiliary mediated additions of zinc homoenolates to aldehydes, as there is precedence for catalysis with zinc homoenolate systems. Our results in this area led us to investigate titanium catalysts for this reaction and this is presented in Chapter Three. Efforts directed towards the development of an enantioselective catalytic system are detailed in Chapter Four.

1.6 REFERENCES

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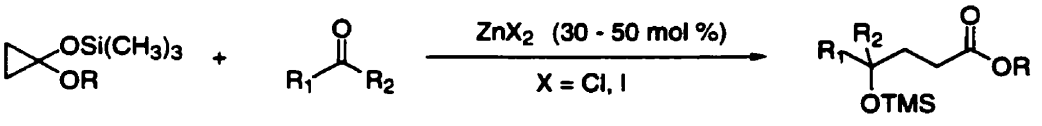
CHAPTER TWO

HOMOALDOL REACTIONS WITH ZINC HOMOENOLATES

2.1 INTRODUCTION

Our interest in the homoaldol reaction lies in the development of an enantioselective catalytic protocol amenable to the synthesis of peptidomimetics and complex natural products containing 1,4-oxygenated substructures. We anticipated that this goal could be achieved through the metal halide ring opening of silyloxycyclopropananone acetals in the presence of a chiral ligand. To date, there have been no reports of enantioselectivity imparted in this process.

The only example of catalysis in this class of homoaldol reactions is the addition of 1-alkoxy-1-(trimethylsilyloxy)cyclopropanes to aldehydes in the presence of substoichiometric amounts of zinc chloride or zinc iodide (Equation 14).[1] As there is precedence for catalysis with zinc homoenolate systems, it represented a logical starting point for an extension into an enantioselective protocol.



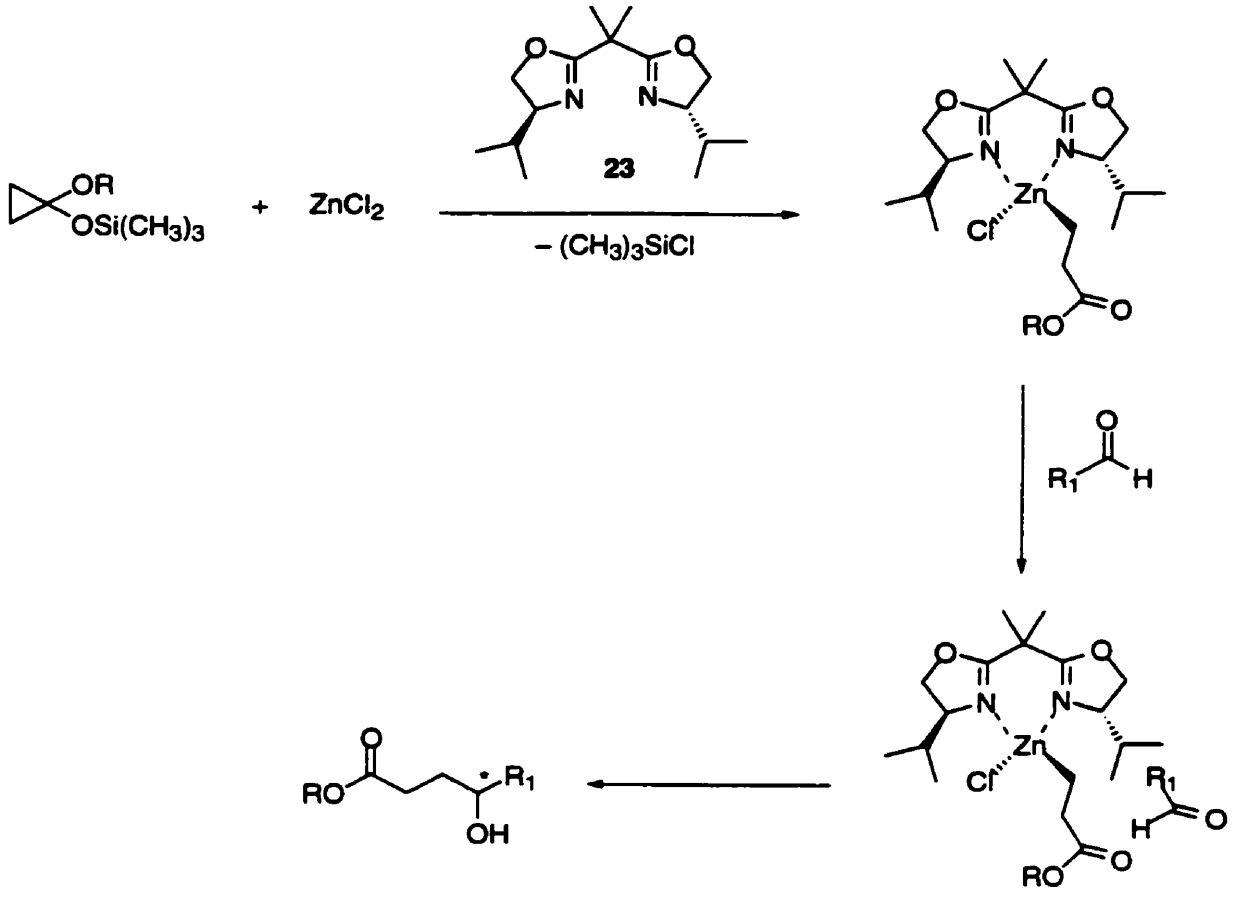
(14)

2.2 BIS-OXAZOLINE MEDIATED ZINC HOMOENOLATE ADDITION TO BENZALDEHYDE

2.2.1 Introduction

The first chiral auxiliary explored for the mediation of zinc homoenolate addition to aldehydes was the bis-oxazoline **23**. Bis-oxazoline complexes of magnesium, iron and copper are effective at mediating enantioselective Diels-Alder, aziridination and cyclopropanation reactions.[2] In addition, the use of bis-oxazoline-zinc complexes in enantioselective allylation of aldehydes[3] as well as a bis-oxazoline-zinc triflate complex as a chiral Lewis acid for enantioselective conjugate radical additions[4] have recently been reported. A C_3 symmetric oxazolinyl ligand has also been used in the catalytic enantioselective addition of diethyl zinc to aldehydes.[5]

The influence of chelating ligands on the structure of zinc homoenolates has been described.[6] The chelation between the lone pair electrons of the carbonyl oxygen and the metal centre in zinc homoenolates is readily displaced by basic ligands such as pyridine or ether. We thus anticipated that the ring opening of a silyloxyalkoxycyclopropane with zinc chloride in the presence of bis-oxazoline **23** would form a zinc homoenolate, in which the more basic oxazoline ligands would replace the carbonyl coordination to the zinc metal (Scheme 4). Approach of an aldehyde from one face of the carbon-zinc bond would take place with the substituent on the aldehyde positioned away from the bulky isopropyl groups of the bis-oxazoline. Subsequent addition by a ligand bound homoenolate would lead to a chiral γ-alkoxyester.



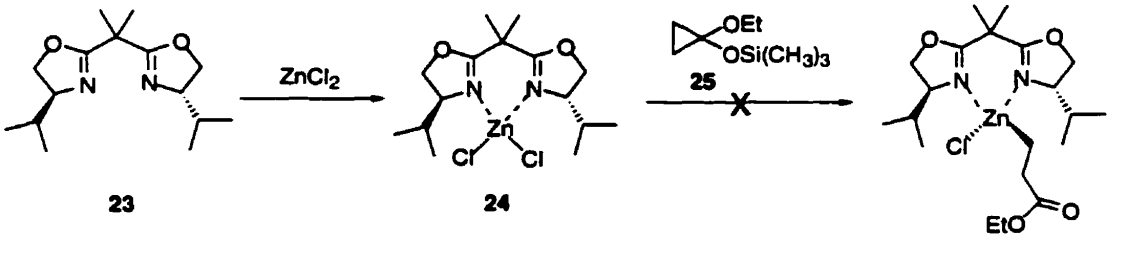
Scheme 4. Anticipated enantioselective homoaldol reactions with a bis-oxazoline-$ZnCl_2$ system.

Zinc homoenolates are very reactive towards aldehydes in the presence of trimethylsilylchloride (TMSCl), which activates the aldehyde towards addition by coordination to the carbonyl oxygen.[1] In order to effectively compete with this non-selective pathway and to maintain the highly ordered transition state required for enantioselective additions, zinc homoenolates were prepared and used under carefully-controlled conditions. The first system studied was a metal-ligand complex between a

bis-oxazoline and $ZnCl_2$, followed by *in situ* formation of a ligand coordinated zinc homoenolate. In the second strategy, pre-formed zinc homoenolates (without TMSCl) were added to a solution of a bis-oxazoline, followed by addition of the aldehyde.

2.2.2 Attempts to form ligand coordinated homoenolates with bis-oxazoline-zinc complexes

The bis-oxazoline-$ZnCl_2$ complex **24** was prepared by addition of a solution of bis-oxazoline **23** (1.03 - 1.40 equivalents) in deuteriochloroform ($CDCl_3$) to a suspension of fused $ZnCl_2$ in $CDCl_3$ (Equation 15). The ^1H NMR spectrum of the resulting solution showed a downfield shift in the methine proton of the isopropyl substituent from δ 1.80 to δ 2.40 ppm (m, 1H). This is consistent with donation of electron density from the nitrogen atom to the zinc metal upon formation of the bis-oxazoline-$ZnCl_2$ complex **24**.



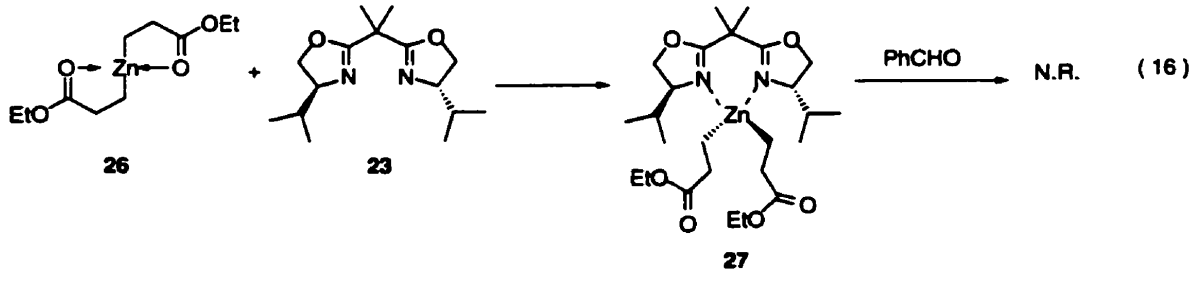
23 24 (15)

However, ^1H NMR indicated no formation of zinc homoenolate upon subsequent addition of one equivalent of cyclopropane **25**, even after 12 hours of heating at reflux. In the event that the active species was formed in amounts not observable by ^1H NMR, one equivalent of benzaldehyde was added to the above reaction mixture. There was no formation of homoaldol products even upon 12 hours

of heating at reflux in $CDCl_3$. Analogous results were obtained when the above reactions were repeated with $ZnCl_2$ in diethyl ether or with more reactive ZnI_2 or zinc triflate ($Zn(OTf)_2$).

2.2.3 Attempts at enantioselective homoaldol reactions with bis-oxazoline coordinated zinc homoenolates

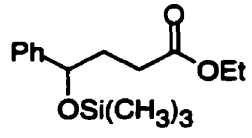
Zinc homoenolates were prepared according to the procedure described by Nakamura from silyloxyethoxycyclopropane **25** and $ZnCl_2$, followed by removal of solvent and liberated TMSCl *in vacuo*.[6] The homoenolate **26** was then dissolved in $CDCl_3$ and added to a solution of bis-oxazoline **23** (1.10 - 1.20 equivalents) in $CDCl_3$ (Equation 16). After 15 min, a 500 μL aliquot was transferred to an argon filled NMR tube. The signals for the methylene protons of the homoenolate were observed at δ 0.20 (t, 2H) and δ 2.37 (t, 2H) ppm, upfield from the respective signals for free zinc homoenolate (δ 0.42 and δ 2.63 ppm). In addition, a downfield shift in the methine proton of the isopropyl substituent of the bis-oxazoline from δ 1.80 to δ 2.20 ppm (m, 1H) was evident. These observations are in accordance with donation of electron density from the nitrogen ligand to the zinc metal and indicate chelation between the zinc homoenolate and the bis-oxazoline to form complex **27**.



(16)

Benzaldehyde was subsequently added at room temperature and the reaction was monitored by ^{1}H NMR. There was no product formation after 12 hours at room temperature followed by 12 hours at reflux or when the reaction was repeated in methylene chloride.

When the reaction in methylene chloride was carried out in the presence of trimethylsilyltiflate (TMSOTf, 1.4 equivalents), a 17 % yield of γ-silyloxyester **28** and a 4 % yield of γ-lactone **29** were obtained. However, the products were racemic, indicating the reaction had proceeded through a non-selective route.



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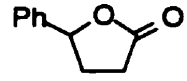

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2.2.4 Conclusions with bis-oxazoline mediated zinc homoenolate addition to benzaldehyde

Homoenolates formed through the ring opening of silyloxyalkoxycyclopropanes require a Lewis acidic metal salt. For example, tributyltin triflate can be used to prepare alkyl tin homoenolates via this route while tributyltin chloride is inert under the same conditions.[6] The diminished reactivity of the bis-oxazoline zinc complex **24** could be due to a drastic reduction of the Lewis acidity of the zinc salt upon coordination to the bis-oxazoline. This prevents cleavage of the cyclopropane to form a bis-oxazoline coordinated zinc homoenolate. Even the presence of a triflate ligand was not sufficient to maintain the Lewis acidity of the complex. These results are surprising since zinc homoenolates can be prepared from

silyloxycyclopropanes and zinc chloride in diethyl ether.[1] The coordination of solvent molecules to the zinc metal centre in this case does not retard the rate of ring opening of the silyloxycyclopropane.

In the second route examined, it was expected that the nucleophilicity of zinc homoenolates would increase upon coordination to the bis-oxazoline due to donation of electron density from the nitrogen atoms. The unreactive nature of the bis-oxazoline coordinated zinc homoenolate **27** towards addition to benzaldehyde implies that activation of the carbonyl group of the aldehyde is essential for addition to occur. Although TMSOTf could be used to promote the addition, the homoaldol products obtained were racemic, indicating that the reaction proceeded through a non-selective pathway, possibly via de-chelation of the zinc homoenolate from the nitrogen ligand by the triflate species.

We concluded that bis-oxazolines were not suitable chiral auxiliaries for the addition of zinc homoenolates to aldehydes. The coordination of the nitrogen ligands to either zinc salts or pre-formed zinc homoenolates results in unreactive complexes. An alternate protocol for this process was required.

2.3 ZINC HOMOENOLATE ADDITION TO ALDEHYDES MEDIATED BY β-AMINO ALCOHOLS AND TITANIUM (IV) ALKOXIDES

2.3.1 Diethyl zinc addition to aldehydes mediated by β-amino alcohols

The addition of diethyl zinc (and more recently, alkynyl, divinyl, alkenyl and other dialkyl zinc reagents) to aldehydes is one of the most widely studied carbon-

carbon bond-forming reactions.[7] Dialkyl zinc reagents do not react with aldehydes in the absence of ligands either in hydrocarbon or ethereal solvents. However, rapid addition does occur in the presence of β-amino alcohols such as proline derivatives, cinchona alkaloids, ephedrine, norephedrine and camphor derivatives (Figure 6).

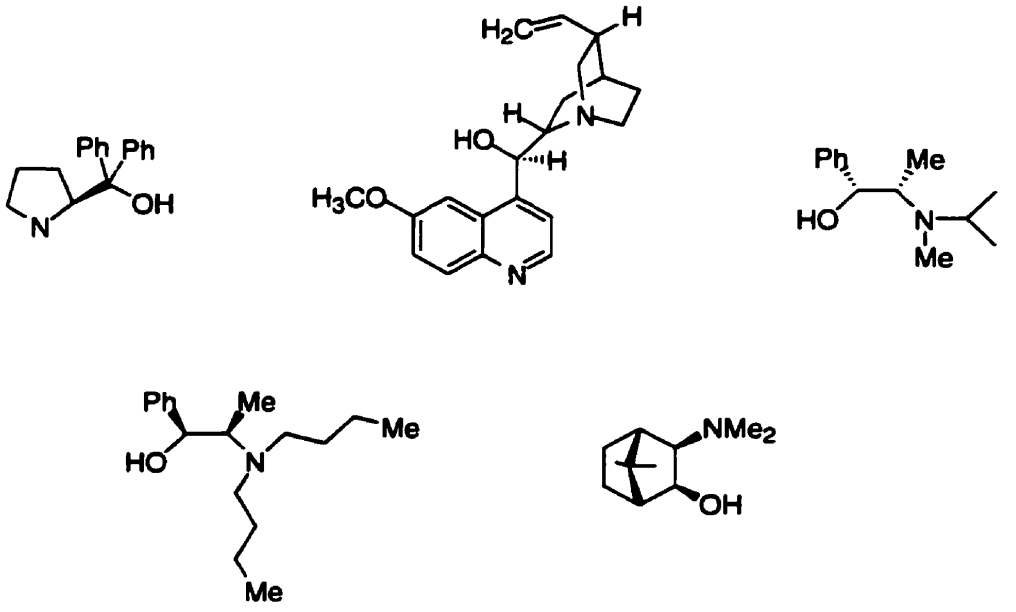
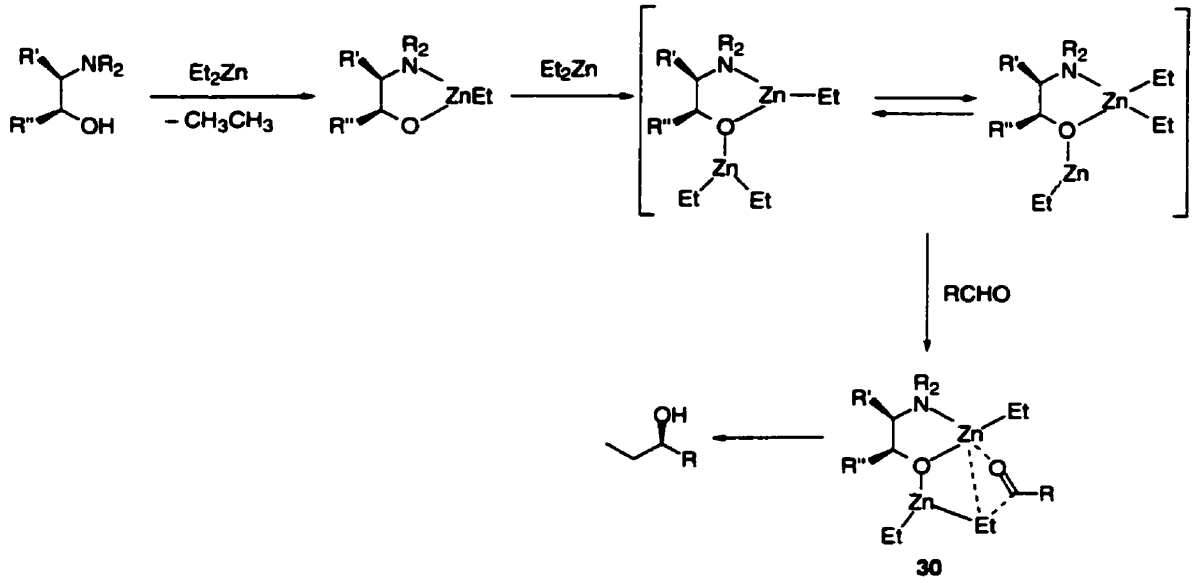


Figure 6. Common β-amino alcohols used for enantioselective catalysis of diethyl zinc addition to aldehydes

One of the mechanisms proposed for the enantioselective addition of diethyl zinc to aldehydes in the presence of β-amino alcohols is outlined in Scheme 5.[8, 7a] Treatment of diethyl zinc with a β-amino alcohol results in coordination of the alkyl zinc species to the ligand with liberation of ethane. This is accompanied by a rehybridization of the zinc atom from linear to tetrahedral and an increase in the zinc-carbon bond length. Dynamic exchange between the alkyl groups occurs upon incorporation of a second equivalent of diethyl zinc. The enantiodetermining step

consists of a bicyclic transition state **30** with two zinc atoms, one amino alcohol and three alkyl groups. The zinc atom with the oxygen and nitrogen donor ligands coordinates to the aldehyde while the alkyl group bridging the two zinc atoms is transferred to yield the chiral alcohol.

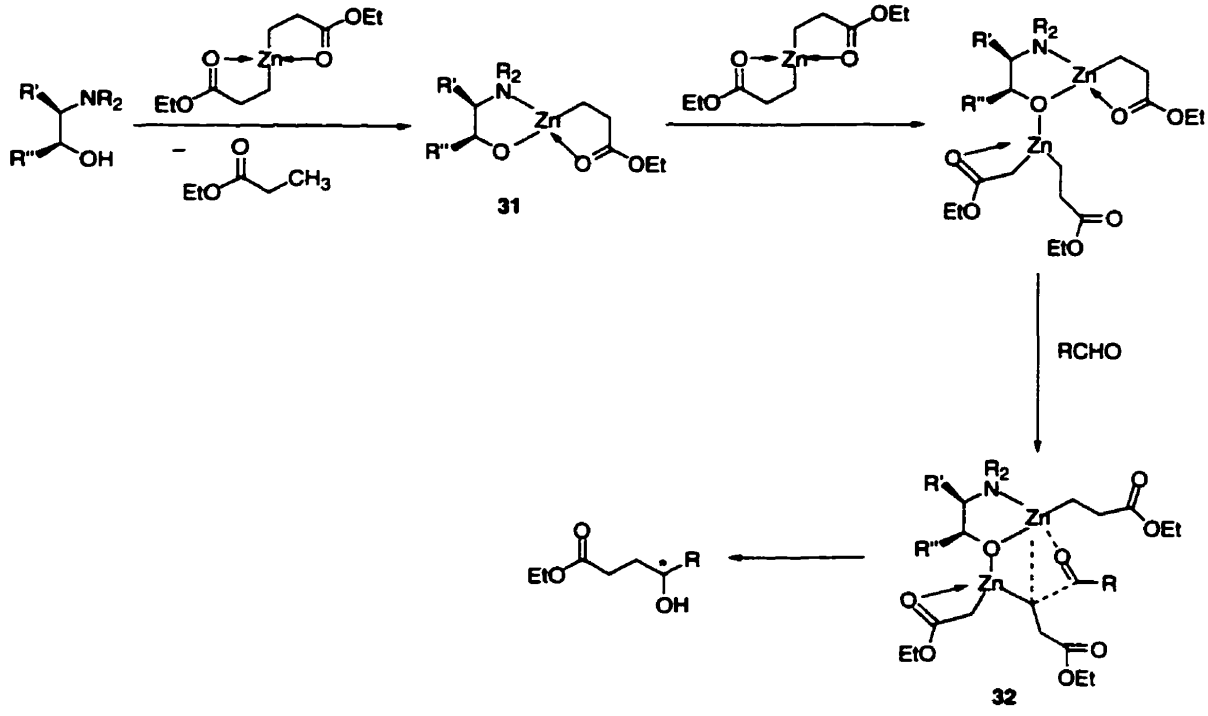


Scheme 5. Proposed mechanism for β-amino alcohol mediated enantioselective addition of diethyl zinc to aldehdyes

2.3.2 Effect of β-amino alcohols on zinc homoenolate addition to aldehydes

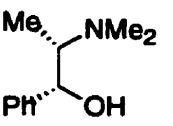
Since zinc homoenolates are dialkyl zinc species, we anticipated that β-amino alcohols would mediate their addition to aldehydes in an analogous manner as diethyl zinc addition. Treatment of a zinc homoenolate with a β-amino alcohol would release ethyl propionate forming the ligand bound homoenolate **31** (Scheme 6). If a bi-metallic complex such as **32** is formed in the transition state, one zinc atom would

activate the aldehyde while the three-carbon alkyl chain would be transferred from the other zinc species.



Scheme 6. Anticipated mechanism for β-amino alcohol mediated enantioselective addition of zinc homoenolates to aldehydes

We chose β-amino alcohols (1R, 2S) N-methyl ephedrine **33** and pyridine t-butyl carbinol **34** as potential chiral mediators for zinc homoenolate addition to aldehydes. The addition of diethyl zinc to benzaldehyde in the presence of **33** (3 mol %) provides phenyl ethyl carbinol in 81 % yield with an enantiomeric excess of 81 %.[9] The same reaction catalyzed by **34** (11 mol %) gave the product in 61 % yield with 78 % ee.[10]



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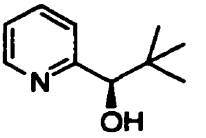

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Zinc homoenolates were prepared according to the procedure described by Nakamura.[6] Prior to use in all experiments, TMSCl along with the solvent and excess cyclopropane were removed *in vacuo* to eliminate the competing non-selective reaction of homoenolate addition to a silyl-activated aldehyde.

(1R, 2S) N-methyl ephedrine **33** (0.16 equivalents) was added to a solution of pre-formed zinc homoenolate in toluene-d_8, followed by addition of benzaldehyde after 15 minutes at room temperature. Observation by ^{1}H NMR indicated broadening of the peaks corresponding to the methylene protons of the zinc homoenolate [δ 0.54 (t, 2H) and δ 2.50 (t, 2H) ppm] indicating dynamic exchange between ligand-bound and free zinc homoenolate. However, no addition was observed after 16 hours at room temperature.

The above reaction was repeated with pyridine t-butyl carbinol **34** (0.12 equivalents) in toluene-d_8. Once again, the signals corresponding to the methylene protons of the zinc homoenolate were broadened upon addition of the chiral ligand. However, as in the previous case, there was no reaction after 16 hours at room temperature.

These results indicate that, as observed with bis-oxazolines as ligands, the electron donation from the β-amino alcohol ligands is not sufficient to increase the nucleophilicity of the homoenolate. In the case of diethyl zinc addition to aldehydes,

the aldehyde is activated by coordination to one of the zinc atoms. It is possible that the internal coordination of zinc homoenolates is not easily displaced by an aldehyde to generate the desired transition state **32**. It appears that activation of the aldehyde is required before addition by zinc homoenolates.

2.3.3 Diethyl zinc addition to aldehydes mediated by chiral titanium (IV) alkoxides

The enantioselective addition of diethyl zinc to aldehydes can also be carried out in the presence of chiral titanium alkoxides such as **35** – **38** (Figure 7).[11,7b]

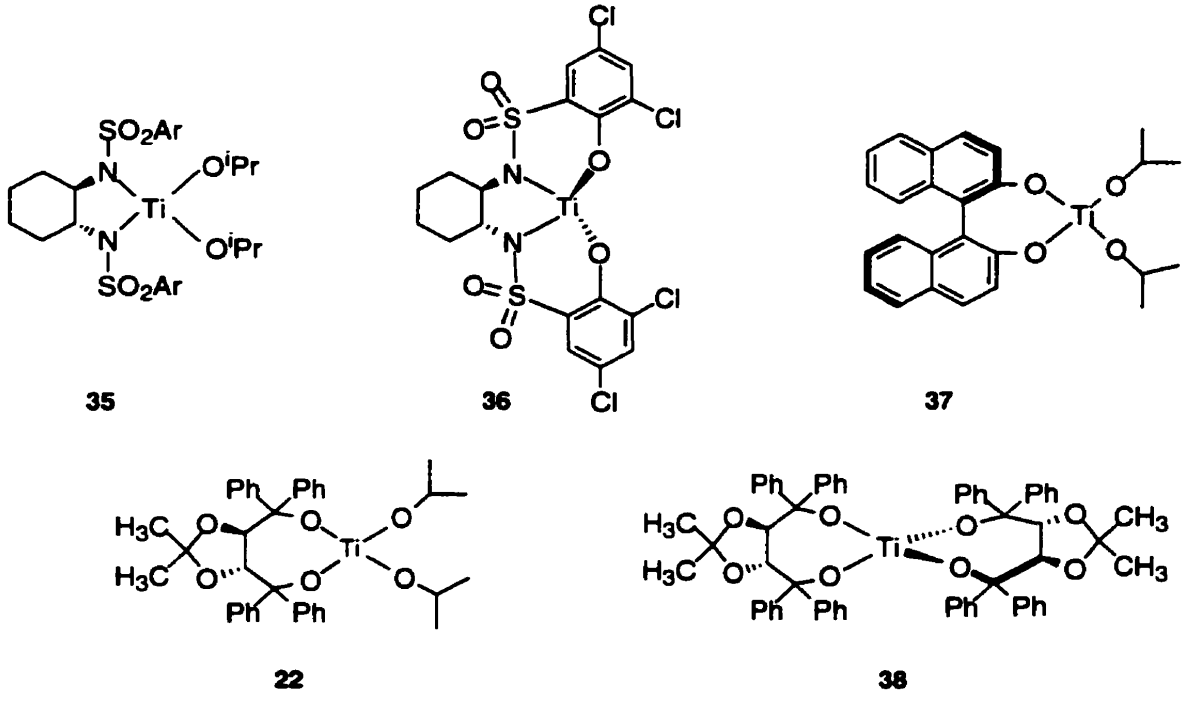
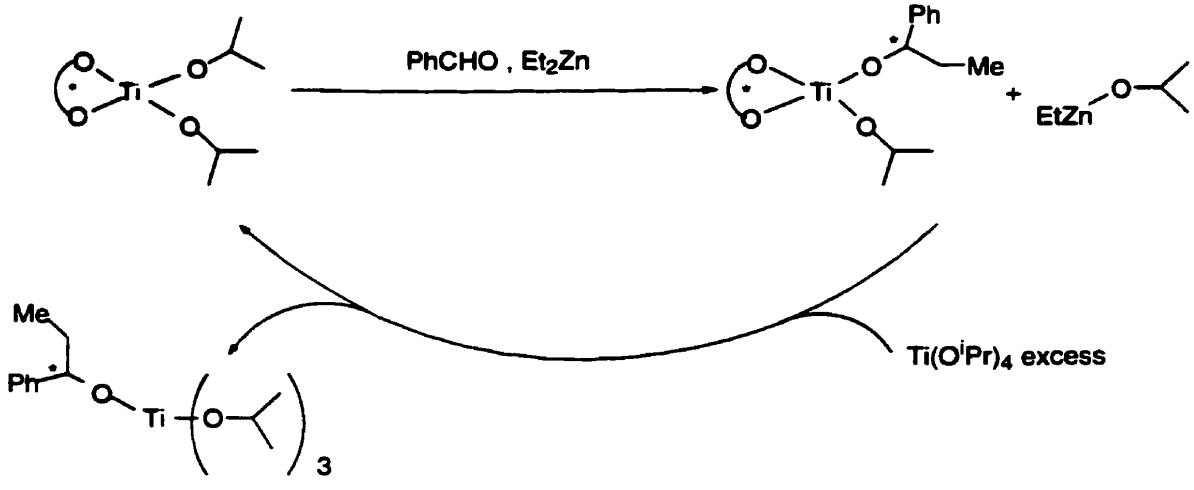


Figure 7. Chiral titanium alkoxides for enantioselective addition of dialkyl zinc reagents to aldehydes

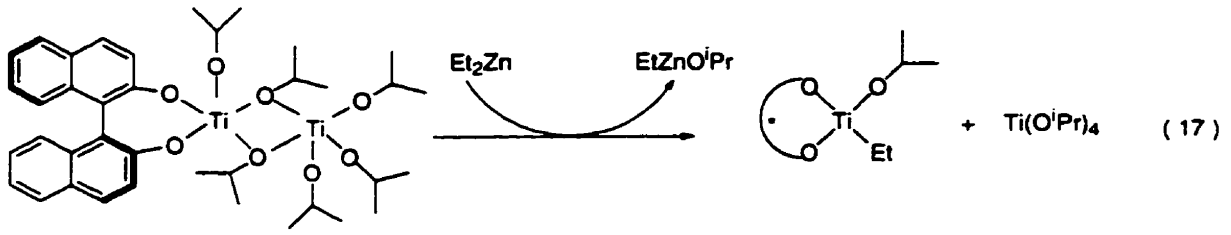
In addition to the chiral titanium alkoxide, excess titanium isopropoxide ($Ti(O^iPr)_4$) is usually required for efficient catalysis. One of the functions of $Ti(O^iPr)_4$ is believed to be the regeneration of the active catalyst by replacement of the product alkoxide on the titanium centre with isopropoxide (Scheme 7). Enantioselective catalysis of diethyl zinc addition to aldehydes with chiral titanium alkoxides is thus a case of ligand-accelerated catalysis wherein the chiral titanium complex is a more active catalyst than $Ti(O^iPr)_4$ alone. The mechanisms which have been proposed for this reaction include transfer of the alkyl group from zinc to titanium prior to addition as well as aldehyde activation by the titanium centre in either a mono- or bi-metallic complex.



Scheme 7. Regeneration of chiral titanium (IV) catalysts by $Ti(O^iPr)_4$

2.3.4 Attempts at zinc-titanium transmetallation with zinc homoenolate systems

Mori and Nakai have recently reported the catalytic asymmetric alkylation of aldehydes with diethyl zinc using 10 mol % of (S) 1,1'-bi-2-naphthol (Binol) with excess $Ti(O^iPr)_4$ (1.2 equivalents).[12] The authors propose the formation of a chiral alkyl titanium species from diethyl zinc and Binol-$Ti_2(O^iPr)_6$, which undergoes addition to benzaldehyde providing the product in 85 % enantiomeric excess (Equation 17).

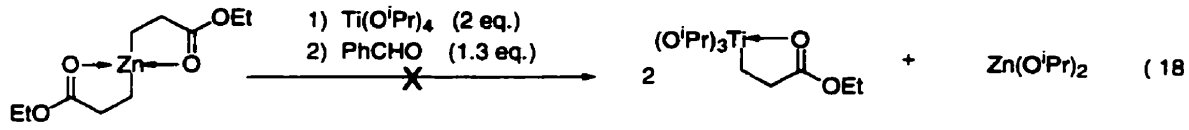


(17)

We anticipated that a similar transmetallation process might occur between zinc homoenolates and a chiral titanium (IV) alkoxide. Analogous to the above results, an enantioselective addition would occur between the resulting chiral trialkoxytitanium homoenolate and an aldehyde.

A solution of pre-formed zinc homoenolate in $CDCl_3$ was treated with 2 equivalents of $Ti(O^iPr)_4$, followed by benzaldehyde (1.3 equivalents) at room temperature (Equation 18). There was no colour change in the reaction mixture, indicating the absence of a titanium homoenolate which is characteristically wine-red in colour.[13] A shift in the methylene protons of the triisopropoxytitanium homoenolate was also expected as the methylene protons of zinc, trichlorotitanium and dichloroisopropoxytitanium homoenolates exhibit very different chemical shifts in the

^{1}H NMR spectrum.[6, 13] However, the ^{1}H NMR of the methylene protons of the homoenolate in the above reaction mixture were identical to those of the zinc homoenolate [δ 0.40 (t, 2H) and δ 2.55 (t, 2H) ppm] indicating that zinc-titanium transmetallation had not occurred to any significant extent in this process.



(18)

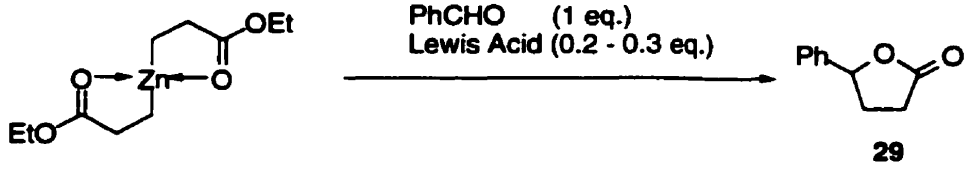
Thus, we were surprised to observe the formation of γ-lactone **29** (30% yield, analyzed by capillary GC) after 23 hours at room temperature. This result was intriguing as zinc homoenolates are unreactive towards aldehydes in the absence of TMSCl (*vide supra*) and there was no evidence for the formation of a titanium homoenolate in the above process. A probable explanation is that, prior to homoenolate addition, the aldehyde is activated by $Ti(O^iPr)_4$ in an analogous manner as TMSCl. Similar aldehyde activation by chiral titanium (IV) alkoxides has been proposed for the addition of diethyl zinc to aldehydes.[14] If this was the case, we were interested if other Lewis acids would mediate this reaction and more importantly if chiral titanium (IV) alkoxides would provide any selectivity in this process.

2.3.5 Lewis acid mediated addition of zinc homoenolates to benzaldehyde

Metal salts which are commonly used as Lewis acids in organic reactions were examined as potential mediators for the addition of zinc homoenolates to aldehydes. For example, cerium trichloride ($CeCl_3$) has been used as a catalyst in aldol and

oxirane ring opening reactions.[15] The use of indium trichloride ($InCl_3$), copper triflate ($Cu(OTf)_2$) and boron trifluoroetherate ($BF_3.OEt_2$) as Lewis acids in aldol reactions of silyl enol ethers has also been reported.[16]

A solution of pre-formed zinc homoenolate, dodecane and benzaldehyde in $CDCl_3$ was treated with 0.2 to 0.3 equivalents of Lewis acids (Equation 19). Aliquots of 200 μL were withdrawn from the reaction mixture at appropriate time intervals, quenched with saturated ammonium chloride and the products extracted into ethyl acetate. The crude reaction mixture was analyzed by capillary GC using a Chirasil-dex column. The percent conversion to γ-lactone **29** over time is shown in Figure 8 for the Lewis acids examined. Some homoaldol product is obtained in the case of the control reaction (no Lewis acid added) due to the residual amounts of TMSCl present after evaporation of the volatile material during the preparation of the zinc homoenolate.



29

(19)

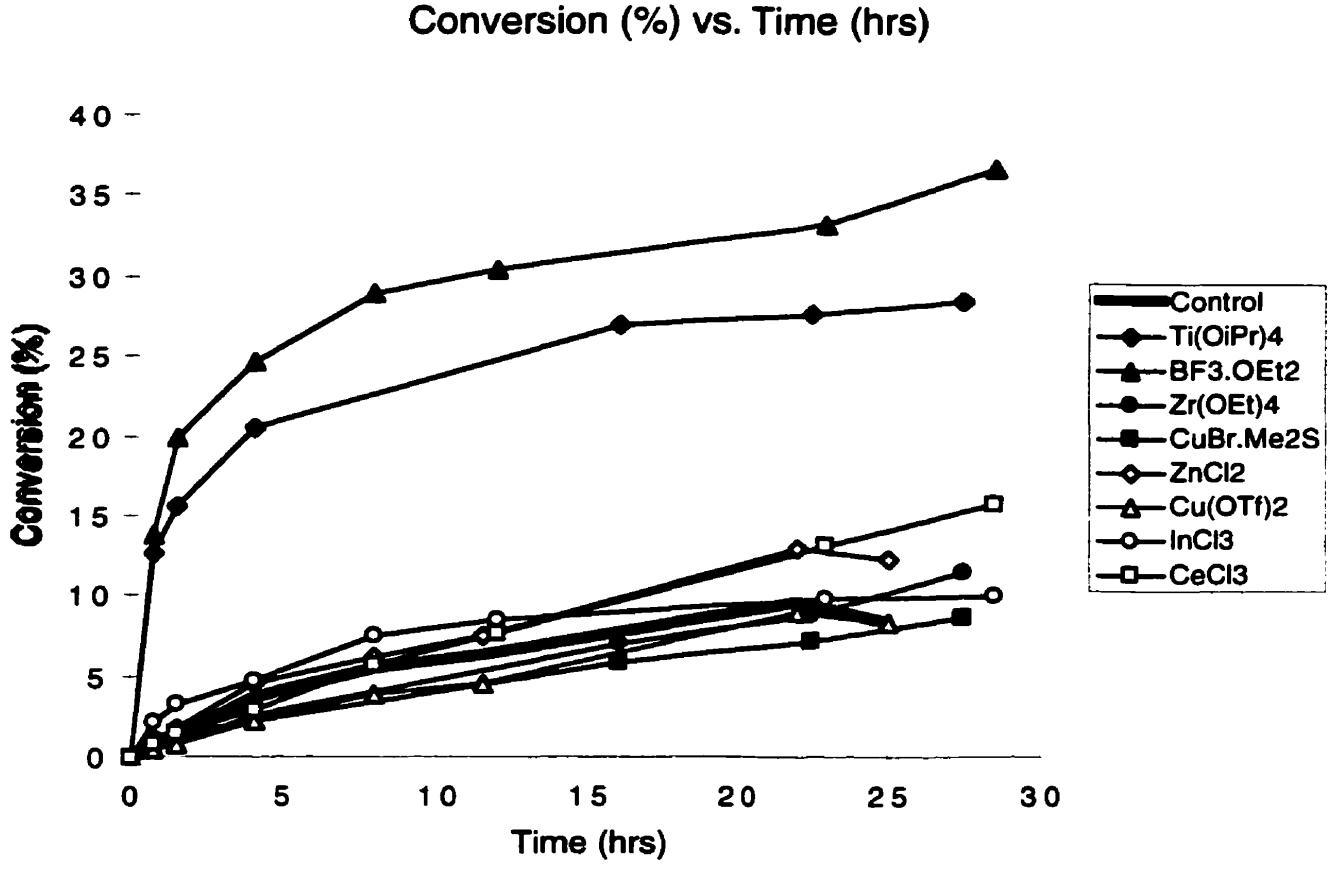


Figure 8. Lewis acid mediation of zinc homoenolate addition to benzaldehyde

Reactions carried out in the presence of zirconium ethoxide ($Zr(OEt)_4$), copper bromide dimethyl sulfide ($CuBr.Me_2S$), zinc chloride ($ZnCl_2$), $Cu(OTf)_2$, $InCl_3$ and $CeCl_3$ yielded the γ-lactone **29** in similar amounts as the control reaction, indicating no

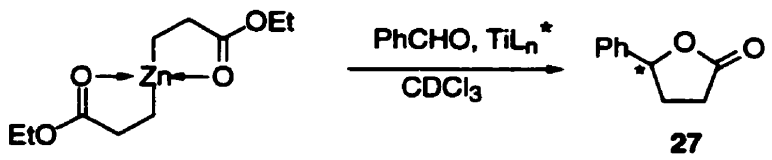
beneficial role of these Lewis acids as mediators in this process. These Lewis acids were expected to coordinate to the aldehyde thereby increasing the electrophilicity of the carbonyl carbon. It is surprising that the zinc homoenolate was still unreactive in these cases.

The Lewis acids $Ti(O^iPr)_4$ and $BF_3.OEt_2$ promoted this reaction providing the γ-lactone **29** in 28 % and 37 % yield respectively after 30 hours. Even though a catalytic amount of the Lewis acid could not be used, the results are interesting as they indicate reagents other than TMSCl and acid chlorides are capable of mediating the addition of zinc homoenolates to aldehydes

2.3.6 Enantioselective addition of zinc homoenolates to benzaldehyde

The $Ti(O^iPr)_4$ promoted addition of zinc homoenolates to benzaldehyde encouraged us to explore the effect of chiral titanium (IV) alkoxides on this reaction. Titanium (IV) alkoxides of Binol and TADDOL[i] were prepared by ligand exchange between the respective diols and $Ti(O^iPr)_4$ in toluene followed by azeotropic removal of the liberated isopropanol.[14a] A solution of 27 to 36 mol % of the chiral titanium alkoxide in $CDCl_3$ was added to a solution of pre-formed zinc homoenolate and dodecane in $CDCl_3$, followed by the addition of benzaldehyde (Equation 20). After 45 minutes, a 500 μL aliquot was transferred to an argon filled NMR tube and the reaction followed by ^1H NMR.

[i] TADDOL : α, α, α', α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol



27

(20)

Table 1. Enantioselective addition of zinc homoenolates to benzaldehyde in the presence of chiral titanium (IV) alkoxides

Entry	TiL_n*	Conditions[a]	Yield (%)[b]	ee (%)[c]
1	**22** (27 mol %)	48 h	15	17
2	**37** (36 mol %)	19 h	32	16
3	**38** (27 mol %)	48 h	17	20

(a) Reactions performed in $CDCl_3$ at 21 °C. (b) GC yield determined with dodecane as an internal standard. c) Determined by GC on a Chirasil-dex column.

The titanium (IV) alkoxides **22**, **37** and **38** were effective at promoting the addition of zinc homoenolates to benzaldehyde, although they could not be used in substoichiometric amounts (Table 1). We were pleased to observe that the γ-lactone **29** was obtained in 16 - 20 % enantiomeric excess. More interestingly, the major enantiomer is the same in all three cases, indicating the same facial approach of the aldehyde to the zinc homoenolate.[ii]

Having accomplished enantioselective homoaldol reactions with zinc homoenolates, we attempted to attain some catalytic turnover with the chiral titanium

[ii] The absolute configuration of the major enantiomer has not yet been dertermined.

(IV) alkoxides. The evidence collected to date suggest that **22**, **37** and **38** are Lewis acid activators for the aldehyde and do not undergo zinc-titanium transmetallation to form a tri-alkoxytitanium (IV) homoenolate. As mentioned earlier, excess $Ti(O^iPr)_4$ is often required to attain a catalytic cycle for the addition of diethyl zinc to aldehydes in the presence of chiral titanium (IV) alkoxides (Scheme 7). To effect similar catalysis in our system, the zinc homoenolate addition to benzaldehyde were carried out with 29 mol % of **37** and 1.2 equivalents of $Ti(O^iPr)_4$. In this case, the γ-lactone **29** was obtained in 37 % yield (GC) and 4 % enantiomeric excess. Similar results were obtained with 23 mol % of **22** and one equivalent of $Ti(O^iPr)_4$. The lower enantiomeric excess observed in these cases indicates that $Ti(O^iPr)_4$ is as active a catalyst for this reaction as the chiral titanium (IV) complexes **22** and **37**. At this point, it is unclear why excess $Ti(O^iPr)_4$ does not afford higher yields of **29** when compared to the substoichiometic amounts used above.

2.4 CONCLUSIONS

The extension of catalytic homoaldol reactions with zinc homoenolates to an enantioselective system proved to be not as straightforward as we had anticipated. Zinc homoenolates are unreactive towards benzaldehyde in the presence of ligands such as bis-oxazolines or β-amino alcohols. Although coordination of the homoenolate to the ligands is evident, no enhancement in its nucleophilicity is observed. Our results indicate that activation of the aldehyde is essential prior to zinc homoenolate addition.

We have demonstrated that Lewis acids such as titanium (IV) isopropoxide and boron trifluoroetherate promote the addition of zinc homoenolates to benzaldehyde. Notably, homoaldol reactions mediated by chiral titanium (IV) alkoxides yield the γ-lactone of benzaldehyde with moderate enantiomeric excess. This is the first example of enantioselectivity imparted in the addition of silyloxyalkoxycyclopropanes to aldehydes.

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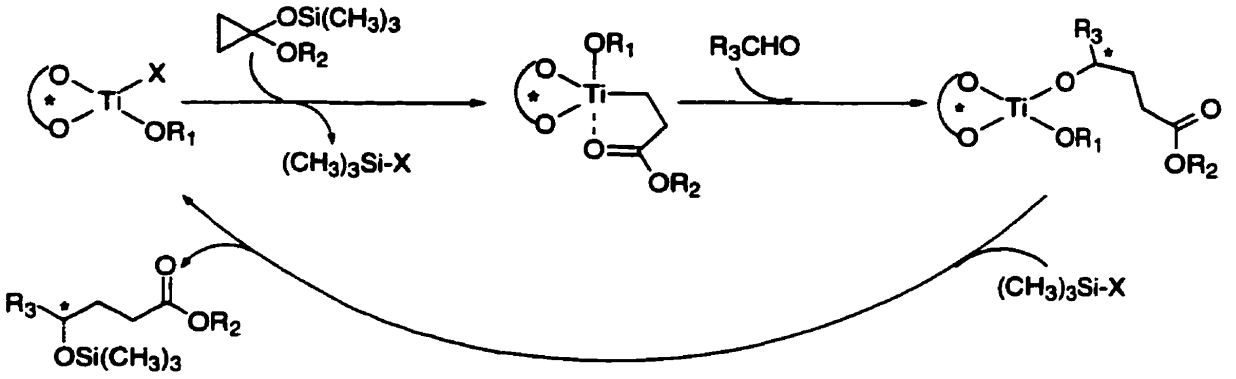
CHAPTER THREE

CATALYSIS OF HOMOALDOL REACTIONS BY TITANIUM (IV) TRIFLATES

3.1 INTRODUCTION

Our investigations with zinc homoenolates clearly indicated that this system would not be amenable to a catalytic enantioselective protocol for homoaldol reactions, as described in Chapter Two. Titanium homoenolates, formed by the ring opening of silyloxyalkoxycyclopropanes with titanium tetrachloride, are the only other class of homoenolates that are reactive in the homoaldol process. They readily add to aldehyes without the need for silicon activation of the substrate. One drawback of titanium homoenolates is that they require a stoichiometric amount of titanium tetrachloride.[1] However, the potential advantages of titanium catalysts such as the relative ease with which chiral ligands may be incorporated,[2] led us to explore the development of titanium (IV) complexes as catalysts for the homoaldol reaction.

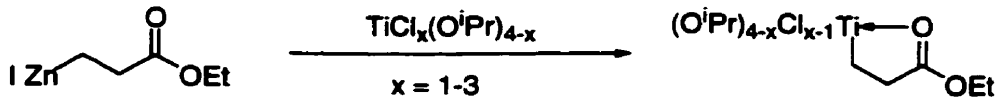
We envisioned a catalytic enantioselective homoaldol process in which a titanium (IV) complex containing for example, a chiral bidentate alkoxide ligand, would react with a silyloxyalkoxycyclopropane to form an alkoxytitanium (IV) homoenolate (Scheme 8). Addition of this species to an aldehyde with subsequent *in situ* silylation of the resulting titanium homoaldolate would yield the desired γ-silyloxyester with regeneration of the active titanium catalyst.



Scheme 8. Envisioned catalytic cycle

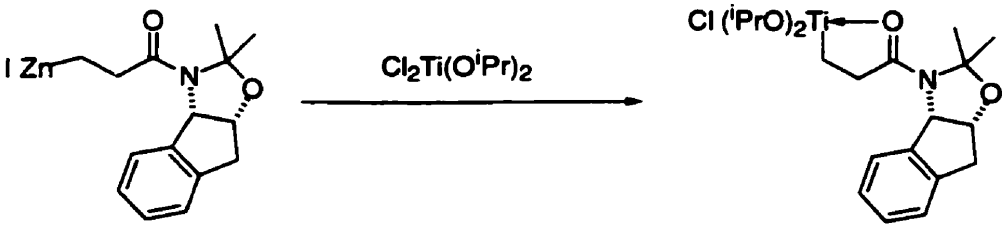
3.2 FORMATION OF ALKOXYTITANIUM (IV) HOMOENOLATES

Our desired catalyst system requires the formation of an intermediate alkoxytitanium (IV) homoenolate. To date, alkoxytitanium (IV) homoenolates have been prepared only through ligand exchange or transmetallation. DeCamp has prepared alkoxy and several chloroalkoxytitanium homoenolates via the transmetallation of an iodozinc ester homoenolate with various chlorotitanium isopropoxide species (Equation 21). These alkoxytitanium (IV) homoenolates were used to synthesize hydroxyethylene didpeptide isosteres by addition to t-Boc-(S)-phenylalaninal.[3] The authors speculate that some of the selectivity in this process was due to *in situ* chelation of the zinc salts with the α-amino aldehyde. Interestingly, the reaction of the aldehyde with a trichlorotitanium homenolate derived from a silyloxycyclopropane precursor resulted in poor yields and reversed stereoselectivity.



(21)

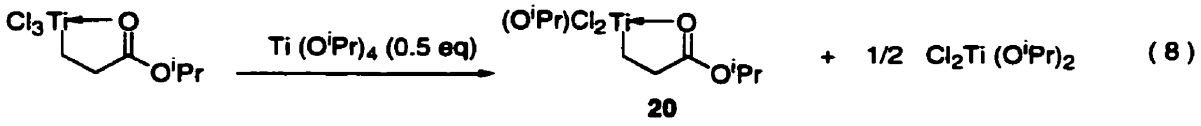
A similar transmetallation process was used by Armstrong to prepare chlorodiisopropoxytitanium (IV) homoenolates from iodozinc amide homoneolates. In this case, the incorporation of an aminoindanol group completely over-rid the inherent chelation control present in the substrate, t-Boc-(S)-phenylalaninal (Equation 22).[4]



(22)

Nakamura has reported the preparation of alkoxytitanium homoenolates via ligand exchange as a means to enhance the nucleophilicity of titanium homoenolates and to prevent the formation of chlorinated by-products which are observed in the addition of trichlorotitanium homoenolates to activated aldehydes such as benzaldehyde.[1] Treatment of a trichlorotitanium homoenolate with 0.5 equivalents of Ti(O^{i}Pr)$_4$ formed a dichloromonoisopropoxytitanium homoenolate **20** (Equation 8). The methylene protons of this alkoxytitanium (IV) homoenolate showed ^{1}H NMR signals at δ 3.03 (t, 2H) and δ 1.88 (t, 2H) ppm, upfield from the respective signals of

a trichlorotitanium homoenolate (δ 3.38 and δ 2.72 ppm). This is in accordance with greater electron density donated by the alkoxide ligand to the titanium centre.



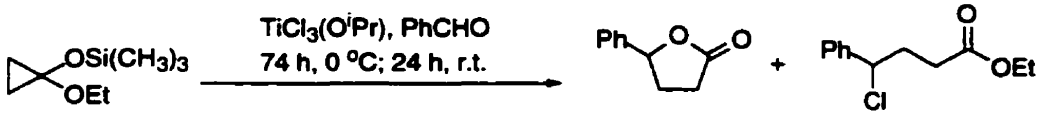
20 (8)

The alkoxide modified homoenolate **20** is reactive towards aromatic and α,β–unsaturated aldehydes giving 4-hydroxyesters in good to excellent yields, without formation of chlorinated by-products. It is also reactive towards ketones, yielding the desired homoaldol products in moderate yields. The nucleophilicity of the homoenolate can be further enhanced through the preparation of the corresponding t-butoxide modified titanium homoenolate, which is reactive towards a range of aryl and aliphatic ketones, giving γ-lactones in good to excellent yields.

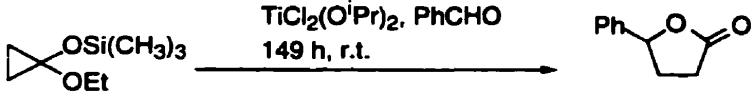
The processes described above for the preparation of alkoxytitanium (IV) homoenolates would not be suitable to the catalyst system we wish to design as it requires the direct formation of these homoenolates from silyloxycyclopropanes. As this reaction has not been previously reported, we initially examined the effect of alkoxide ligands on the ring opening of cyclopropane **25.**

Treatment of **25** with trichlorotitanium isopropoxide in $CDCl_3$ produced a brown-red solution, indicative of titanium homoenolate formation (Equation 23a). Subsequent addition of benzaldehyde at 0 °C, and observation of the reaction by ^1H NMR revealed the slow formation of both lactone **29** and chloride **39**. After 74 h at 0 °C and 24 h at 21 °C, **29** and **39** were isolated in 23 % and 53 % yield, respectively. The low reactivity of the dichloroisopropoxytitanium homoenolate as well as the

formation of chloride **39** in this reaction contrasts the results of Nakamura (*vide supra*). A possible explanation for this discrepancy may be that in Nakamura's case, the dialkoxydichlorotitanium species produced during the ligand exchange acts as a Lewis acid activator for the aldehyde, increasing the rate of the reaction. The milder conditions and shorter reaction time (typically 0 °C, 1hour) may also minimize ionization of the 4-hydroxyester, which is required prior to γ-chloroester formation.



25 **29** **39** (23a)



25 **29** (23b)

When the reaction was repeated with $TiCl_2(O^iPr)_2$, only lactone **29** was observed, with no formation of chloride **39** (Equation 23b). However the ring opening of **25** was very slow with this reagent, requiring 149 h at 21 °C, and only a 30% yield of product was obtained.

Although we were pleased to find that homoaldol reactions could indeed be carried out by the direct ring-opening of **25** with either $Cl_3Ti(O^iPr)$ or $Cl_2Ti(O^iPr)_2$, these reactions were slow and afforded low yields of the desired homoaldol adducts. Furthermore, as with $TiCl_4$, the above reactions required a stoichiometric amount of the metal salt. The results clearly indicated that if a bidentate ligand were to be used for chiral induction, a more reactive titanium complex would be required.

3.3 DEVELOPMENT OF TITANIUM (IV) TRIFLATES AS CATALYSTS FOR THE HOMOALDOL REACTION

In order to address the low reactivity, formation of chlorinated by-products and most importantly the lack of catalysis, we chose to explore alkoxytitanium (IV) triflates as catalysts for this process. Titanium (IV) triflates are efficient catalysts for Diels Alder, ene, Mukaiyama cross-aldol and Sakurai reactions and are conventionally prepared from the corresponding titanium chlorides with silver triflate.[5]

We expected that a triflate counterion would offset the decrease in Lewis acidity of the titanium metal centre resulting from the incorporation of alkoxide ligands and in effect, enhance the reactivity of the titanium complex. One of the main obstacles to attaining a catalytic cycle with $TiCl_4$ or $TiCl_n(O^iPr)_{4-n}$ is the silylation of the titanium homoaldolate. The bond strength of Ti-Cl and Ti-O bonds in $TiCl_4$ and $Ti(O^iPr)_4$ have been estimated at 103 kcal/mol and 115 kcal/mol respectively, a difference of 12 kcal/mol.[6] In order to effect silylation of a titanium alkoxide with trimethylsilylchloride to regenerate a titanium chloride based catalyst, a comparable difference in bond dissociation energy between Si-Cl and Si-O bonds is required. However, the bond strength for Si-Cl and Si–O bonds in for example, $(CH_3)_3Si–Cl$ and $(CH_3)_3Si–OEt$ are 113 kcal/mol and 116 kcal/mol respectively, a difference of only 3 kcal/mol.[7] The magnitude of the differences in bond strengths clearly indicates that silylation of titanium homoaldolates with trimethylsilyl chloride is thermodynamically unfavorable.

Although the bond dissociation energy for titanium triflates has not been reported, it is reasonable to assume that the difference in bond energy between a titanium (IV) triflate and a titanium (IV) alkoxide would be much smaller and

comparable to the difference in bond dissociation energy between the Si-O bonds in a $(CH_3)_3Si$–triflate and a $(CH_3)_3Si$–alkoxide. Thus it was anticipated that a catalytic cycle could be achieved through the incorporation of a triflate ligand.

In order to simultaneously evaluate the reactivity and selectivity of an alkoxytitanium (IV) triflate catalyst, the preparation of titanium triflate complexes of (R) 1,1'-bi-2-naphthol (Binol) was undertaken. The use of chiral auxiliaries developed from enantiomerically pure 1,1'-bi-2-naphthols in stoichiometric and catalytic asymmetric reactions has been well documented. For example, they are excellent chiral inducers in asymmetric reductions, Diels Alder and aza Diels Alder reactions, ene reactions, Michael reactions, hydroformylations, alkylations, oxidations, epoxidations and nitroaldol reactions.[8]

(R)-Binol-$TiCl_2$ was prepared by addition of n-butyllithium to a solution of (R)-Binol in ether at 0 °C, followed by addition of $TiCl_4$ (Scheme 9).[9] After removal of solvents *in vacuo*, the red-brown solid was suspended in toluene and transferred to a suspension of silver triflate in toluene.[5e] The reaction mixture was stirred at room temperature for 67 hours, then passed through a Schlenk filter under an argon atmosphere to remove silver chloride and excess silver triflate salts. Removal of the solvent *in vacuo* provided (R)-Binol-$Ti(OTf)_2$ **40** as a dark red solid which was dissolved in $CDCl_3$, cooled to 0 °C and used immediately for the homoaldol reaction. The titanium monotriflate **41** was prepared analogously using a solution of $Cl_3Ti(O^iPr)$ in toluene.[i]

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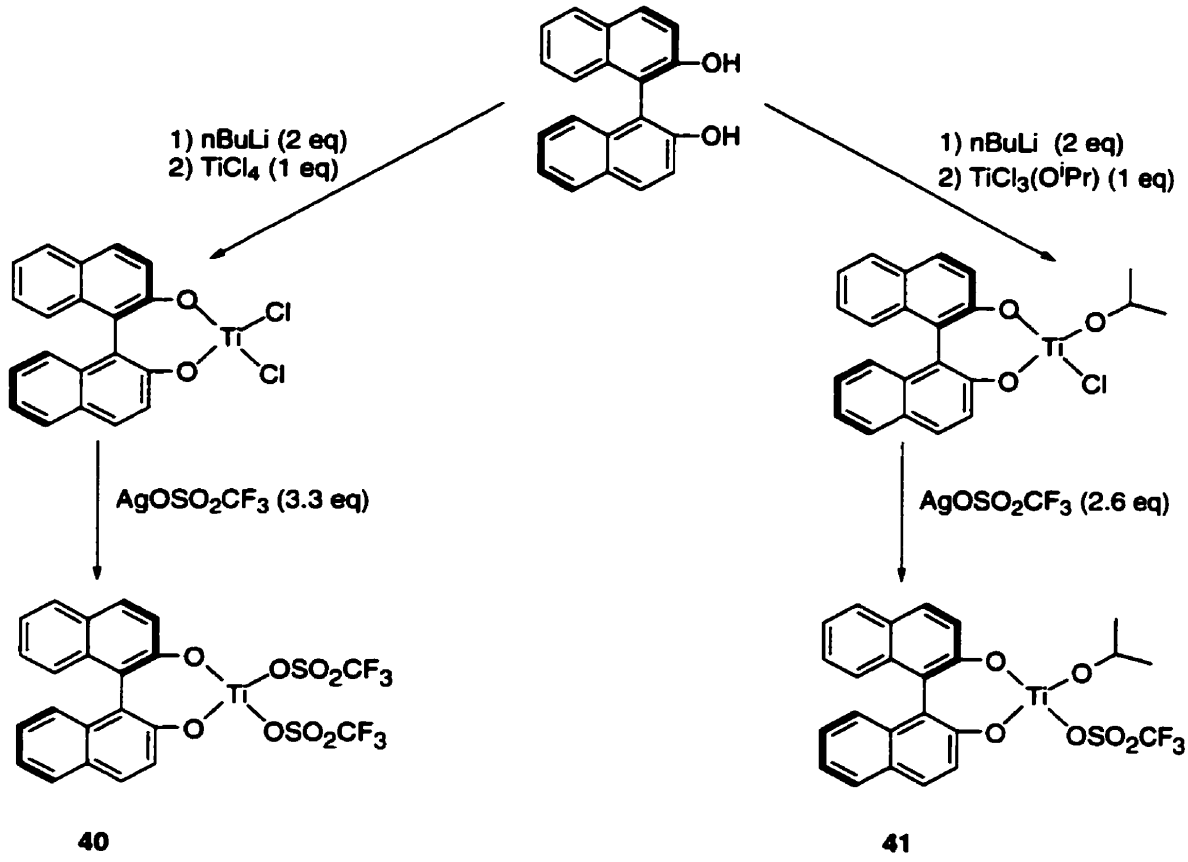
[i] The titanium triflates **40** and **41** have not been fully characterized and are shown as monomers for representation purposes only. ^1H NMR of these complexes in $CDCl_3$ indicate the presence of multiple interconverting species at room temperature (*vide infra*).

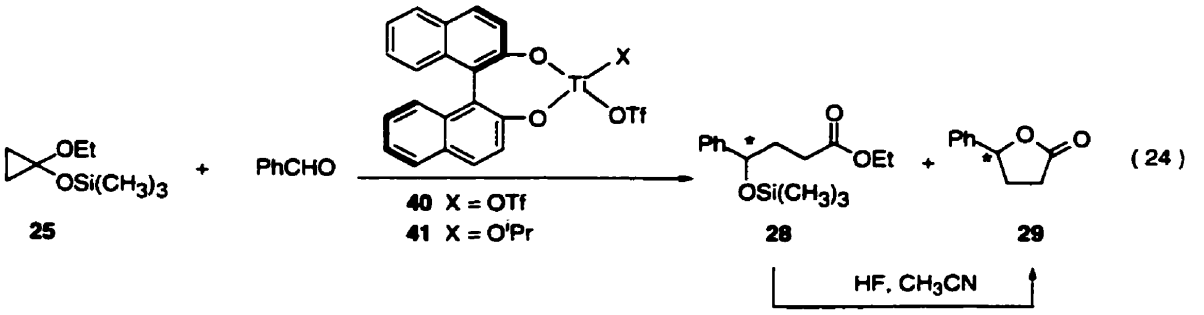


Scheme 9. Preparation of alkoxytitanium (IV) triflates via treatment of titanium chloride complexes with silver triflate

3.4 TITANIUM CATALYSIS OF THE HOMOALDOL REACTION

The reactivity of (R)-Binol-Ti(OTf)$_2$ **40** was examined by the addition of cyclopropane **25** (1 equivalent) and benzaldehyde (1 equivalent) to a solution of **40** (0.25 equivalents) in $CDCl_3$ at 0 °C. After 20 minutes, a 500 μL aliquot was transferred to an argon-filled NMR tube and the reaction was monitored by ^{1}H NMR. Immediate formation of the γ-silyloxyester ether **28** and γ-lactone **29** were observed (Equation 24). Upon consumption of cyclopropane **25** (40 hours), the reaction mixture was quenched

by addition of sodium hydroxide (1 M) and the products were extracted into ethyl acetate. Analysis of the reaction mixture by capillary GC indicated a 63 % yield of homoaldol adducts (16 % **28**, 47 % **29**),



25 **40** X = OTf, **41** X = O^{i}Pr **28** **29** (24)

Since the formation of titanium homonenolates from titanium triflates has not been reported, it is uncertain whether the ring opening of **25** with a titanium ditriflate would result in two homoenolates per titanium centre. It is conceivable that a titanium ditriflate complex would behave analogously to $TiCl_4$, which forms a single homoenolate only. In either case, the maximum theoretical yield in this reaction is 50 %. A 63 % yield of homoaldol products indicates that some catalyst turnover had taken place in this reaction.

The homoaldol products obtained were converted to lactone **29** by treatment with HF in acetonitrile in order to assess the enantioselectivity of the reaction. Analysis by capillary GC (Chirasil-dex column) indicated that the reaction had proceeded with a modest level of enantioselectivity (17 % ee).

The reaction catalyzed by the monotriflate **41** (0.25 equivalents) was slower, requiring 143 hours for complete consumption of **25** (Equation 24). However, the yield of products (61 %) and enantioselectivity (15 % ee) were comparable to those obtained with the ditriflate **40**, suggesting a similar mechanism for both reactions.

In the case of the titanium monotriflate **41**, only one homoenolate can be generated per metal centre and thus the theoretical yield is 25 %. A 61 % yield of products clearly indicates that at least one full turnover of the catalyst has been accomplished. This result also demonstrates that a single triflate ligand is sufficient to maintain the Lewis acidity of the alkoxytitanium (IV) complex towards ring opening of the cyclopropane.

The above result is the first clear example of titanium catalysis in the addition of silyloxycyclopropanes to aldehydes. These are also the first examples of enantioselective catalysis in this class of homoaldol reactions. Although the products were obtained with low enantiomeric excess, the results indicate that the Binol ligand plays an active role in the enantiodetermining step of the process.

3.5 NOVEL ROUTE FOR THE PREPARATION OF TITANIUM (IV) TRIFLATES

Titanium and zirconium triflates are conventionally prepared by ligand exchange between the metal chlorides and silver triflate.[5] There have been some examples for their formation from triflic acid or triflic anhydride. For example, Mikami reported the preparation of alcohol coordinated titanium ditriflates by treatment of $Ti(O^iPr)_4$ or $Ti(O^tBu)_4$ with triflic acid in pentane (Equation 25).[10] The crystal structure of the t-butoxy derivative showed incorporation of two water molecules in a dinuclear complex (*vide infra).*

$$(RO)_4Ti \xrightarrow{HOTf,\ 0\ ^oC} (RO)_2Ti(OTf)_2(ROH)_2 \qquad (25)$$

$R = {}^iPr, {}^tBu$

Titanium ditriflates have also been prepared by the treatment of $TiCl_4$ with triflic acid or via the addition of excess triflic anhydride to $Ti(OEt)_4$ (Equations 26a and 26b).[11] The formation of $Ti(OEt)_2(OTf)_2$ had to be carried out under carefully controlled conditions to avoid decomposition of the solid material into an uncharacterizable oil.

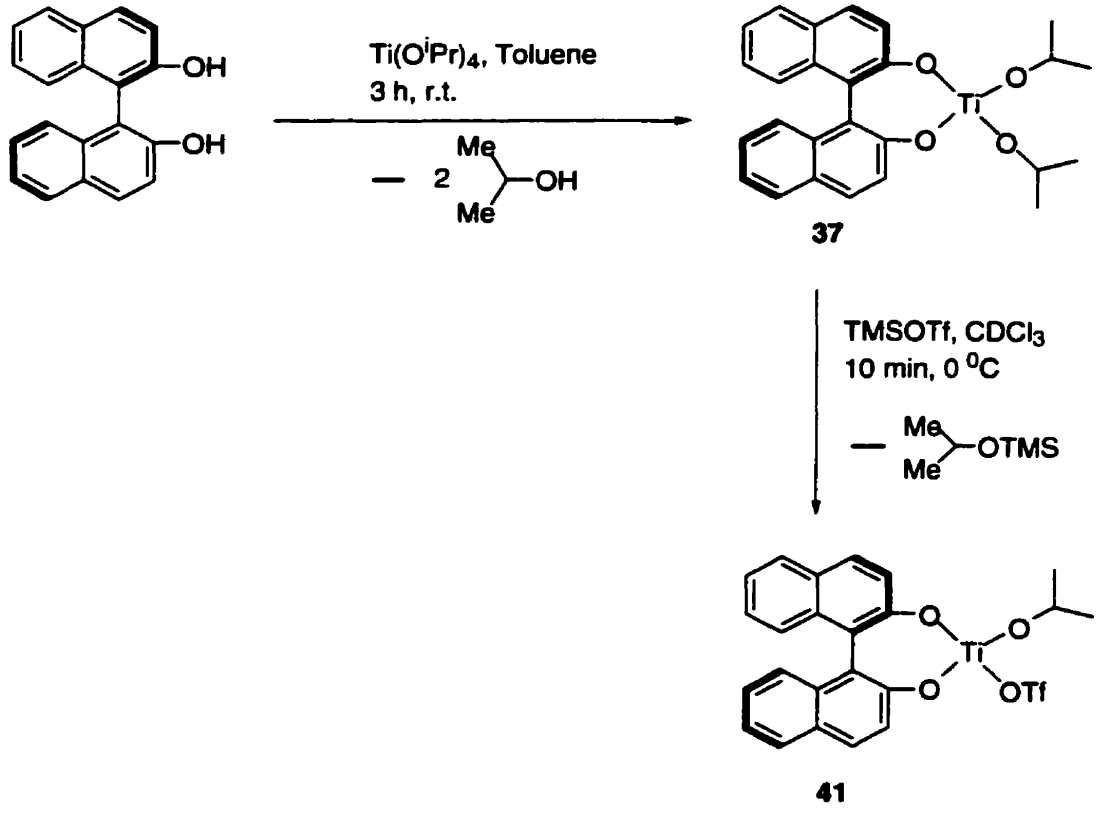
$$\underset{(2:1)}{TiCl_4} + HOTf \xrightarrow{20\ ^\circ C} TiCl_3OTf \xrightarrow{73-80\ ^\circ C} TiCl_2(OTf)_2 \qquad (26a)$$

$$\underset{(1:2)}{Ti(OEt)_4} + (CF_3SO_2)O \xrightarrow{20\ ^\circ C} Ti(OEt)_2(OTf)_2 \qquad (26b)$$

We desired an acid- and moisture-free method for the preparation of alkoxy titanium (IV) triflate complexes for use in homoaldol reactions as homoenolates are very moisture-sensitive species. Examination of the final step of our envisioned catalytic cycle suggested that titanium triflates might be prepared by the addition of trimethylsilyltriflate (TMSOTf) to titanium (IV) alkoxides (Scheme 8).

(R)-Binol-Ti(O^iPr)$_2$ **37** was prepared by ligand exchange between (R)-Binol and $Ti(O^iPr)_4$ in toluene, followed by azeotropic removal of the liberated isopropanol.[12] Addition of TMSOTf (0.25 equivalents) to a solution of **37** (0.25 equivalents) in $CDCl_3$ at 0 °C rapidly generates TMSO^iPr, as observed by ^1H NMR of the wine-red solution (Scheme 10). Presumably catalyst **41** is also formed in this process, as subsequent

addition of **25** (1 equivalent) and benzaldehyde (1 equivalent) proceeds to completion within 20 hours providing the γ-silyloxyester **28** in 74 % isolated yield (10 % ee).[ii]



Scheme 10. Preparation of titanium triflates via treatment of titanium (IV) alkoxides with trimethylsilyltriflate

[ii] Ditriflate complex **40** cannot be prepared by this method, as the addition of two equivalents of TMSOTf to Binol-Ti(O^{i}Pr)$_2$, followed by addition of **25** and benzaldehyde results in complete decomposition of the starting materials.

This alternate route for catalyst preparation is operationally more facile than the conventional method of ligand exchange between titanium (IV) chlorides and silver triflate. More importantly, it results in a significantly faster reaction rate which is important for synthetic applications.

3.6 STRUCTURE OF TITANIUM (IV) ALKOXIDES

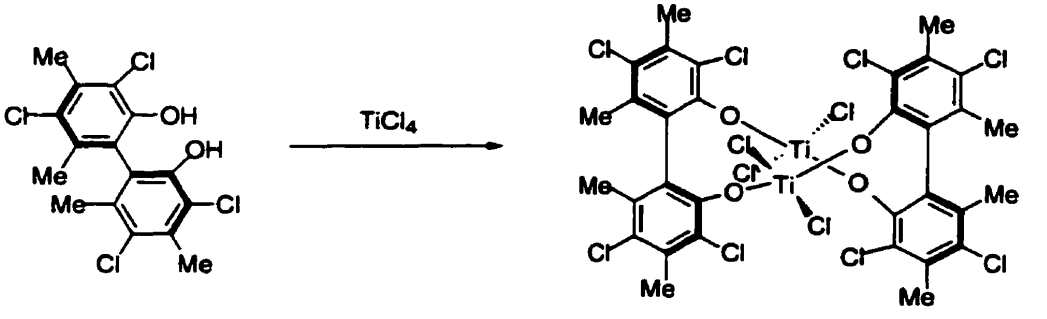
3.6.1 Characterization of titanium (IV) alkoxides

Most titanium (IV) alkoxides exist either as dimers or other oligomers in solution in order to increase the coordination state of the central metal.[13, 2] The presence of these interconverting oligomers in solution renders characterization of titanium (IV) alkoxides by ^{1}H and ^{13}C NMR difficult. This is further complicated by exchange between bridging and terminal ligands, overlap of resonances and broadening of the signals due to the quadrupolar effects of ^{47}Ti and ^{49}Ti (nuclear spins I = 5/2 and 7/2 respectively).[14, 6] Although titanium complexes have been characterized by X-ray crystallography, mass spectral analysis and elemental analysis, these methods only give information about the solid state structures and may not be an indication of the active catalyst species. Valuable information about structures of titanium complexes in solution can be obtained from solution molecular weight studies, infra-red and Raman spectral analysis.

3.6.2 Effect of ligands on the structure of titanium (IV) alkoxides

The extent of oligomerization of titanium complexes in solution decreases with an increase in the size of the substituents of the alkoxide. For example, $Ti(OCH_3)_4$ is tetrameric in solution while $Ti(OCMe_3)_4$ and $Ti(OPh)_4$ are monomers.[6]

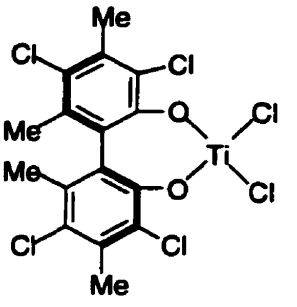
The types of ligands on the titanium centre also play an important role in determining the structure of a titanium complex. For example, X-ray crystallography of the complex formed between (R) 3, 3', 5, 5'-tetrachloro-4, 4', 6, 6'-tetramethyl-2, 2'-bisphenol **42** and $TiCl_4$ in dichloromethane showed a 14-membered titanacycle **43** with two titanium and four oxygen atoms (Equation 27).[15]



42 **43**

(27)

The electronegative chlorine substituents presumably withdraw sufficient electron density from the titanium centre, resulting in an increase in electron donation from the oxygen ligands. This strong n to d electron donation is evident by an increase in the Ar-O-Ti bond angle of **43** to near linearity (168 ° and 169 °). The authors conclude that this large increase in bond angle imposes a geometrical constraint that prevents formation of the 7-membered titanacycle **44**.



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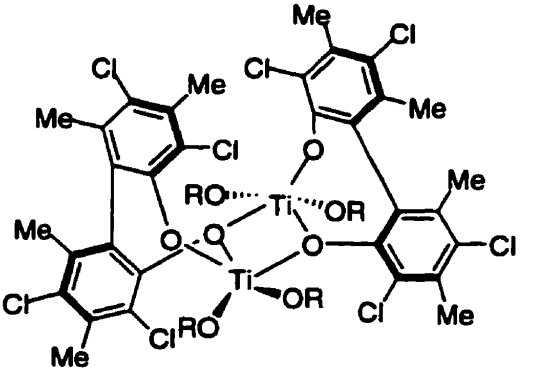
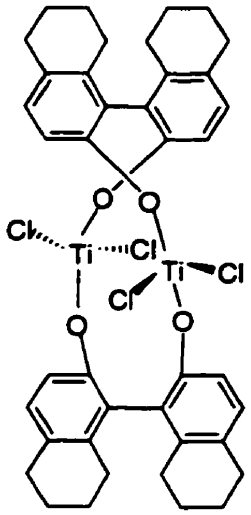
The crystal structure of a complex prepared from bisphenol **42** and $Ti(O^iPr)_4$ indicated a dimeric 7-membered titanacycle **45** with the phenol oxygens acting as μ-oxo bridges. In this case, the O^iPr ligands do not withdraw as much electron density from the titanium centre leading to less n to d electron donation from the oxygen ligands. This results in a smaller Ar-O-Ti bond angle which permits the formation of a 7-membered titanacycle.



45 R = ^{i}Pr

A similar ligand effect is observed in titanium complexes of 5, 5', 6, 6', 7, 7', 8, 8'-octahydrobinaphthol.[16] X-ray crystallography of a complex formed between the bis(trimethylsilyl) ether of octahydrobinaphthol and titanium tetrachloride in toluene showed a 14-membered dititanamacrocycle **46** in which each titanium centre is four-

coordinate. The extremely short Ti-O bond lengths (average of 1.742 Å) and the nearly linear C-O-Ti bond angle (168 °) once again indicate strong electron donation from the oxygen atoms of the aryl ligands.



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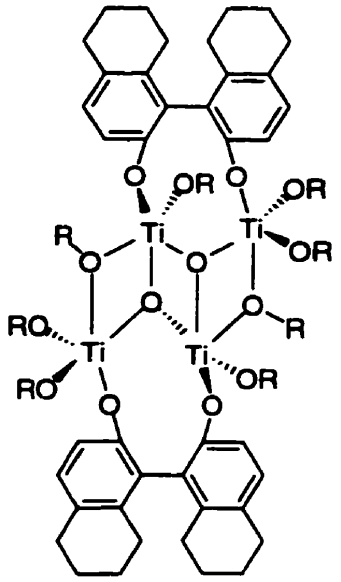


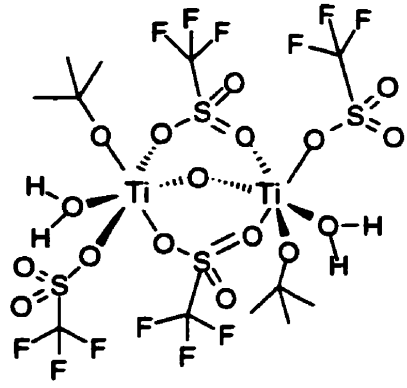
47

Treatment of partially hydrated octahydrobinaphthol with $Ti(O^iPr)_4$ resulted in the formation of a tetratitanium di-μ3-oxo cluster $[Ti_4(RO)_2(O^iPr)_8O_2]$ **47**, also characterized by single crystal X-ray analysis. The core of the complex is a $Ti_4(\mu_3\text{-}O)_2$ unit in which both oxo ligands serve as triply bridging ligands between the titanium centres.

3.6.3 Structure of titanium (IV) triflates

Although titanium (IV) triflates are extensively used as catalysts in organic reactions, few of these complexes have been characterized. A triflate ligand can exhibit several degrees of coordination to a titanium metal centre. In addition to σ-

coordination through the S-O bond, electron donation from the lone pairs of the oxygen of the sulfonyl group [S(O)] is also possible. For example, as mentioned earlier, the crystal structure of $(t\text{-Bu})_2Ti(OTf)_2(t\text{-BuOH})_2$ prepared by treatment of $(t\text{-BuO})_4Ti$ with triflic acid showed incorporation of two water molecules in the dinuclear complex with bridging oxygen (μ-O) and two bridging triflate ligands as shown in **48**.[10] Each titanium centre is six-coordinate with distorted octahedral geometry and the μ-O and H_2O ligands are *trans* to each other. In this complex, two of the triflate ligands are monodentate, while two are bridging and bidentate in nature, coordinating to the titanium centre through the sulfonyl oxygen.



48

The structures of some triflate complexes of $TiCl_4$ and $Ti(OEt)_4$ have been proposed by Pascal based on infra-red and Raman spectra.[11] For example, the authors suggest either a dimeric or a polymeric structure for $TiCl_3OTf$ to account for the tridentate nature of the triflate ligand, determined from the stretching frequencies of the CF_3, SO, SO_3 and CS groups. On the other hand, both triflate ligands are bridging and bidentate in $TiCl_2(OTf)_2$, suggesting a polymeric structure. A polymeric structure

was also assigned to $Ti(OEt)_2(OTf)_2$, in which both monodentate and bridging bidendate triflate groups were observed.

3.6.4 Possible explanation for route-dependent difference in reactivity of titanium triflate 41

In theory, both routes examined for the preparation of alkoxytitanium (IV) triflate **41** should form the same complex. In practice however, the TMSOTf mediated route results in a more efficient catalyst. Although the exact structure of these triflate complexes is not known at present, the propensity of titanium alkoxide and triflate complexes to exhibit varying structural complexities, as explained above, may contribute to the differences in reactivity of the titanium triflate **41** prepared by the two routes.

A possible explanation for this difference is that the TMSOTf initiated route results in a more reactive structure of **41**. The longer procedure required for the AgOTf mediated route may result in a more stable titanium complex through equilibration between different oligomeric species. The TMSOTf protocol is comparitively faster and thus **41** prepared by this route may not have sufficient time to attain the same stable structure. It would be interesting to examine the reactivity of **41** prepared via the TMSOTf procedure in the same time frame as the AgOTf protocol. Clearly, crystal structures of these complexes would be required in order to understand some of the reasons for the differences in reactivity. Our attempts to obtain crystal structures of these complexes have not yet been successful.

3.7 EFFECT OF SOLVENTS ON THE CATALYTIC HOMOALDOL REACTION

The addition of **25** to benzaldehyde was carried out in a variety of solvents using 25 mol % of **41** prepared via the TMSOTf mediated route (Table 2). The reaction rate was retarded in non-polar solvents such as toluene, as well as in strongly coordinating solvents such as diethyl ether (Et_2O) or tetrahydrofuran (THF). It was significantly enhanced in the presence of the weakly coordinating solvent deuterioacetonitrile (CD_3CN). The optimum conditions utilize a 3:1 mixture of CD_3CN and $CDCl_3$. The mixture of solvents is necessary as the titanium complexes are only slightly soluble in acetonitrile alone. Under these conditions, the addition of silyloxycyclopropane **25** to benzaldehyde could be accomplished in 2 hours with an increase in the yield (82 %). The increase in reaction rate from these modifications allows the amount of catalyst to be reduced to 10 mol % with no significant change in the isolated yield of the products. The reaction can also be done with 5 mol % catalyst at the expense of a longer reaction time (6 days). If the catalyst loading is reduced further, to for example 2 mol%, the reaction is very slow taking about two weeks for complete consumption of benzaldehyde.

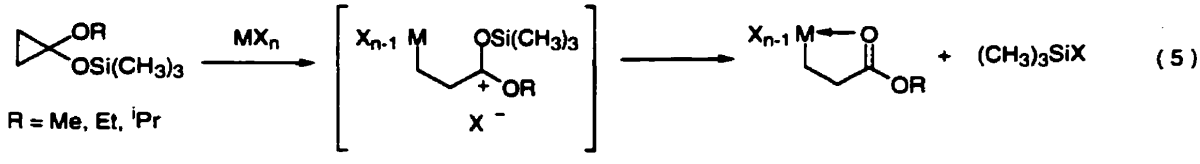
Monitoring the homoaldol reaction of benzaldehyde by ^1H NMR indicated that the only competing reaction was quenching of the homoenolate by adventitious water with no other by-product formation. Excess cyclopropane **25** can be used to compensate for this quenching. For example, the yield of γ-lactone **29** from the reaction carried out in $CD_3CN/CDCl_3$ could be increased to 99 % by using 1.5 equivalents of **25**.

Table 2. Effect of solvent on the BINOL-Ti(O^iPr)(OTf) catalyzed homoaldol reaction of benzaldehyde

Entry	Conditions [a]	Time	Yield (%)[b]
1	$CDCl_3$	19 h	74
2	Toluene-d_8	139 h	64
3	Diethyl ether	72 h	78
4	Tetrahydrofuran	99 h	51
5	CD_3CN : $CDCl_3$ (3 : 1)	2 h	82

a) Reactions done with 25 mol % of **41**. b) Isolated yield of **29** after treatment of the crude reaction mixture with p-toluenesulfonic acid in benzene.

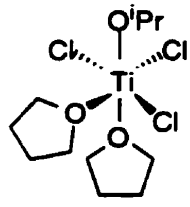
The rate of any reaction is almost always dependent on the nature of the solvent. The proposed mechanism for the formation of homoenolates involves initial σ-coordination of the metal to one of the carbon-carbon bonds of the cyclopropane followed by cleavage of this bond to form an oxygen-stabilized carbocation. The metal homoenolate is formed upon loss of trimethylsilyl halide (Equation 5).[17] The weak ability of toluene at stabilizing the intermediate cation may contribute to a decrease in the reaction rate in this solvent.



R = Me, Et, ^{i}Pr (5)

Reactions involving carbanionic intermediates such as enolates for example, are usually carried out in polar coordinating solvents such as dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), THF or dimethoxyethane (DME). In addition to stabilizing ionic intermediates, the coordinating ability of these solvents makes them good cation solvators which results in dissociation of enolate-metal ion pairs leading to

more reactive enolates. While the coordinating ability of Et_2O and THF are beneficial to enolate alkylations, the coordination of these solvent molecules to the titanium centre may explain the decrease in the reaction rate observed in our case. Crystal structures of chloroisopropoxytitanium complexes with Et_2O or THF have been reported in which the titanium complexes are monomeric, six-coordinate structures as shown by **49** and **50**.[18] The monomeric nature of these complexes indicates that the coordinatively unsaturated titanium complexes are extensively stabilized by electron donation from the solvent molecules.



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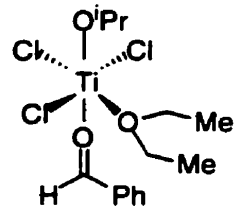


50

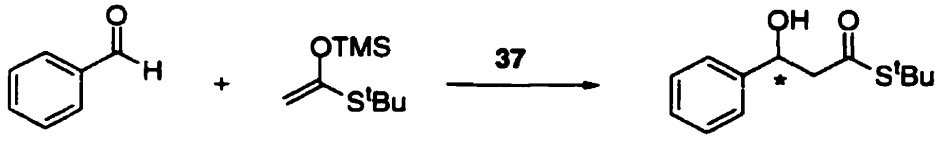
Similar coordination of Et_2O or THF to titanium in the homoaldol reaction would decrease the Lewis acidity of the titanium centre in the triflate complex **41** which translates to a slower rate of ring opening of the cyclopropane **25**.

Since acetonitrile is a weakly coordinating solvent, it does not significantly reduce the Lewis acidity of the titanium triflate **41** towards ring opening of **25**. Furthermore, acetonitrile being more polar than ether or THF facilitates homenolate formation as well as nucleophilic addition between the titanium homoenolate and the carbonyl substrate.

It is conceivable that the solvent also plays a role in determining the structure of the titanium complexes formed. ^1H NMR of Binol-Ti(O^{i}Pr)(OTf) **41** in $CD_3CN/CDCl_3$ (3 : 1) shows better signal definition than in $CDCl_3$, indicating the extent of

oligomerization is reduced in the presence of CD_3CN. This may also contribute to an enhancement in the rate of the reaction.

Surprisingly, no notable change in the enantiomeric excess of the product was observed upon variation of the solvent. Significant variation in enantioselectivity in the Binol-Ti(O^iPr)$_2$ catalyzed Mukaiyama aldol condensation of 1-(tert-butylthio)-1-((trimethylsilyl)oxy)ethene with benzaldehyde in methylene chloride, toluene and ether has been reported (Equation 28).[19] This variation in selectivity may arise from aldehyde coordination to different structures of the titanium catalyst in each solvent. Although this reaction is admittedly different from the homoaldol reaction developed here, it suggests that the latter reaction proceeds without aldehyde coordination to the titanium centre.

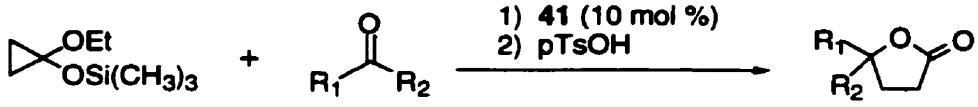


(28)

3.8 SUBSTRATE VARIATION IN THE CATALYTIC HOMOALDOL REACTION

The general applicability of our catalytic homoaldol reaction was determined by examining a variety of carbonyl substrates (Table 3). These reactions were done in $CD_3CN/CDCl_3$ (3 : 1) using 10 mol % of **41** and excess cyclopropane **25** to compensate for adventitious quenching of the homoenolate.

Table 3. Catalysis with BINOL-Ti(O^{i}Pr)(OTf).



Entry	Substrate	Conditions[a]	Yield[b]
1	PhCHO	0 ^{0}C, 26 h	99 %
2	p-ClPhCHO	0 °C, 80 h	84 %
3	TMS–C≡C–CHO	0 °C, 36 h	82 %
4	Ph–C≡C–CHO	0 °C, 36 h	76 %
5	$PhCOCH_3$	45 – 50 ° C, 60 h	78 %
6	t-C_4H_9CHO	45 – 50 °C, 54 h	52 %
7	p-MeOPhCHO	0 °C, 5 h	31 %
8	$C_6H_{11}CHO$	0 °C, 24 h	30 %[c]
9	$PhCH_2CH_2CHO$	0 °C, 24 h	11 %[d]
10	PhCH=CHCHO	0 ° C, 2 h	[d]

a) All reactions performed in $CD_3CN/CDCl_3$ (3:1) using 1 - 2 equivalents of **25** b) Isolated yield of γ-lactone after treatment of crude reaction mixture with p-toluenesulfonic acid in benzene. c) Reaction in $CDCl_3$ afforded a slightly higher yield (37%) of product. d) See text.

Ideal substrates for this reaction are acetylenic and aryl aldehydes which are un-substituted or which contain an electron-withdrawing substitutent. They afford homoaldol adducts in good to excellent yields (entries 1 – 4). In these reactions, the γ-silyloxyester was observed by ^{1}H NMR within 45 minutes and the reaction proceeded without the formation of by-products.

Homoenolate addition to less reactive substrates such as acetophenone and pivaldehyde can also be accomplished although elevated temperatures are required (entries 5 and 6). These results demonstrate that the catalyst system is stable at temperatures upto 50 °C for an extended period of time.

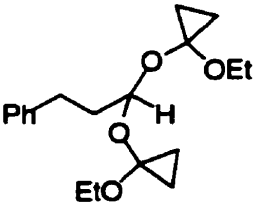
Aryl aldehydes with electron donating groups, such as p-methoxybenzaldehyde, are very reactive under the conditions examined (entry 7). Although the aldehyde was

consumed within 5 hours at 0 °C, ^{1}H NMR of the reaction mixture indicated several by-products and the γ-lactone was obtained in only 31 % yield. Ionization of the initially formed γ-silyloxyester is favoured with p-methoxybenzaldehyde as the substitutent is capable of stabilizing the benzylic cation (*vide infra*). This may account for the low yield of isolated product as well as the formation of undesired products.

Alkyl aldehydes undergo addition to give modest yields of homoaldol product (entry 8). In the case of substrates which contain acidic protons, quenching of the homoenolate is a significant competing reaction in both $CDCl_3$ and $CD_3CN/CDCl_3$. Quenching of the homoenolate, forming ethyl propionate, was observed within 45 minutes even when freshly distilled reagents were used. The consistently low yield of desired product and significant formation of ethyl propionate suggested enolization of the aldehyde served as the proton source in the reaction. Although the enolate could undergo an aldol reaction with cyclohexanecarboxaldehyde, no aldol products were isolated from this reaction.

The reaction was carried out with hydrocinnamaldehyde to ascertain whether enolization would be a common problem with aliphatic aldehydes (entry 9). Monitoring the reaction by ^{1}H NMR indicated a triplet at δ 5.30 ppm within 45 minutes. This peak was too far downfield to correspond to the methine proton of either the γ-lactone or γ-silyloxyester of hydrocinnamaldehyde. In this case as well, significant quenching of the homoenolate was observed, the cyclopropane **25** being consumed within 24 hours at 0 °C. The same results were obtained in $CDCl_3$.

Isolation of the products of the reaction by column chromatography provided a compound with the above triplet as the major fraction in addition to 11% yield of the desired γ-lactone. ^{1}H NMR, ^{13}C NMR, homonuclear decoupling, HMBC, HMQC and mass spectral analysis indicated the major compound to be the acetal **51**.

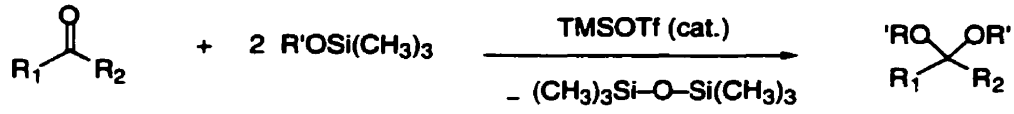


51

A control reaction carried out with cyclopropane **25**, TMSOTf (10 mol %) and hydrocinnamaldehyde in $CDCl_3$ indicated no formation of either the γ-lactone or γ-silyloxyester, although the cyclopropane was consumed within 1 hour at 0 °C. There appeared to be the formation of several acetals, evident by triplets between δ 5.00 and δ 5.30 ppm. Isolation of these products by column chromatography proved to be difficult. Although these compounds were not fully characterized, the control reaction indicates that acetal formation occurs independent of the titanium complex. Acetal formation is perhaps more prevalent with aliphatic than aromatic or acetelynic aldehydes due to the low reactivity of the former towards nucleophilic addition by the homoenolate.

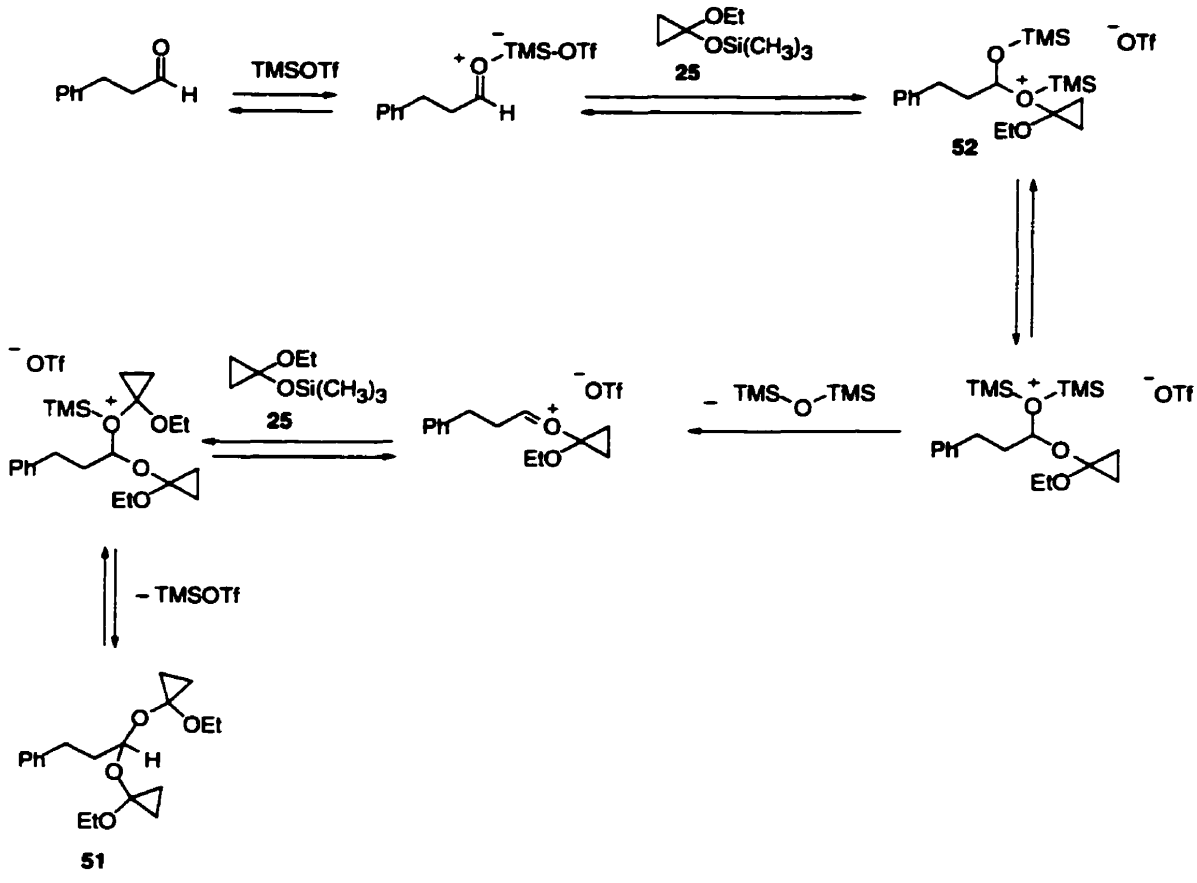
Noyori has developed a procedure for the acetalization of aldehydes and ketones with trimethylsilylethers in the presence of a catalytic amount of TMSOTf (Equation 29).[20] This procedure is used to form acetals under aprotic conditions as well as to form acetals of α,β-unsaturated aldehydes and ketones without olefin migration. The

formation of hexamethylsiloxane is the driving force for shifting the equilibrium towards the formation of acetal products.



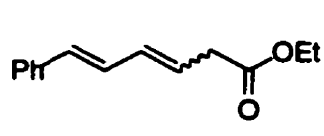
(29)

It is conceivable that acetal **51** is formed in an analogous manner from cyclopropane **25** (Scheme 11). Nucleophilic addition of the silyl ether oxygen of **25** to a TMS-activated aldehyde forms intermediate **52**. Intramolecular transfer of the TMS group is followed by elimination of hexamethylsiloxane, forming an oxonium ion. This undergoes addition with a second equivalent of silyloxycyclopropane, followed by loss of TMSOTf to yield the acetal **51**. A potential method for preventing the formation of such acetals in the homoaldol reaction is through the use of silyloxycyclopropanes with silicon substituents such as t-butyldimethylsilyl and t-butyldiphenylsilyl. The larger substituents should render the silyl ether oxygen less nucleophilic towards aldehyde addition. These cyclopropanes can be prepared from commercially available **25** via treatment with methanol, followed by silylation with the desired silylchloride.[21]

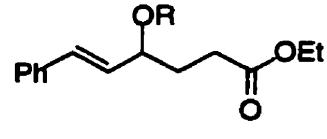


Scheme 11. Proposed mechanism for the formation of acetal **51**

α,β-Unsaturated aldehydes are extremely reactive in the homoaldol reaction, affording addition products in less than 2 hours at 0 °C (entry 10). However, the products are unstable to the reaction conditions and undergo ionization and allylic rearrangement to form a mixture of dienes **53a** (4 %) and allyl ethers (13 % **53b**, 21 % **53c**).

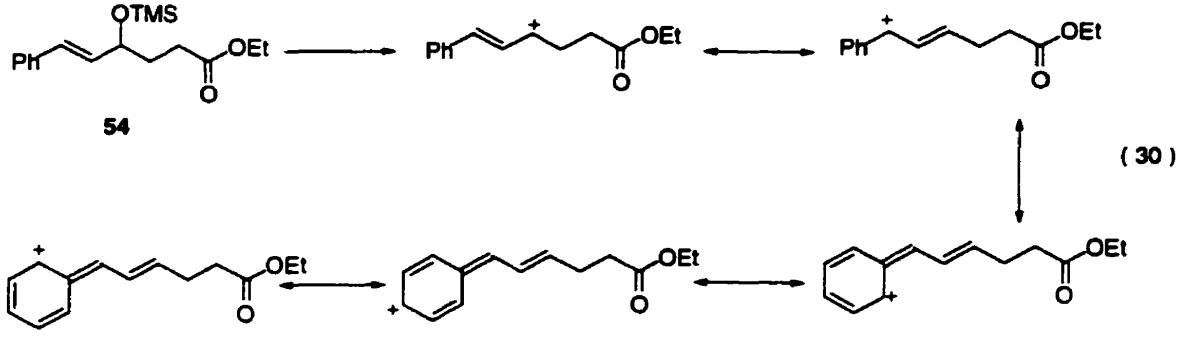


53a



53b R = ^{i}Pr
53c R = Et

It was expected that ionization of the γ-silyloxyester **54** would be minimized in the less polar solvent $CDCl_3$. Although cyclopropane **25** was consumed within 3.5 hours at 0 °C, allylic rearrangement still occurred providing dienes **53a** in 23 % yield and allyl ethers **53b** and **53c** in 17 % and 5 % yield respectively. Surprisingly, when the reaction was repeated in an even more non-polar solvent, toluene, ^1H NMR of the crude reaction mixture indicated the mixture of dienes **53a**. Ionization in non-polar solvents may be favoured in the case of cinnamldehyde, as the cation formed upon ionization is stabilized through the allylic and benzylic systems (Equation 30).



The reaction was repeated at lower temperatures in an attempt to prevent ionization of the initially formed γ-silyloxyester **54**. Cyclopropane **25** was added at 0 °C to a solution of **41** (10 mol %) in CH_2Cl_2. After 5 minutes, the reaction mixture was cooled to - 78 °C, followed by addition of cinnamaldehyde. No reaction was observed by thin layer chromatography (TLC) after 5 hours at -78 °C. The reaction mixture was warmed to - 40 °C for 3 hours, followed by 2 hours at - 20 °C. No products were observed by TLC, indicating negligible homonenolate formation and addition at temperatures below - 20 °C.

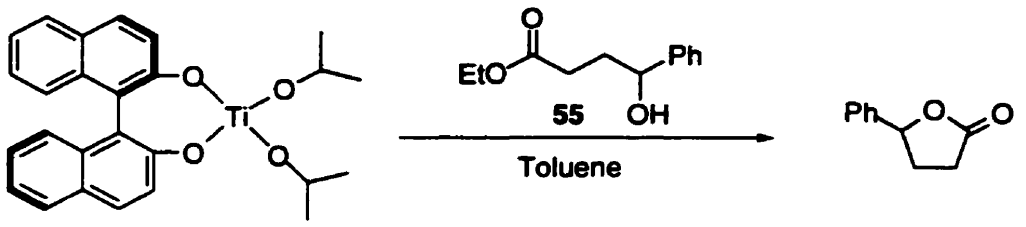
Several compounds were observed when the reaction was repeated with 1-hexenal in $CDCl_3$. Isolation of these compounds by column chromatography did not yield characterizable compounds, indicating that the homoaldol adducts of α,β-unsaturated aldehydes are unstable to the reaction conditions.

3.9 MECHANISTIC STUDIES

3.9.1 Silylation of titanium (IV) tetraalkoxides

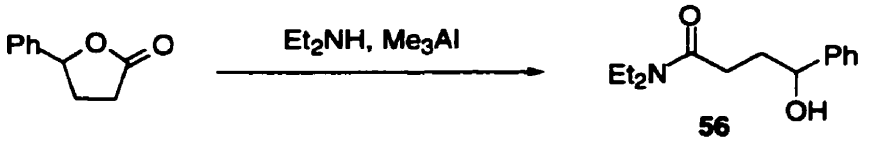
The development of this methodology was based upon an envisaged three step catalytic cycle namely, (1) homoenolate formation, (2) aldehyde addition and (3) homoaldolate silylation (Scheme 8). For a better understanding of the mechanism, a control experiment was designed where an independently prepared titanium (IV) tetraalkoxide containing an isopropoxide and a homoaldolate ligand was treated with one equivalent of TMSOTf in $CDCl_3$.

Titanium (IV) tetraalkoxides have been prepared by the treatment of Binol-Ti(O^iPr)$_2$ with aromatic and aliphatic alcohols in toluene.[22] Attempts to prepare a titanium (IV) tetraalkoxide by treating Binol-Ti(O^iPr)$_2$ with 1 equivalent of the 4-hydroxyester of benzaldehyde **55** resulted in rapid lactonization only (Equation 31). This was the first indication that the postulated mechanism may not be entirely accurate, as negligible lactonization is observed in the homoaldol reaction catalyzed by **41**.



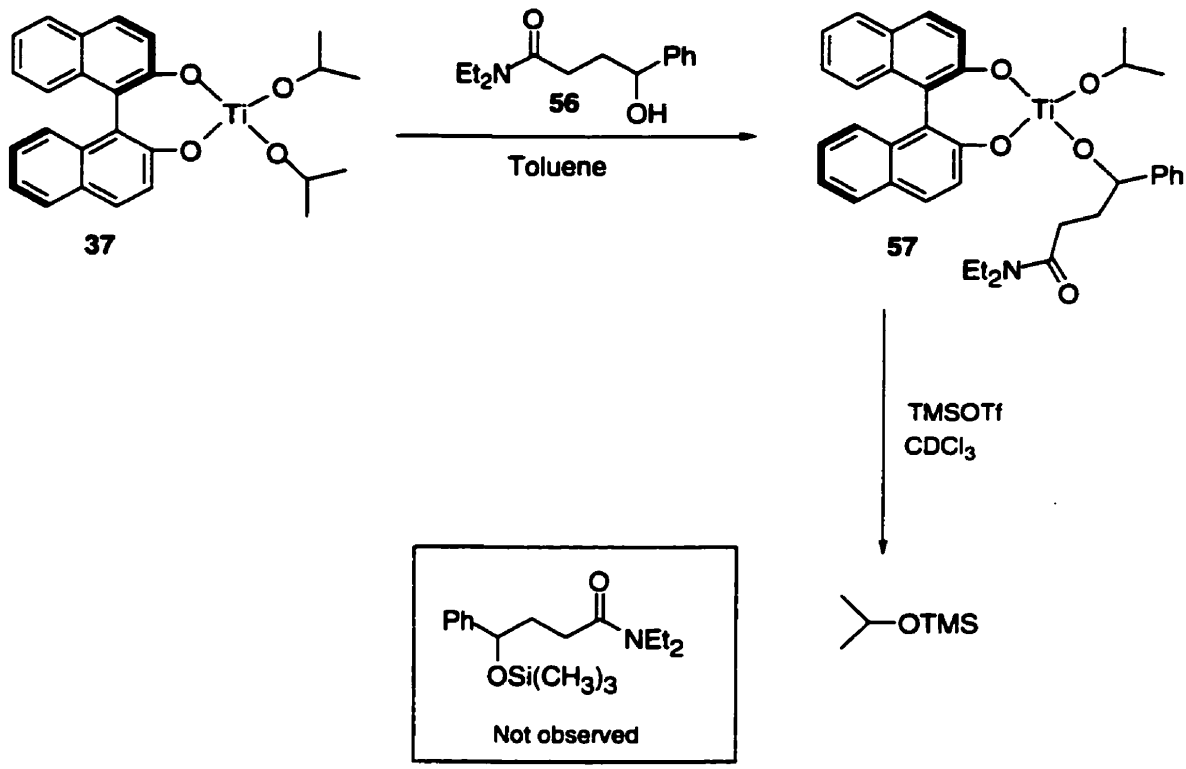
(31)

γ-hydroxyamide **56** which is less prone to lactonization, was prepared in 90 % yield by treatment of the γ-lactone **29** with diethylamine in methylene chloride in the presence of trimethylaluminum at 40 °C for 24 hours (Equation 32).[23]



(32)

Treatment of an orange solution of **37** with **56** (1 equivalent) in toluene resulted in an orange red solution, indicating ligand exchange (Scheme 12). Removal of the solvent and liberated isopropanol after 3 hours generated complex **57**, which was dissolved in $CDCl_3$ to form an orange solution. Subsequent addition of one equivalent of TMSOTf at 0 °C afforded a wine red solution ^1H NMR indicated the immediate formation of a significant amount of the TMS ether of isopropanol [δ 3.89 (m, 1H), δ 1.08 (d, 6H) ppm)]. More importantly, the formation of the silyl ether of **56** was not observed in this reaction.



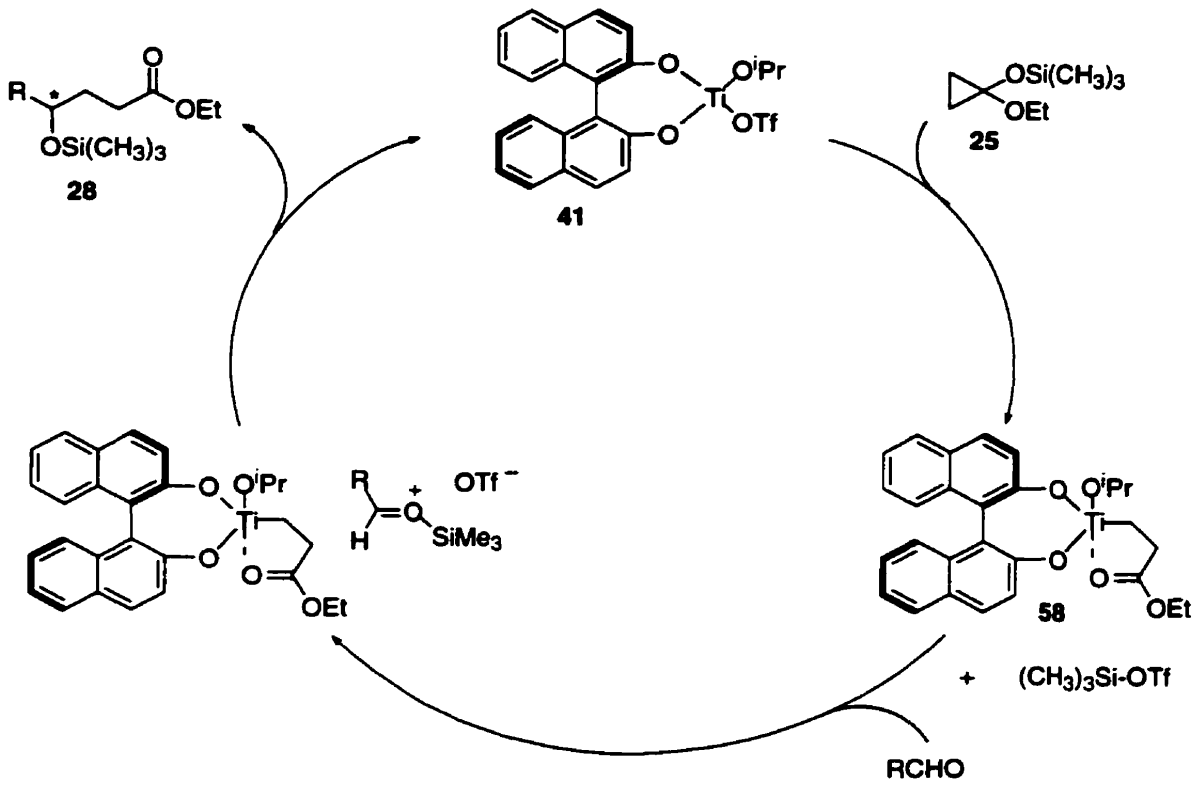
Scheme 12. Silylation of a titanium (IV) tetraalkoxide

The above results are contrary to what is observed in the actual catalytic process. Although TMSO^{i}Pr is observed when Binol-Ti(O^{i}Pr)$_2$ is treated with TMSOTf, no further generation of TMSO^{i}Pr is evident during the reaction. Furthermore, when **41** is prepared using the AgOTf mediated route, only silylated homoaldol product is observed in the reaction, with no formation of TMSO^{i}Pr. These observations clearly indicate that the homoaldol process developed here does not involve silyation of a titanium (IV) tetraalkoxide. This implies that titanium (IV) tetraalkoxides are not intermediates in this catalytic process and that the reaction does not proceed through a direct addition of the titanium (IV) homoenolate to the aldehyde.

3.9.2 Proposed catalytic cycle

An alternate mechanism for this reaction is proposed in Scheme 13. The ring opening of **25** with titanium triflate **41** leads to the formation of an alkoxytitanium (IV) homoenolate. The TMSOTf that is liberated in this process reacts with the aldehyde to form an activated complex that undergoes addition with the homoenolate **58** to form the γ-silyloxyester **28** directly, regenerating the active catalyst in the process. Although titanium homoenolates reported to date do not require silicon activation in order to add to aldehydes, similar activation of aldehydes is proposed for the homoaldol reaction of zinc homoenolates.[24] The activation of carbonyls and acetals by trimethylsilyl iodide has also been noted.[25] In addition, silicon activation of aldehydes has been reported as a viable mechanism in the Mukaiyama aldol and Sakurai allylation reactions.[26]

The mechanism described above also accounts for the low levels of enantioselectivity observed in this process, as the enantiodetermining step occurs in a relatively open transition state. It is anticipated that a highly enantioselective process can be obtained by increasing the steric environment around the titanium metal centre as this should lead to greater facial differentiation of the aldehyde as it approaches the homoenolate.



Scheme 13. Proposed catalytic cycle for alkoxytitanium (IV) homoenolate addition to aldehydes

^{1}H NMR of the reaction mixture prior to the addition of benzaldehyde does not reveal any signals indicative of a titanium homoenolate (expected between δ 3.40 and δ 1.50 ppm). However, ^{1}H NMR of the oil obtained after removal of the volatile material showed two triplets at δ 2.20 and δ 3.20 ppm that were coupled to each other. It is proposed that these correspond to the methylene protons of the alkoxytitanium homoenolate **58**, with the protons adjacent to the titanium centre giving the signal at higher field. However, the intensity of these triplets was significantly smaller than that

in the aromatic region, indicating that free alkoxytitanium (IV) homoenolate is not visible by ^{1}H NMR during the reaction.

It is important to note that TMSOTf does not promote the homoaldol reaction of **25** with aldehydes in the absence of **41**. This observation, along with the analogy to Nakamura's work,[1] suggests that the titanium homoenolate **58** is an intermediate in this process even though it has not been fully characterized.[iii]

3.10 CONCLUSIONS

Alkoxytitanium homoenolates have thus far been prepared only via indirect methods from pre-formed titanium or zinc homoenolates. We have shown that they can be prepared through the direct ring opening of silyloxycyclopropanes with alkoxytitanium chlorides and alkoxytitanium triflates, the latter affording more reactive homoenolates.

The methodology developed here is applicable to a range of carbonyl substrates, affording good to excellent yields of homoaldol adducts with acetylenic aldehydes and aryl aldehydes which are unsubstituted or substituted with electron-withdrawing groups. It is noteworthy that the catalyst system is thermally stable such that addition to less reactive substrates can also be accomplished.

[iii] The alkoxytitanium homoenolate **58** could not be prepared via transmetallation between zinc homoenolate and Binol-Ti(O^{i}Pr)Cl in $CDCl_3$. ^{1}H NMR indicated signals at δ 2.65 (t, 2H) and δ 0.45 (t, 2H) ppm corresponding to zinc homoenolate only.

An alternate and new route for the preparation of titanium (IV) triflates has been developed through the treatment of titanium (IV) alkoxides with trimethylsilyltriflate. This method is operationally more facile than the conventional procedure of ligand exchange between titanium chlorides and silver triflate. Furthermore, it results in a more reactive catalyst for the homoaldol reaction developed here. It would be interesting to examine the reactivity and selectivity of titanium triflates prepared via this procedure in other reactions such as Diels Alder and ene reactions where the titanium triflate catalysts are prepared by conventional methods.[5]

Our results are the first example of titanium catalysis of the homoaldol addition of silyloxycyclopropanes to aldehydes, which is a significant contribution to the field of homoenolate chemistry.[27] Mechanistic investigations provide insight into rational catalyst design to effect enantioselective catalysis. Our efforts in this area are described in Chapter Four.

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CHAPTER FOUR

CATALYTIC ENANTIOSELECTIVE HOMOALDOL REACTIONS

4.1 INTRODUCTION

Having achieved our primary goal of attaining titanium catalysis of the homoaldol reaction through the use of alkoxytitanium (IV) triflates, we focused our attention on improving the enantioselectivity of the process. The evidence described in Chapter Three indicates that the aldehyde is activated by a silicon species prior to homoenolate addition (Figure 9). Although homoaldol products with low enantiomeric excess were obtained (*ca* 10 % ee), the results indicated that the chiral Binol ligand played an active role in controlling the approach of the aldehyde towards the titanium homoenolate. The absence of titanium coordination of the aldehyde may account for the reduced enantiofacial discrimination of the substrate.

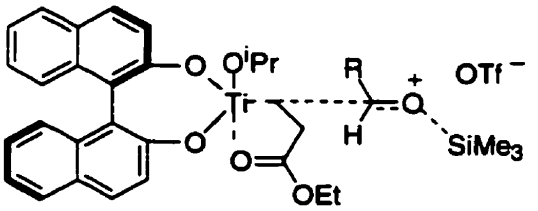


Figure 9. Proposed transition state for alkoxytitanium (IV) homoenolate addition to aldehydes

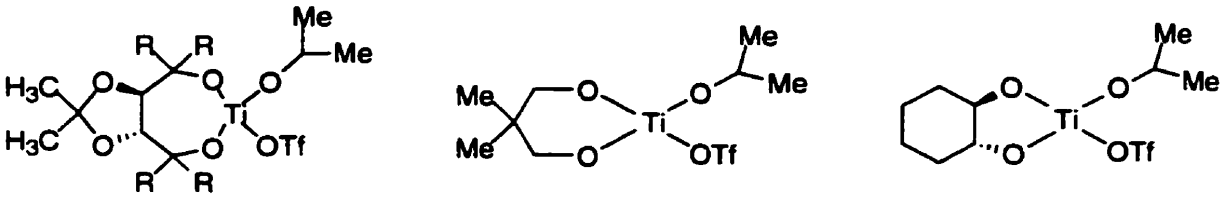
We anticipated that the enantioselectivity of this process could be enhanced by increasing the sterics of the ligand or alternatively through the incorporation of a third alkoxide ligand linked to the Binol framework. This latter modification would replace the isopropoxide ligand that appears to be dormant in this process. The effect, in either case, is to increase the non-bonded interactions between the substrate and the ligand, which might lead to greater facial differentiation of the aldehyde as it approaches the homoenolate. We also explored cationic titanium (IV) complexes as a means for removing the silicon activation of the aldehyde.

4.2 REACTIVITY OF TITANIUM (IV) TRIFLATES DERIVED FROM BIDENTATE LIGANDS

4.2.1 Titanium (IV) triflates derived from bidendate alkoxide ligands

In order to determine the types of ligands that could be incorporated in this catalytic homoaldol process, titanium (IV) triflate complexes derived from aliphatic 1,4-, 1,3- and 1,2-diols were investigated (Figure 10). These were prepared by ligand exchange between the appropriate diol and $Ti(O^iPr)_4$, followed by azeotropic removal of the liberated isopropanol.[1] The alkoxytitanium diisopropoxide complexes were then dissolved in $CDCl_3$, treated with one equivalent of TMSOTf and used directly for the homoaldol reaction of cyclopropane **25** with benzaldehyde. Titanium (IV) triflates **59a**, **59b**, **60** and **61** (25 mol %) catalyzed the homoaldol reaction providing the γ-lactone **29** in isolated yields of 65 - 80 %, after treatment of the crude reaction mixture

with p-toluene sulfonic acid. In the case of the TADDOL-derived titanium triflate **59a**, the γ-lactone was obtained in 11 % enantiomeric excess.[1]



59a R = Ph
59b R = H

60

61

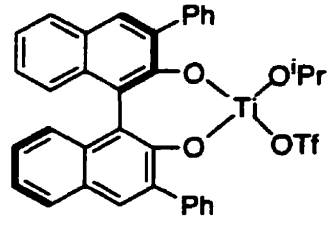
Figure 10. Titanium (IV) triflate catalysts derived from bidendate alkoxide ligands

These results indicate that there is some flexibility in the ring size around the titanium metal centre that can be tolerated in this process, which enables the design and synthesis of a variety of new ligands for this reaction. The presence of a bidentate ligand is a definite requirement however, as $(^{i}PrO)_3TiOTf$ does not promote this reaction to any extent. This implies that the bidentate ligands play an important role in controlling the aggregation state and thus the reactivity of the metal catalyst.

Homoaldol reactions of **25** with benzaldehyde carried out with sterically encumbering substitutents on the Binol framework resulted in homoaldol products with lower levels of enantioselectivity. For example, when the titanium triflate **62** derived from 3,3'-diphenyl Binol was used as a catalyst, the γ-lactone **29** was obtained in 5 % enantiomeric excess.[2] The substituents on the Binol ring may enforce an extended transition state along the carbon-carbon bond forming axis which minimizes

[1] TADDOL : α, α, α', α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol

interactions between the aldehyde and the chiral ligand. This may account for the lower levels of enantioselectivity observed with this ligand.



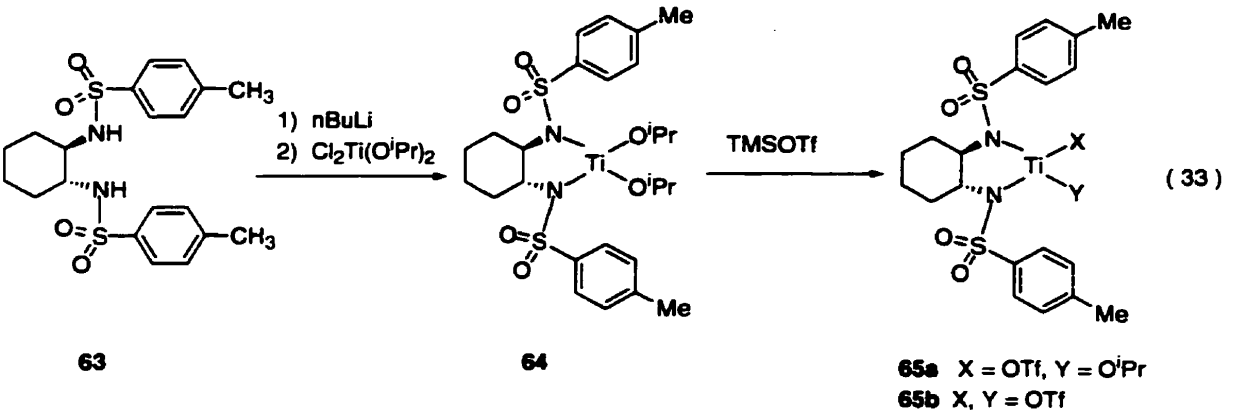
62

4.2.2 Titanium (IV) triflates derived from bidendate sulfonamide ligands

In order to examine whether non-alkoxide based ligands could serve as catalysts for this process, titanium (IV) triflate complexes of cyclohexane p-toluene disulfonamide were examined. Disulfonamide-Ti(O^iPr)$_4$ systems have been used as chiral mediators in the addition of diethyl zinc to aldehydes.[3] In our case, it was expected that the electron withdrawing sulfonamide groups would offset the basicity of the nitrogen ligands, thus maintaining the Lewis acidity of the titanium triflate towards ring opening of the cyclopropane **25**.

Unlike titanium complexes derived from alcohols, titanium alkoxide complexes of amines cannot be prepared by facile ligand exchange between the amine and Ti(O^iPr)$_4$ as elevated temperatures are required for activation of the proton on the nitrogen atom.[4] Thus, the disulfonamide isopropoxide titanium complex **64** had to be prepared by addition of the dilithio salt, obtained via treatment of **63** with n-butyllithium in diethyl ether, to a solution of $Cl_2Ti(O^iPr)_2$ in toluene (Equation 33). Removal of solvents *in vacuo* afforded a yellow solid which was dissolved in $CDCl_3$.

Subsequent addition of one or two equivalents of TMSOTf provided the triflate complexes **65a** and **65b**.

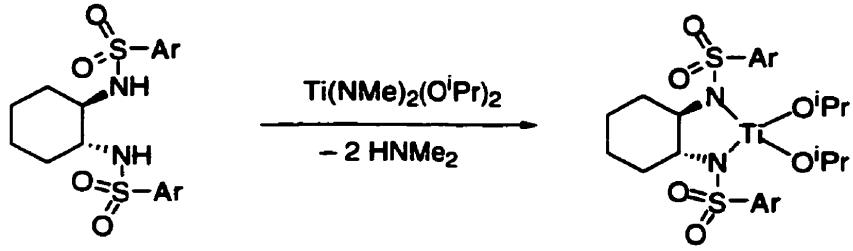


(33)

The homoaldol reactions carried out with **65a** and **65b** were not as efficient as the ones performed with alkoxytitanium (IV) triflates. There was no reaction between the silyloxycyclopropane **25** and benzaldehyde in the presence of 25 mol % of the monotriflate **65a** even after heating at reflux in $CDCl_3$ for 8 hours. The reaction mediated by the ditriflate complex **65b** required heating at reflux in $CDCl_3$ for 9 hours for complete consumption of the cyclopropane. In this case, racemic **29** was obtained in 55 % yield (GC). The observation that a single triflate ligand was not sufficient to maintain the Lewis acidity of **65a** indicates that the basicity of the ligands is an important parameter in this reaction.

It is conceivable that the decrease in the reaction rate with **65a** and **65b** is due to the basicity of the nitrogen ligands not being appreciably diminished by the electron withdrawing sulfonamide groups. It is also possible that coordination of the sulfonyl oxygens to the titanium centre occurs which would further decrease the Lewis acidity of these titanium triflate complexes. The presence of such coordination has been

reported in bis-sulfonamido titanium alkoxide complexes prepared from bis-sulfonamides upon treatment with dialkoxytitanium diamides (Equation 34).[4b] X-ray diffraction of a crystal structure of **66** indicated that the ligand was tetradentate in nature, exhibiting coordination to the titanium centre through the sulfonamido nitrogens as well as the sulfonyl oxygens.



66

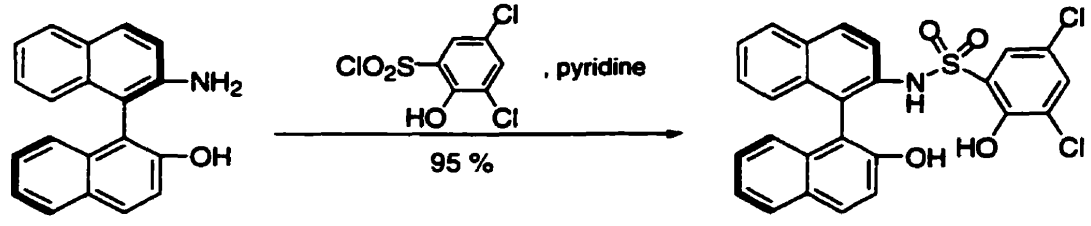
(34)

4.3 REACTIVITY AND SELECTIVITY OF TITANIUM (IV) TRIFLATE COMPLEXES DERIVED FROM TRIDENTATE LIGANDS

4.3.1 Tridentate hydroxyaminosulfonamides as ligands for titanium (IV) triflate catalyts

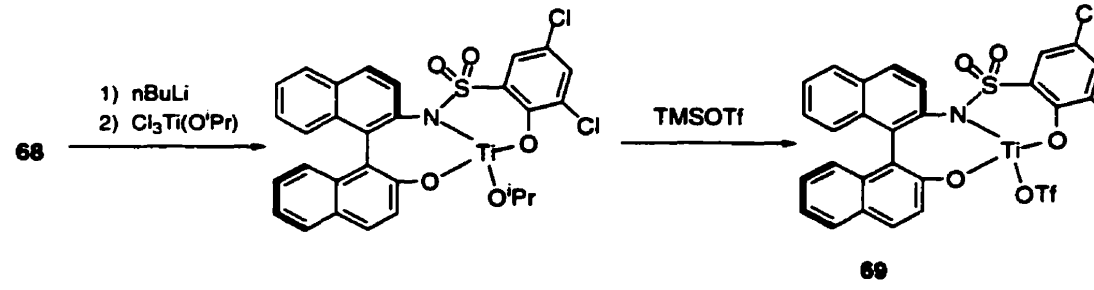
The first tridentate ligand examined was the dihydroxysulfonamide **68** in the anticipation that the electronics of this ligand could be easily varied by treatment of the hydroxyamine **67** with different sulfonyl chlorides. We expected the effect of the single nitrogen ligand to be compensated by the electron-withdrawing substituents on the phenol ring.

2-amino-2'-hydroxy-1,1'-binaphthyl was prepared by oxidative coupling between 2-naphthylamine and 2-naphthol as described by Smrcina and Kocovsky.[5] Subsequent treatment with 3,5-dichloro-2-hydroxybenzenesulfonyl chloride in the presence of pyridine provided the dihydroxysulfonamide **68** in 95 % yield (Equation 35).



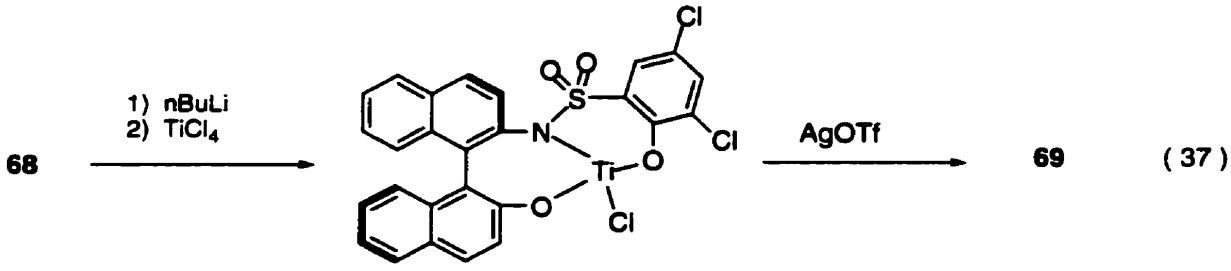
67 **68** (35)

Treatment of a solution of **68** in diethyl ether with n-butyllithium, followed by addition of $Cl_3Ti(O^iPr)$ in toluene afforded an orange solid after removal of solvents *in vacuo* (Equation 36). Addition of TMSOTf to this dihydroxysulfonamide titanium isopropoxide in $CDCl_3$ provided the triflate **69**. The homoaldol reaction of cyclopropane **25** and benzaldehyde was carried out with 25 mol % of **69** in $CDCl_3$. However, monitoring the reaction by ^1H NMR indicated only a trace amount of γ-lactone **29**, even upon heating to 50 °C for 10 hours.



69 (36)

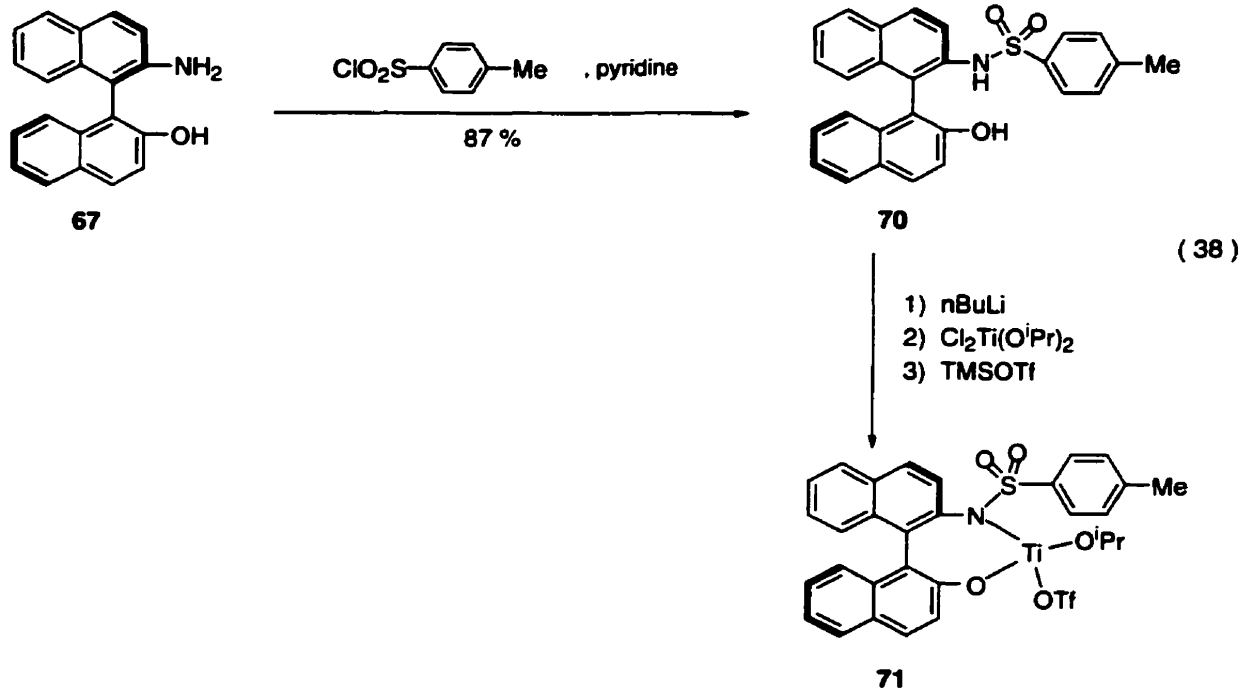
Similar results were obtained when the titanium triflate **69** was prepared by the conventional route of ligand exchange between a titanium chloride and silver triflate (Equation 37).[6]



(37)

Two potential explanations for the low reactivity of the dihydroxysulfonamide titanium triflate **69** in the homoaldol reaction are a decrease in the Lewis acidity of the titanium complex as explained earlier or steric encumberance around the titanium centre by the tridentate ligand, which would prevent facile ring opening of the cyclopropane.

In order to differentiate between these possibilities, the reaction was carried out with hydroxysulfonamido titanium triflate **71**. The hydroxysulfonamide **70** was prepared in 87 % yield by treatment of **67** with p-toluenesulfonylchloride and pyridine in methylene chloride (Equation 38). Addition of n-buthyllithium to a solution of **70** in toluene afforded the dilithio salt which upon addition to $Cl_2Ti(O^iPr)_2$ in toluene provided an orange-red solid after removal of solvents *in vacuo*. Dissolution of the solid in $CDCl_3$ followed by addition of TMSOTf afforded **71**.



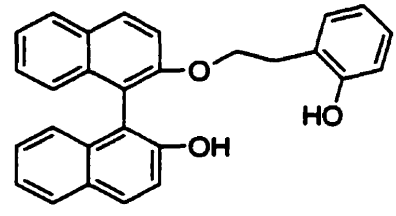
(38)

When **71** (25 mol %) was used as a mediator in the addition of silyloxycylopropane **25** to benzaldehyde, a trace amount of γ-lactone **29** was observed after heating for 69 hours at 40 - 45 °C. This suggests that the low reactivity of these sulfonamide titanium complexes is probably due to a decrease in the Lewis acidity of the titanium centre (*vide supra*).

4.3.2 Tridentate Binol derivatives as ligands for titanium (IV) triflate catalyts

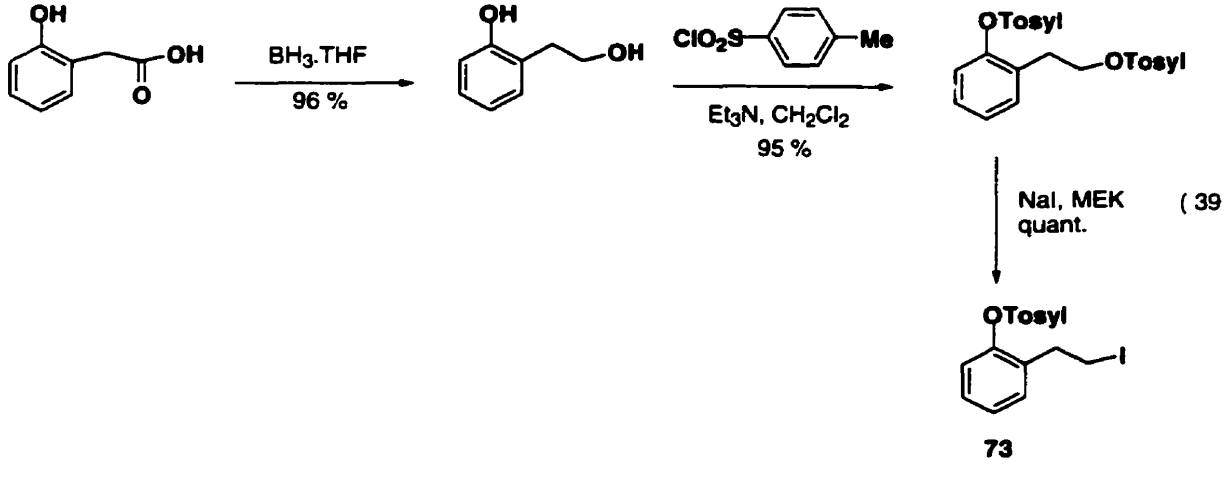
4.3.2.1 Synthesis and reactivity of an ether linked Binol derivative

We investigated Binol-derived tridentate ligands such as **72a** as the ether functionality might provide some flexibility upon formation of a titanium triflate complex by acting as a dative metal-ligand linkage.[ii]



72a

The requisite iodide **73** for the synthesis of **72a** was prepared in three steps from 2-hydroxyphenylacetic acid via borane reduction (96 % yield), followed by bis-tosylation (95 % yield). A Finkelstein reaction on the bis-tosylate in methyl ethyl ketone (MEK) provided **73** in quantitative yield (Equation 39).

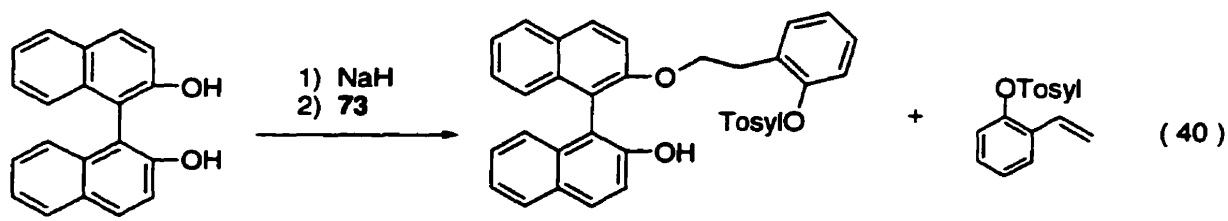


(39)

73

[ii] An analogous tridentate Binol derivative with a one-carbon ether link was also prepared but proved to be unstable to purification.

Treatment of Binol with one equivalent of sodium hydride in N,N-dimethyl formamide (DMF), followed by addition of iodide **73** predominantly resulted in elimination of the iodide to form styrene derivative **75** with only a 10 % yield of desired ether **74** (Equation 40). The styrene derivative was the major product even when the lithium or cesium anions of Binol were used. The desired diol **72a** was obtained in quantitative yield upon removal of the tosyl group with n-butyllithium in toluene.



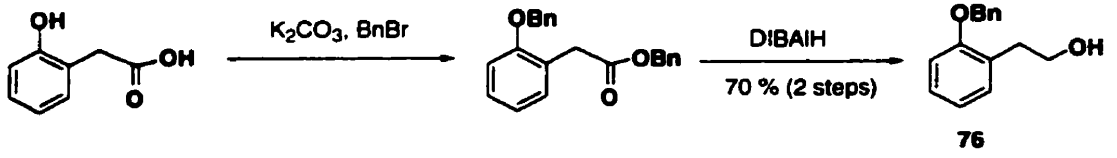
74 **75** (40)

The titanium triflate complex of **72a** (25 mol %) was readily prepared as described earlier by treatment with $Ti(O^iPr)_4$ and TMSOTf. Subsequent addition of cyclopropane (1 equivalent) **25** and benzaldehyde (1 equivalent) in $CDCl_3$ proceeded to completion in 6.5 hours at 0 °C. The γ-lactone **29** was obtained in 71 % isolated yield after treatment of the crude reaction mixture with p-toluenesulfonic acid. This was the first indication that titanium (IV) triflates prepared from tridentate alkoxide ligands could be used to catalyze the addition of **25** to aldehydes.

An alternate efficient route was desired for the synthesis of **72a** from enantiopure Binol. The most commonly used method for the regioselective acylation, alkylation and oxidation of diols is through the formation of an intermediate stannylene acetal, as the sterically encumbering tin substituent only permits alkylation

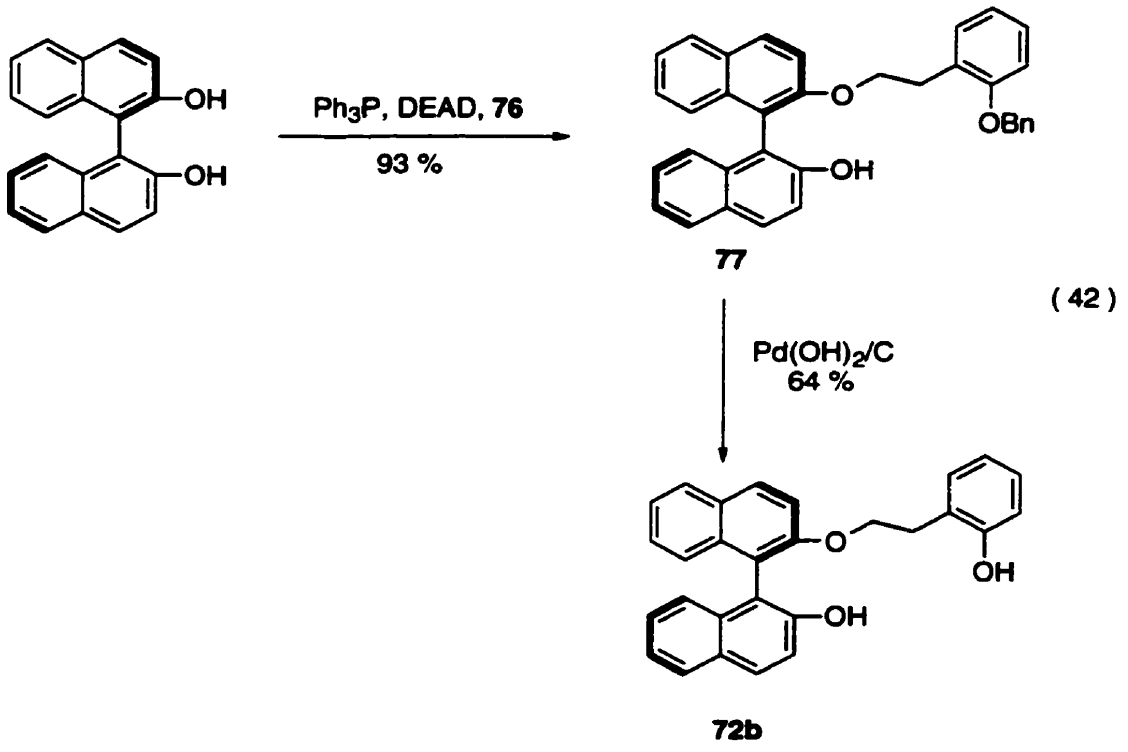
at one oxyanion.[7] Our attempts to effect mono-alkylation of Binol with **73** through the formation of a stannylene acetal were not successful.[8]

An alternate method reported by Manhas for the synthesis of alkyl aryl ethers under Mitsonobu conditions was examined.[9] This method has recently been used for the synthesis of mono-alkyl ethers of Binol.[10] The alcohol **76** required for our synthesis was prepared in 70 % overall yield by dibenzylation of 2-hydroxyphenylacetic acid, followed by reduction of the benzyl ester with diisobutylaluminum hydride (DIBAlH) (Equation 41).



76 (41)

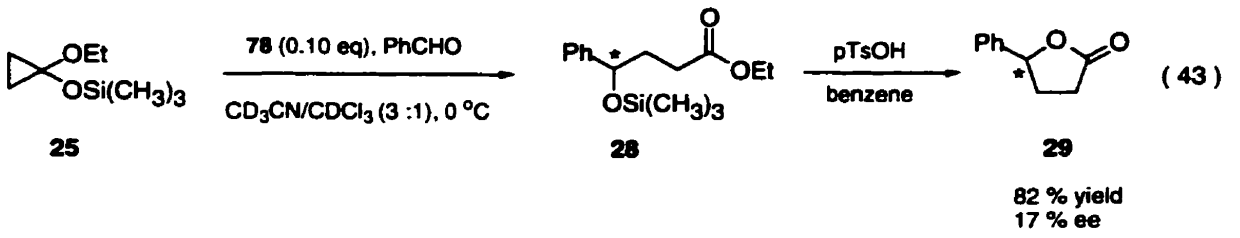
Treatment of Binol with one equivalent of **76**, triphenyl phosphine (Ph_3P) and diethylazodicarboxylate (DEAD) in tetrahydrofuran provided the deisred mono-alkylated product **77** in 93 % yield (Equation 42). The presence of di-alkylated Binol was not observed in the ^1H NMR spectrum of the crude reaction mixture. The diol **72b** was obtained upon removal of the benzyl group with palladium (II) hydroxide on carbon under a hydrogen atmosphere.



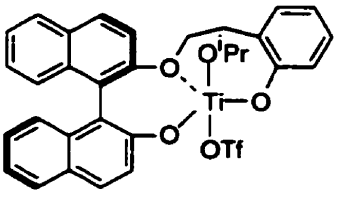
(42)

The titanium complex **78** (10 mol %) prepared from **72b** catalyzed the addition of silyloxycyclopropane **25** to benzaldehyde in 49 hours in a 3 : 1 mixture of $CD_3CN/CDCl_3$ (Equation 43). The γ-lactone **29** was obtained in 82 % yield with 17 % enantiomeric excess after treatment of the crude reaction mixture with p-toluenesulfonic acid. This result demonstrates that the enantioselectivity of the reaction can be improved by increasing the steric environment around the titanium metal centre. It is interesting that the major enantiomer in this case is the same as the one observed when Binol-Ti(O^{i}Pr)(OTf) **41** is used as a catalyst, indicating that the facial approach of the aldehyde towards the titanium homoenolate is the same in both complexes.[iii]

[iii] The absolute configuration of lactone **29** has not yet been determined.



(43)



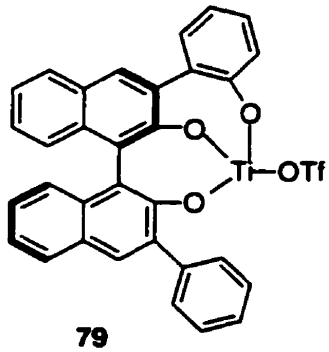
78

4.3.2.2 Reactivity of a titanium (IV) triflate with a 3,3'-substituted tridentate Binol ligand

Although we were pleased with the improvement in enantioselectivity with **78**, we were also interested in the reactivity and selectivity of a ligand which would form three formal bonds to the titanium centre. 3-hydroxyphenyl-3'-phenyl Binol was prepared for this purpose according to the procedure by Yamamoto.[11]

The titanium triflate **79**, derived from this ligand, catalyzed the homoaldol reaction of **25** with benzaldehyde demonstrating that titanium (IV) triflates derived from triols can also be used as catalysts in this reaction. However, no significant change in the enantioselectivity of the reaction was observed compared to Binol-Ti(O^{i}Pr)(OTf) **41**. The γ-lactone **29** was obtained in 9 % ee. This may be due to the rigidity of the complex imposed by the ligand. The flexibility permitted by the ether linker in **78** may allow the alkoxide on the phenol substituent to occupy a distal coordination site on the titanium centre, thereby increasing the steric environment

around the catalyst. Crystal structures of **78** and **79** would be required before the differences in selectivity can be fully rationalized.

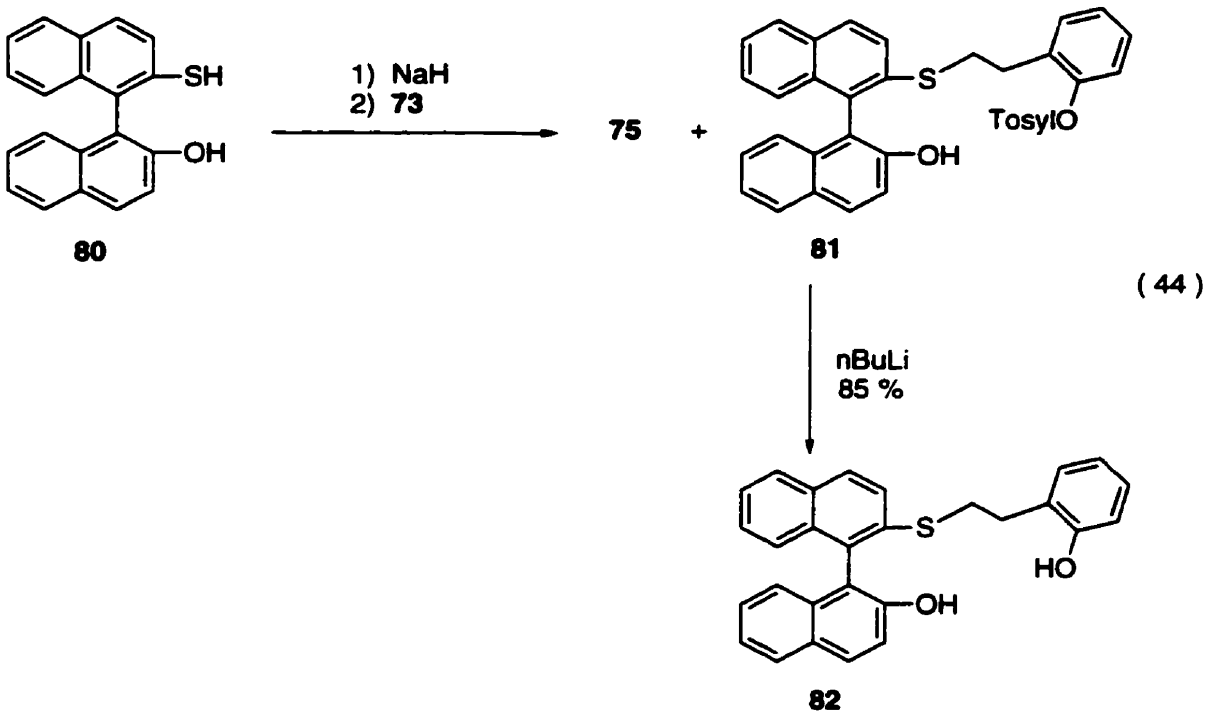


79

4.3.3 Tridentate derivatives of 2-thio-2'-hydroxy-1,1'-binaphthyl as ligands for titanium (IV) triflate catalysts

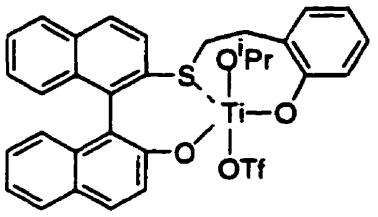
In light of the improvement in selectivity with **72b**, we were interested in 2-thio-2'-hydroxy-1,1'-binaphthyl **80** as a scaffold for the construction of tridentate sulfur analogs and in their subsequent reactivity in the homoaldol reaction upon formation of titanium (IV) triflate complexes.

The hydroxy thiol **80** was prepared according to the procedure of Woodward.[12] Although **80** has two sites for alkylation, the higher acidity of the aryl thiol (pK_a 6 - 8) compared to the aryl alcohol (pK_a 8 - 11) should permit facile deprotonation of the thiol, providing S-alkylation only. De-protonation of **80** with sodium hydride in N,N-dimethyl formamide (DMF), followed by alkylation with iodide **73** provided styrene derivative **75** as the major product, in addition to 33 % yield of the desired sulfide **81**. Removal of the tosyl group with n-buthyllithium provided dihyroxysulfide **82** in 85 % yield (Equation 44).



(44)

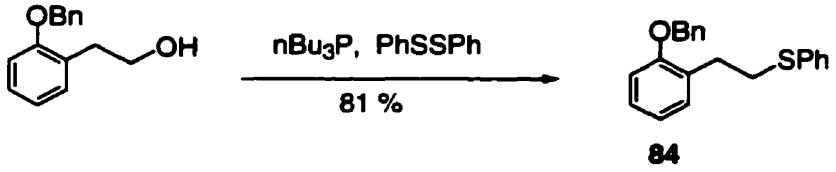
The homoaldol reaction of benzaldeyde catalyzed by **83** (25 mol %) proceeded at a comparable rate to **78** (6.5 hours at 0 °C) although the γ-lactone **29** was obtained in lower yield (68 %). This result was nonetheless interesting as it indicated sulfur based ligands could also be used to form titanium (IV) triflates which are capable of catalyzing the homoaldol reaction. Thus, an alternate direction for the design of ligands for this reaction, which incorporates thiols or sulfides, is feasible.



83

The synthesis of enantiopure **82** was attempted via the Mitsonobu reaction as it proved to be successful in the synthesis of the tridentate Binol ligand **72b**. The higher acidity of the aryl thiol was expected to favour S-alkylation only. However, treatment of hydroxy thiol **80** with alcohol **76** under the Mitsonobu conditions in tetrahydrofuran resulted in the formation of several products, with no desired sulfide. The formation of several by-products in this case could be due to initial nucleophilic attack by the thiol onto DEAD before Ph_3P. This could then lead to a cascade of undesired reactions.

The synthesis of phenylthioethers has been reported through the treatment of an alcohol with tri-n-butylphosphine in the presence of an excess of phenyldisulfide.[13] To probe the applicability of this method, the thioether **84** was synthesized in 81 % yield from **76** and phenyldisulfide (Equation 45). Although this reaction has not been attempted on hydroxythiol **80** yet, a viable approach to the synthesis of **82** in enantiopure form has been outlined.



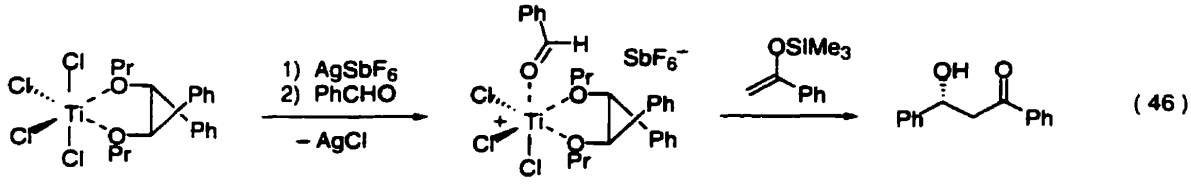
(45)

84

4.4 CATIONIC TITANIUM (IV) COMPLEXES

Besides utilizing ligands with increased sterics around the titanium centre, an alternate strategy for enhancing the enantioselectivity of the catalytic homoaldol reaction is designing a system in which the aldehyde coordinates to the chiral titanium complex prior to homoenolate addition. We explored a cationic titanium (IV) complex for this purpose.

Akiba has recently reported that enriched aldol products (56 % ee) were obtained from the addition of a silyl enol ether to benzaldehyde in the presence of silver hexafluoroantimonate ($AgSbF_6$) and the $TiCl_4$ coordinated chiral diether complex **85**. Only racemic products were obtained in the absence of the silver salt (Equation 46).[14]

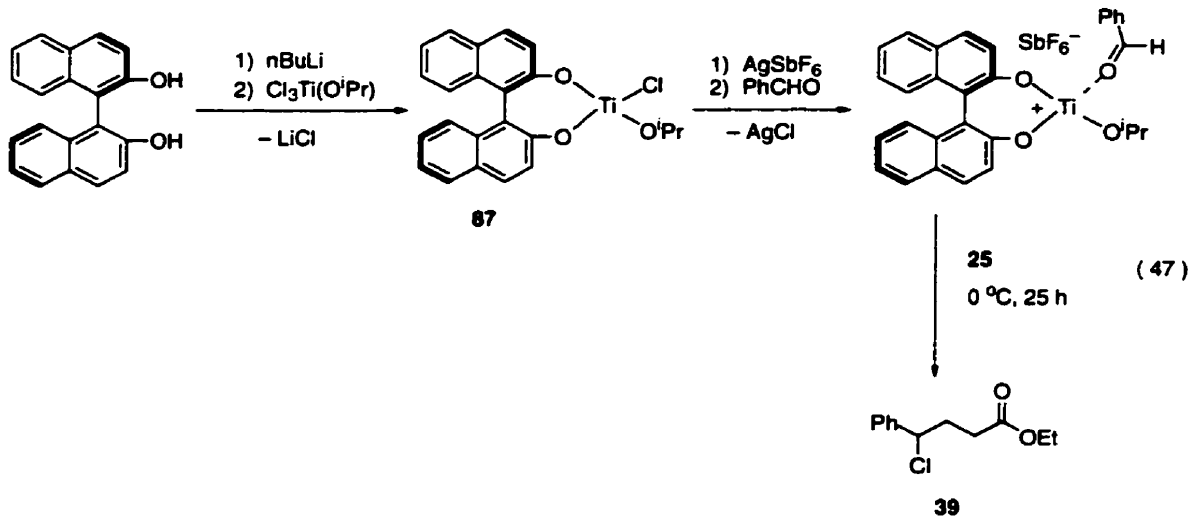


85 **86** (46)

The authors propose the formation of a cationic titanium (IV) complex **86** upon treatment of **85** with $AgSbF_6$. It is conceivable that benzaldehyde would coordinate to this electron deficient titanium centre. Enriched products are obtained upon subsequent aldol addition to the titanium-coordinated aldehyde. In addition, the isolation of the β-hydroxyester instead of the β-silyloxyester suggests that the reaction proceeds by aldehyde coordination to the titanium centre prior to addition.

We examined the above concept in our homoaldol system (Equation 47). Binol-Ti(O^{i}Pr)Cl **87** was prepared by the treatment of Binol (1 equivalent) with n-

butyllithium (2 equivalents) followed by $Cl_3Ti(O^iPr)$. Addition of $AgSbF_6$ (1 equivalent) in the presence of benzaldehyde (1 equivalent), followed by addition of the cyclopropane **25** (1 equivalent) yielded the γ-chloroester **39** after 25 hours at 0 °C.



(47)

Our investigations with chloroalkoxytitanium (IV) complexes indicated that ring-opening of **25** with dialkoxytitaniumdichlorides was very slow. For example, reaction of **25** with benzaldehyde in the presence of $Cl_2Ti(O^iPr)_2$ required 149 hours while the reaction carried out with Binol-$TiCl_2$ indicated only minimal γ-lactone formation after two hours at room temperature. The trialkoxytitanium (IV) chloride complex **87** is expected to be an even weaker Lewis acid and should require an even longer reaction time. The observation that the cyclopropane was consumed within 25 hours at 0 °C indicates that a reactive cationic complex was formed in this reaction, presumably with benzaldehyde coordination. It would be interesting to repeat the reaction under salt free conditions to isolate the initially formed γ-hydroxyester **55** and evaluate its selectivity.

4.5 CONCLUSIONS

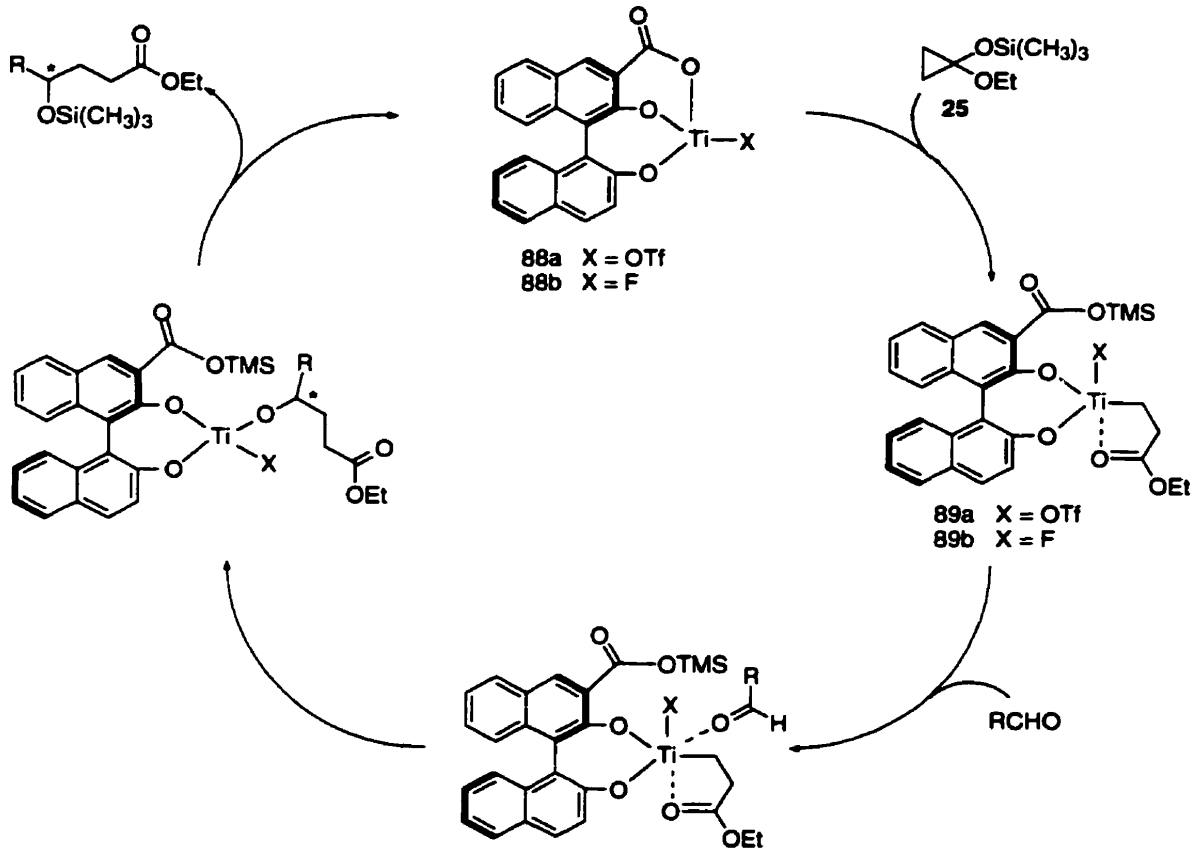
We have initiated research into several avenues for increasing the enantioselectivity of the catalytic homoaldol reaction described in Chapter Three. Our investigations with titanium (IV) triflates derived from tridentate alkoxide ligands indicate that ligand flexibility appears to be important for an enhancement in selectivity. An increase in enantioselectivity (17 %) has been achieved in the addition of silyloxycyclopropane **25** to benzaldehyde with the tridentate titanium (IV) triflate **78**. Although this may seem moderate, this route is promising as there are no prior examples of enantioselective catalysis in this class of homoaldol reactions. As a prelude for the design of improved catalysts for this reaction, we have demonstrated that titanium (IV) triflates containing a range of alkoxide ligands as well as ligands with sulfide linkages can be used to catalyze the homoaldol reaction.

Preliminary work indicates that a cationic titanium (IV) complex generated from Binol-Ti(O^iPr)Cl and silver hexafluoroantimonate can also be used to effect the addition of cyclopropane **25** to benzaldehyde. Literature precedent suggests that the reaction proceeds via aldehyde coordination to the chiral titanium centre. This is a means for eliminating silicon activation of the aldehyde, which is a potential method for increasing the enantioselectivity of this reaction.

4.6 FUTURE DIRECTION

Our research in homoaldol reactions has led to the development of the first example of titanium catalysis of the addition of silyloxycyclopropanes to aldehydes. In our efforts to develop a highly enantioselective variant of this process, we are interested in the design of new titanium-based catalysts for this reaction.

An approach which we are currently exploring is elimination of silicon activation of the aldehyde through the use of the titanium triflate **88a**.[15] Ring opening of the cyclopropane **25** would effect silylation of the carboxylate ligand to form the alkoxytitanium homoenolate **89a** (Scheme 14). At this point in the reaction, there would be no free silicon species in solution to activate the aldehyde which could coordinate to the chiral titanium centre. We anticipate an increase in selectivity upon subsequent addition of the homoenolate to a titanium-coordinated aldehyde. Intramolecular silylation of the titanium homoaldolate would yield the desired γ-silyloxyester with regeneration of the catalyst.[16]



Scheme 14. Anticipated catalytic enantioselective homoaldol reactions with a silicon shuttle

As an alternative to alkoxytitanium (IV) triflates, we would like to explore the reactivity of alkoxytitanium (IV) fluoride complexes such as **88b** in the homoaldol reaction (Scheme 14).[17] The electronegativity of the fluorine ligand should maintain the Lewis acidity of **88b** towards ring opening of the cyclopropane. Silylation of the fluoride ligand during the reaction to form trimethylsilylfluoride (TMSF) would be thermodynamically unfavourable as the bond strength of a Ti-F bond (140 kcal/mol) is greater than that of a Si-F bond (135 kcal/mol).[18]

As a prelude to the application of this methodology to the synthesis of peptidomimetic substructures and complex natural products containing 1,4-oxygenated subunits, it would be interesting to examine the regioselectivity of the ring-opening of chiral alkoxytrimethylsilyloxycylopropanes with Binol-Ti(O^iPr)(OTf) **41**. This could lead to the synthesis of α-substituted γ-hydroxy carbonyl compounds in a stereoselective manner. This aspect is promising as there is precedence for the synthesis of optically active zinc homoenolates through the regioselective ring opening of chiral silyloxycyclopropanes.[19]

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EXPERIMENTAL SECTION

4.9 GENERAL PROCEDURES

All reactions were performed using flame-dried glassware under an argon atmosphere. Preparation of catalysts and homoaldol reactions were carried out in Schlenk flasks using distilled reagents. Gas-tight syringes were used for transferring reagents for homoaldol reactions. Diethyl ether and tetrahydrofuran were distilled over sodium or potassium benzophenone ketyl prior to use. Methylene chloride, toluene and triethylamine were distilled over calcium hydride. Deuterated acetonitrile was distilled over calcium hydride and stored over molecular sieves for 24 hours prior to use. Deuterated chloroform was distilled over phosphorus pentoxide and stored over molecular sieves for 48 hours prior to use. Titanium (IV) chloride, titanium (IV) isopropoxide and trimethylsilyltriflate were distilled neat and stored over molecular sieves. Benzaldehyde was distilled over calcium hydride and stored neat. Dodecane, acetophenone and all aldehydes used in homoaldol reactions were distilled over calcium hydride and stored over molecular sieves.

Thin-layer chromatography was performed on silica gel glass plates (250 μm) and viewed by exposure to UV light and/or immersing in a staining solution of phosphomolybdic acid, followed by heating. Flash chromatography was performed using Silicycle silica gel, 230 - 400 mesh, using the eluent specified.

^{1}H and ^{13}C NMR spectra were recorded on a JEOL-270 spectrometer. COSY, HMQC and HMBC spectra were obtained on a Varian Unity 500 spectrometer. Data for ^{1}H NMR spectra are reported as follows : chemical shift, multiplicity, integration and coupling constant. Chemical shifts are reported in parts per million (δ). Coupling constants (*J* values) are given in Hertz (Hz) and the spin multiplicity are indicated as follows : s (singlet), d (doublet), t (triplet) and m (multiplet), bs (broad singlet).

Gas chromatograms were run on a Hewlett Packard GC with a CP-Chirasil-Dex CB column (25 m x 0.25 mm x 0.25 μm) with helium as the carrier gas.

4.10 CATALYST PREPARATION

Preparation of BINOL-Ti(OTf)$_2$ 40

n-Butyllithium (1.4 mL, 2.72 M in hexanes, 3.81 mmol, 2.05 equiv) was added to a solution of 2, 2'-binaphthol (0.531 g, 1.86 mmol, 1 equiv) in diethyl ether (6 mL) at 0 °C in a 25 mL Schlenk flask. The resulting white suspension was stirred at 0 °C for 20 minutes, after which $TiCl_4$ (205 µL, 1.87 mmol, 1.01 equiv) was added. The ensuing orange suspension was stirred at 0 °C for 2 hours, after which the solvent was removed *in vacuo*, at room temperature. The brown-red solid was dissolved in toluene (2 x 5 mL) and the solvent removed *in vacuo* after each dissolution. The solid was dried *in vacuo* for 0.5 hours, then re-suspended in toluene (7 mL) and transferred via cannula to a suspension of silver triflate (1.386 g, 5.39 mmol, 2.90 equiv) in toluene (7 mL) in a 50 mL Schlenk flask. A red brown was formed. The reaction mixture was stirred at room temperature for 67 hours, then passed through a Schlenk filter under an argon atmosphere into a 100 mL Schlenk flask. The solvent was removed *in vacuo* and the resulting red brown solid was dissolved in $CDCl_3$ (2 x 5 mL) and the solvent removed *in vacuo* after each dissolution. The solid was dried *in vacuo* for 0.5 hours, dissolved in $CDCl_3$ (5 mL), cooled to 0 °C and used immediately for the homoaldol reaction.

Preparation of BINOL-Ti(O^{i}Pr)(OTf) 41 via AgOTf route (Scheme 9)

n-Butyllithium (560 µL, 2.75 M in hexanes, 1.54 mmol, 2.04 equiv) was added to a 0 °C solution of 2,2'-binaphthol (0.216 g, 0.754 mmol, 1 equiv) in diethyl ether (2.5 mL) in a 25 mL Schlenk flask. The resulting white suspension was stirred at 0 °C for 1 hour, after which a light yellow solution of $TiCl_3(O^iPr)$ (0.753 mmol, 1 equiv, prepared via comproportionation between $TiCl_4$ (62 µL, 0.565 mmol) and $Ti(O^iPr)_4$ (56 µL, 0.188 mmol)) in toluene (2 mL) was added via cannula. The resulting brown-red suspension was stirred at 0 °C for 2.5 hours, after which the volatile material was removed *in vacuo*, at room temperature. The brown-red solid was dissolved in toluene (2 x 5 mL) and the solvent removed *in vacuo* after each dissolution. The solid material was dried *in vacuo* for 3 hours, then re-suspended in toluene (5 mL) and

transferred via cannula to a suspension of silver triflate (0.5115 g, 1.99 mmol, 2.63 equiv) in toluene (5 mL) in a 50 mL Schlenk flask. A red-brown suspension was formed. The reaction mixture was stirred at room temperature for 36 hours, then passed through a Schlenk filter under an argon atmosphere into a 100 mL Schlenk flask. The solvent was removed *in vacuo* and the resulting red brown solid dissolved in $CDCl_3$ (2 x 5 mL) and the solvent removed *in vacuo* after each dissolution. The solid material was dried *in vacuo* for 0.5 hours, dissolved in $CDCl_3$ (5 mL), cooled to 0 °C and used directly for the homoaldol reaction.

Preparation of BINOL-Ti(O^{i}Pr)(OTf) 41 via TMSOTf route (Scheme 10)

Titanium (IV) isopropoxide (110 μL, 0.373 mmol, 1.02 equiv) was added dropwise to a suspension of (R)-2, 2'-binaphthol (0.1046 g, 0.365 mmol, 1 equiv, > 99 % ee) in toluene (5 mL) at 0 °C in a Schlenk flask. Immediate formation of an orange-red solution was observed. The reaction mixture was warmed to room temperature and stirred for 3 hours, after which the solvents were removed *in vacuo*. The resulting orange-red solid was dissolved in toluene (2 x 5 mL) and the volatile material removed *in vacuo* after each dissolution. The solid material was dried *in vacuo* for 15 hours, then re-dissolved in a mixture of CD_3CN and $CDCl_3$ (6:2 mL) and cooled to 0 °C. Trimethylsilyl triflate (68 μL, 0.376 mmol, 1.03 equiv) was added, affording a dark red solution. The reaction mixture was stirred at 0 °C for 15 minutes, then used directly for the homoaldol reaction.

4.11 PROCEDURES FOR HOMOALDOL REACTIONS

Preparation of zinc homoenolates

Zinc homoenolate was prepared according to a modified procedure by Nakamura as follows:[1] Zinc chloride (0.2215 g) was placed in a pre-weighed Schlenk flask and heated to the melting point *in vacuo* with a bunsen burner. The salt was re-weighed (0.2178 g, 1.60 mmol, 1 equiv) and ether (6 mL) was added. The reaction flask was sonicated in an ice-water bath until complete dissolution of the salt (*ca* 15 minutes). The reaction mixture was degassed three times and then cyclopropane **25** (800 μL,

3.99 mmol, 2.49 equiv) was added and the reaction mixture stirred at room temperature for 22 hours. The volatile material was removed *in vacuo* and the residue dissolved in $CDCl_3$ (3 x 5 mL) and the volatile material removed *in vacuo* after each dissolution. The zinc homoenolate was dried *in vacuo* for 2 hours, then re-dissolved in $CDCl_3$ (5.5 mL). Dodecane (726 μL, 3.19 mmol, 2.00 equiv) was added and the reaction mixture stirred for 15 minutes after which a 500 μL aliquot was transferred to an argon filled NMR tube and the yield of the homoenolate was determined by integration of the ^1H NMR spectrum (57 %). This solution of zinc homoenolate and dodecane in $CDCl_3$ was used directly for subsequent homoaldol reactions.

Zinc homoenolate addition to benzaldehyde mediated by $Ti(O^iPr)_4$

To a solution of zinc homoenolate (0.800 mmol, 1 equiv) and dodecane (1.84 mmol, 1.84 equiv) in $CDCl_3$ (3 mL) was added $Ti(O^iPr)_4$ (240 μL, 0.806 mmol, 1.01 equiv), followed by benzaldehyde (80 μL, 0.787 mmol, 0.98 equiv). After half an hour, a 500 μL aliquot was transferred to an argon filled NMR tube. The reaction mixture was quenched after 23 hours with saturated NH_4Cl (5 mL) and filtered through Celite. The products were extracted into ethyl acetate (3 x 10 mL). The organic layer was washed once with brine (15 mL), dried over Na_2SO_4 and filtered. Analysis of the crude reaction mixture by GC indicated a 30 % yield of lactone **29**.

Lewis acid mediated addition of zinc homoenolates to aldehydes (described for $Ti(O^iPr)_4$)

$Ti(O^iPr)_4$ (70 μL, 0.235 mmol, 0.26 equiv) was added to a solution of zinc homoenolate (0.900 mmol, 1 equiv), dodecane (1.67 mmol, 1.85 equiv) and benzaldehyde (0.902 mmol, 1.00 equiv) in $CDCl_3$. At appropriate time intervals, 200 μL aliquots were withdrawn from the reaction mixture and quenched with saturated NH_4Cl (1 mL). The products were extracted into ethyl acetate (3 x 5 mL). The organic layer was washed once with brine (10 mL), dried over Na_2SO_4, filtered and analyzed by GC to determine conversion to lactone **29**.

Enantioselective addition of zinc homoenolate to benzaldehyde in the presence of chiral titanium (IV) alkoxides (described for Binol-Ti(O^iPr)$_2$)

A solution of Binol-Ti(O^iPr)$_2$ (0.248 mmol, 0.36 equiv)[2] in $CDCl_3$ (3 mL) was transferred via cannula to a solution of zinc homoenolate (0.685 mmol, 1 equiv), dodecane (1.27 mmol, 1.85 equiv) and benzaldehyde (70 μL, 0.689 mmol, 1.01 equiv) in $CDCl_3$ (3 mL). After 45 minutes, a 500 μL aliquot was transferred to an argon filled NMR tube. The reaction mixture was quenched after 19 hours with saturated NH_4Cl (5 mL) and filtered through Celite. The products were extracted into ethyl acetate (3 x 10 mL). The organic layer was washed once with brine (15 mL), dried over Na_2SO_4 and filtered. Analysis of the crude reaction mixture by GC indicated a 32 % yield of lactone **29** with 16 % ee.

Catalytic homoaldol reactions with BINOL-Ti(O^iPr)(OTf) (described for Table 3, entry 1)

Ethoxytrimethylsilyloxycyclopropane (1.12 mL, 5.57 mmol, 1.51 equiv) was added to a 0 °C solution of BINOL-Ti(O^iPr)(OTf) (0.365 mmol, 0.099 equiv, prepared as described above, Scheme 10) in CD_3CN (6 mL) and $CDCl_3$ (2 mL). After 10 minutes, benzaldehyde (430 μL, 3.69 mmol, 1 equiv) was added. After 45 minutes, a 500 μL aliquot was transferred to an argon filled NMR tube and the reaction monitored by ^1H NMR. After 26 hours at 0 °C, the reaction was quenched with 1 M HCl (10 mL) and the products were extracted into ethyl acetate (3 x 15 mL). The organic layer was washed once with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The crude reaction mixture was dissolved in benzene (6 mL), pTsOH (cat.) was added and the reaction mixture stirred overnight. Saturated $NaHCO_3$ (5 mL) was added and the products extracted into ethyl acetate (3 x 10 mL). The organic layer was washed once with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 30% hexanes in methylene chloride as eluent afforded 0.590 g of **29** (99 %). ^1H NMR ($CDCl_3$) δ 7.24 - 7.39 (m, 5H), 5.46 (dd, 1H, J = 7.9, 6.2), 2.54 - 2.67 (m, 3H), 2.04 – 2.22 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.8, 139.2, 128.5, 128.2, 125.1, 81.0, 30.7, 28.7; HRMS calcd for $C_{10}H_{11}O_2$ (M + H) 163.0759, found 163.0758.

Characterization data for homoaldol adducts (Table 3)

Homoaldol adduct of p-ClPhCHO (entry 2). ^{1}H NMR ($CDCl_3$) δ 7.30 (d, 2 H, J = 8.6), 7.22 (d, 2 H, J = 8.6), 5.41 (dd, 1H, J = 5.9, 6.4), 2.52 – 2.67 (m, 3H), 2.00 – 2.18 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 176.4, 137.8, 134.0, 128.7, 126.6, 80.3, 30.7, 28.7.

Homoaldol adduct of TMS-C≡C-CHO (entry 3). ^{1}H NMR ($CDCl_3$) δ 5.07 (t_{app}, 1H, J_{app} = 6.4), 2.43 – 2.66 (m, 3H), 2.23 – 2.31 (m, 1H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 175.9, 100.9, 92.9, 69.2, 29.7, 27.7, - 0.5; HRMS calcd for $C_9H_{15}O_2Si$ (M + H) 183.0841, found 183.0841.

Homoaldol adduct of Ph-C≡C-CHO (entry 4). ^{1}H NMR ($CDCl_3$) δ 7.23 – 7.45 (m, 5H), 5.35 (t_{app}, 1H, J_{app} = 5.8), 2.34 – 2.75 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 176.0. 131.7, 129.0, 128.3, 121.5, 87.3, 84.9, 69.5, 29.8, 27.8; HRMS calcd for $C_{12}H_{11}O_2$ (M + H) 187.0759, found 187.0758.

Homoaldol adduct of PhCOCH$_3$ (entry 5). ^{1}H NMR ($CDCl_3$) δ 7.24 – 7.40 (m, 5H), 2.34 – 2.67 (m, 4H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 176.4, 144.2, 128.5, 127.5, 124.0, 86.9, 36.0, 29.3, 28.8; HRMS calcd for $C_{11}H_{13}O_2$ (M + H) 177.0916, found 177.0916.

Homoaldol adduct of t-C$_4$H$_9$CHO (entry 6). ^{1}H NMR ($CDCl_3$) δ 4.16 (dd, 1H, J = 8.9, 6.9), 2.46 – 2.54 (m, 2H), 1.86 – 2.16 (m, 2 H), 0.92 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 177.3, 88.2, 33.8, 29.3, 24.9, 22.9; HRMS calcd for $C_8H_{15}O_2$ (M + H) 143.1072, found 143.1073.

Homoaldol adduct of p-OMePhCHO (entry 7). ^{1}H NMR ($CDCl_3$) δ 7.23 (d, 2 H, J = 8.7), 6.89 (d, 2 H, J = 8.7), 5.43 (t_{app}, 1 H, J_{app} = 7.0), 3.78 (s, 3 H), 2.52 – 2.66 (m, 3 H), 2.12 – 2.26 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 176.9, 159.7, 131.1, 126.9, 114.0, 81.3, 55.2, 30.8, 29.1.

Homoaldol adduct of $C_6H_{11}CHO$ (entry 8). ^1H NMR ($CDCl_3$) δ 4.18 (q_{app}, 1H, J_{app} = 7.5), 2.46 – 2.52 (m, 2H), 2.22 (sextuplet$_{app}$, 1H, J_{app} = 6.5), 0.94 – 1.97 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 177.3, 85.0, 42.7, 29.0. 28.9, 27.7, 26.2, 25.7, 25.6, 25.4; HRMS calcd for $C_{10}H_{17}O_2$ (M + H) 169.1229, found 169.1228.

Homoaldol adduct of $PhCH_2CH_2CHO$ (entry 9). ^1H NMR ($CDCl_3$) δ 7.17 – 7.32 (m, 5 H), 4.46 (quint$_{app}$, 1 H, J_{app} = 6.9), 2.66 – 2.88 (m, 2 H), 2.52 (dd, 2 H, J = 9.1), 2.29 (sextuplet$_{app}$, 1 H, J_{app} = 6.5), 1.78 – 2.11 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 177.0, 140.7, 128.5, 128.4, 126.1, 79.8, 37.3, 31.6, 28.8, 27.9.

Acetal 51 of hydrocinnamaldehyde

^1H NMR ($CDCl_3$) δ 7.15 – 7.31 (m, 5 H), 5.35 (t, 1 H, J = 5.2), 3.70 – 3.82 (m, 2 H), 3.54 – 3.64 (m, 2 H), 2.70 – 2.76 (m, 2 H), 2.03 – 2.11 (m, 2 H), 1.12 – 1.25 (m, 8 H), 0.83 – 0.96 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 141.9, 128.3, 128.2, 125.7, 100.9, 89.0, 61.8, 38.1, 30.3, 15.2, 13.6, 12.4; HRMS calcd for $C_{19}H_{27}O_3$ (M + H – H_2O) 303.1960, found 303.1960.

Diene 53a

Trans : cis 2.8 : 1 (from ^1H NMR)

Trans #: ^1H NMR (CD_3CN) δ 7.20 – 7.50 (m, 5 H), 6.87 (dd, 1 H, J = 15.8, 5.44), 6.55 (d, 1 H, J = 15.6), 6.31 (t_{app}, 1 H, J_{app} = 12.7), 5.90 (quintuplet$_{app}$, 1 H, J_{app} = 7.4), 4.11 (q, 2 H, J = 7.1), 3.15 (d, 2 H, J = 7.2), 1.22 (t, 3 H, J = 7.2); ^{13}C NMR (CD_3CN) δ 172.2, 138.3, 134.5, 132.7, 129.6, 128.5, 127.6, 127.2, 124.8, 61.4, 38.6, 14.5.

Cis # : ^1H NMR (CD_3CN) δ 7.20 – 7.50 (m, 5 H),7.10 (dd, 1 H, J = 13.4, 4.4), 6.64 (d, 1 H, J = 15.6), 6.31 (t_{app}, 1 H, J_{app} = 12.7), 5.65 (m, 1 H), 4.11 (q, 2 H, J = 7.1), 3.35 (d, 2 H, J = 5.7), 1.22 (t, 3 H, J = 7.2); ^{13}C NMR (CD_3CN) δ 172.2, 138.3, 134.6, 132.1, 129.5, 128.8, 127.5, 127.2, 124.7, 61.4, 38.6, 14.5.

LRMS calcd for $C_{14}H_{19}O_2N$ (M + NH_3) 233, found 233.

Isopropyl ether 53b

^{1}H NMR (CD_3CN) δ 7.16 – 7.39 (m, 5 H), 6.51 (d, 1 H, J = 15.8), 6.07 (dd, 1 H, J = 15.9, 8.4), 4.10 (q, 2 H, J = 7.2), 3.95 (q_{app}, 1 H, J_{app} = 6.8), 3.67 (quintuplet$_{app}$, 1 H, J_{app} = 6.1), 2.42 (t, 2 H, J = 7.4), 1.86 (q_{app}, 2 H, J_{app} = 7.2), 1.23 (t, 3 H, J = 7.2), 1.13 (t_{app}, 6 H, J_{app} = 5.7); ^{13}C NMR (CD_3CN) δ 173.6, 136.7, 131.4, 131.1, 128.6, 127.7, 126.5, 76.9, 68.9, 60.3, 31.2, 30.4, 23.5, 21.6, 14.3;

Ethyl ether 53c

^{1}H NMR (CD_3CN) δ 7.21 – 7.43 (m, 5 H), 6.53 (d, 1 H, J = 15.8), 6.20 (dd, 1 H, J = 15.8, 8.2), 4.40 (q_{app}, 1 H, J_{app} = 6.8), 4.05 (q, 2 H, J = 6.9), 3.63 (q, 2 H, J = 7.2), 2.34 (t, 2 H, J = 7.3), 1.81 – 2.20 (m, 2 H), 1.19 (t, 3 H, J = 6.9), 1.08 (t, 3 H, J = 7.2); ^{13}C NMR (CD_3CN) δ 173.9, 137.9, 132.1, 131.6, 129.5, 128.5, 127.2, 78.0, 62.3, 60.9, 31.8, 30.7, 14.6, 14.3

4.12 SYNTHETIC PROCEDURES

Synthesis of TMS-propargyl aldehyde (Table 3, entry 3)

To a solution of propargyl alcohol (5 mL, 0.086 mol, 1 equiv) in THF (100 ml) at – 78 °C was added n-butyllithium (2.72 M in hexanes, 35 mL, 0.095 mol, 1.11 equiv) to form a turbid solution. After 15 minutes, TMSCl (12 mL, 0.095 mol, 1.10 equiv) was added to form a white suspension. The reaction was stirred at – 78 °C for half an hour after which n-butyllithium (2.72 M in hexanes, 35 mL, 0.095 mol, 1.11 equiv) was added to form a pale yellow suspension. After half an hour, TMSCl (12 mL, 0.095 mol, 1.10 equiv) was added and the reaction mixture stirred at – 78 °C for 2 hours, then quenched with 0.1 N HCl (45 mL) and the mixture stirred at room temperature for 1 hour. The products were extracted into diethyl ether (3 x 40 mL). The organic layer was washed once with brine (60 mL), dried over Na_2SO_4, filtered and concentrated on a rotary evaporator without application of vacuum (bath temperature *ca* 70 °C). The crude alcohol was dissolved in methylene chloride (100 mL) and pyridinum chlorochromate (28.43, 0.131 mol, 1.54 equiv) was added portionwise at

room temperature. The reaction mixture was stirred overnight, then filtered through Celite and concentrated on a rotary evaporator without application of vacuum (bath temperature *ca* 50 °C). The residue was purified by short-path distillation (b.p. 67 – 69 °C @ 60 mm Hg; collecting flasks were cooled in a dry ice-acetone bath) to give 4.043 g of TMS-propargyl aldehdye (37 % overall yield). ^{1}H NMR ($CDCl_3$) δ 9.11 (s, 1 H), 0.21 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 176.5, 102.7, 102.1, – 1.0.

Synthesis of phenyl-propargyl aldehyde (Table 3, entry 4)

Propargyl alcohol (2.20 mL, 0.038 mol, 2.00 equiv) was added to a room temperature solution of bromobenzene (2.00 mL, 0.019 mol, 1 equiv) in t-butylamine (15 mL), followed by the addition of tetrakis(triphenylphosphine) palladium(0)[3] The resulting yellow suspension was heated to reflux for 48 hours, then cooled to room temperature and saturated NH_4Cl was added (10 mL). The products were extracted into diethyl ether (3 x 20 mL). The organic layer was washed once with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 20 % ethyl acetate in hexanes as eluent afforded 2.13 g of phenyl propargyl alcohol (85 %). ^{1}H NMR ($CDCl_3$) δ 7.24 – 7.45 (m, 5 H), 4.49 (s, 2 H), 2.46 (bs, 1 H). Pyridinum chlorochromate (9.32 g, 0.0439 mol, 2.68 equiv) was added portionwise to the above alcohol (2.13 g, 0.016 mol, 1 equiv) in methylene chloride (40 mL) at room temperature and the reaction mixture stirred overnight, filtered through Celite and concentrated. Purification of the residue by column chromatography on silica gel using 2 % ethyl acetate in toluene as eluent afforded 0.3079 g of phenyl propargyl aldehyde (15 %) along with impure fractions. ^{1}H NMR ($CDCl_3$) δ 9.41 (s, 1 H), 7.24 – 7.61 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 176.7, 133.2, 131.2, 128.7, 119.4, 95.0, 88.4.

Synthesis of hydroxyamide 56

Trimethylaluminum (2.0 M in hexanes, 2.5 ml, 5.00 mmol, 2.02 equiv) was added to a solution of diethyl amine (520 μL, 5.03 mmol, 2.03 equiv) in methylene chloride (12 mL) at room temperature. After 15 minutes, a solution of lactone **29** (0.4006 g, 2.47 mmol, 1 equiv) in methylene chloride (9 mL) was added via cannula and the reaction

mixture stirred at room temperature for 3 hours and at 40 °C for 24 hours. The reaction mixture was cooled to room temperature and 1 M HCl (10 mL) was added slowly. After gas evolution subsided, the products were extracted into methylene chloride (3 x 15 mL). The organic layer was washed once with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 70 % ethyl acetate in hexanes afforded 0.5255 g of **56** (90 %). ^{1}H NMR ($CDCl_3$) δ 7.19 – 7.36 (m, 5 H), 4.78 (quintuplet$_{app}$, 1 H, J_{app} = 3.8), 4.56 (d, 1 H, J = 4.2), 3.36 (dq$_{app}$, 2 H, J_{app} = 6.9, 5.4, 1.7), 3.22 (q, 2 H, J = 7.2), 2.44 (t, 2 H, J = 6.3), 2.03 – 2.13 (m, 2 H), 1.11 (t, 2 H, J = 7.0). ^{13}C NMR ($CDCl_3$) δ 172.8, 145.0, 128.2, 126.9, 125.7, 42.2, 40.5, 33.9, 29.6, 14.1, 12.9; LRMS calcd for $C_{14}H_{21}O_2N$ (M) 235, found 235.

Synthesis of tridentate sulfonamide 68

Pyridine (270 μL, 3.34 mmol, 3.24 equiv) was added to a suspension of aminohydroxy binaphthyl **67**[4] (0.2939 g, 1.03 mmol, 1 equiv) in methylene chloride (5 mL) at 0 °C followed by a solution of 3,5-dichloro-2-hydroxybenzenesulfonyl chloride (0.6735 g, 2.57 mmol, 2.50 equiv) in methylene chloride (4 mL) via cannula. The reaction mixture was warmed to room temperature and stirred overnight, then quenched with 1 M HCl (8 mL). The products were extracted into ethyl acetate (3 x 15 mL). The organic layer was washed once with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 30 – 60 % ethyl acetate in hexanes as eluent afforded 0.4976 g of 68 (95 %). ^{1}H NMR ($CDCl_3$) δ 7.85 – 8.07 (m, 6 H), 7.43 – 7.49 (m, 1 H), 7.15 – 7.36 (m, 6 H), 7.06 (d, 1 H, J = 8.2), 6.89 (s, 1 H), 6.67 (d, 1 H, J = 8.4), 4.65 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 151.3, 148.6, 136.6, 134.4, 133.1, 132.9, 132.7, 132.1, 131.6, 130.7, 129.3, 129.0, 128.4, 128.3, 127.6, 126.6, 126.4, 125.8, 125.7, 125.1, 124.2, 123.4, 122.2, 117.6, 112.5.

Synthesis of bidentate sulfonamide 71

Pyridine (400 μL, 4.95 mmol, 6.20 equiv) was added to a suspension of aminohydroxy binaphthyl **67**[4] (0.2276 g, 0.798 mmol, 1 equiv) in methylene chloride

(2 mL) at 0 °C followed by a solution of p-toluenesulfonyl chloride (0.3775 g, 1.98 mmol, 2.48 equiv) in methylene chloride (2 mL) via cannula. The reaction mixture was warmed to room temperature and stirred for 29 hours, then quenched with 1 M HCl (5 mL). The products were extracted into ethyl acetate (3 x 10 mL). The organic layer was washed once with brine (15 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 30 – 50 % diethyl ether in hexanes in eluent afforded 0.3037 g of **71** (87 %). ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1 H, J = 8.9), 7.85 – 7.99 (m, 4 H), 6.99 – 7.46 (m, 10 H), 6.62 (d, 1 H, J = 8.4), 6.45 (s, 1 H), 4.50 (s, 1 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.8, 144.0, 136.0, 134.7, 132.9, 131.5, 131.2, 130.6, 129.6, 129.3, 129.2, 128.4, 128.2, 127.6, 127.5, 127.2, 125.6, 125.2, 123.9, 123.7, 119.2, 118.3, 117.8, 111.9, 21.5.

Reduction of 2-hydroxyphenylacetic acid

A solution of borane in tetrahydrofuran (1 M solution, 140 mL, 0.140 mol, 4.12 equiv) was added via addition funnel to a 0 °C solution of 2-hydroxyphenylacetic acid (5.174 g, 0.034 mol, 1 equiv) in tetrahydrofuran (40 mL) in a three-necked 500 mL round bottom flask. After addition was complete and gas evolution subsided, the reaction mixture was warmed to room temperature and stirred for 1.5 hours. 1M NaOH (50 mL) was added at 0 °C via the addition funnel. After gas evolution subsided, the reaction mixture was transferred to a 1 L Erlenmyer flask and 1 M NaOH (250 mL) was added at 0 °C. The contents were stirred at room temperature for 45 minutes, then acidified with concentrated HCl. The products were extracted into diethyl ether (3 x 100 mL). The organic layer was washed once with brine (150 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 30 – 50 % ethyl acetate in hexanes as eluent afforded 4.40 g of 2-hydroxyphenylethylalcohol (94 %). ^{1}H NMR ($CDCl_3$) δ 8.12 (bs, 1 H), 7.03 – 7.16 (m, 2 H), 6.81 – 6.88 (m, 2 H), 3.90 (t, 2 H, J = 5.4), 2.86 (t, 2 H, J = 5.4), 3.31 (bs, 1 H). ^{13}C NMR ($CDCl_3$) δ 155.0, 130.9, 128.2, 126.5, 120.5, 116.7, 64.3, 34.5.

Bis-tosylation of 2-hydroxyphenylethylalcohol

Triethyl amine (16 mL, 0.114 mol, 3.60 equiv) was added to a 0 °C solution of 2-hydroxyphenylethylalcohol (4.39 g, 0.031 mol, 1 equiv) in methylene chloride (40 mL). After 10 minutes, a solution of p-toluenesulfonyl chloride (18.29 g, 0.096 mol, 3.02 equiv) in methylene chloride (40 mL) was added. The reaction mixture was stirred at room temperature for 5 hours after which it was cooled to 0 °C and quenched with 1 M HCl (100 mL). The products were extracted into ethyl acetate (3 x 75 mL). The organic layer was washed once with brine (60 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 30 – 50 % ethyl acetate in hexanes as eluent afforded 13.44 g of desired material (95 %). ^{1}H NMR ($CDCl_3$) δ 7.66 (dd, 4 H, J = 7.9), 7.28 (dd, 4 H, J = 11.6), 7.10 – 7.14 (m, 3 H), 6.91 – 6.96 (m, 1 H), 4.11 (t, 2 H, J = 6.9), 2.81 (t, 2 H, J = 6.9), 2.43 (s, 1 H), 2.40 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 148.4, 146.1, 145.1, 133.2, 133.1, 131.8, 130.3, 130.2, 130.1, 128.6, 128.1, 127.6, 122.8, 69.4, 30.0, 22.1, 21.9.

Synthesis of iodide 73

Sodium iodide (12.30 g, 0.082 mol, 3.19 equiv) was added portionwise to a 0 °C solution of the bis-tosylate of 2-hydroxyphenylethylalcohol (11.49 g, 0.025 mol, 1 equiv) in methyl ethyl ketone (130 mL). The resulting orange solution was heated to reflux for 40 hours, then cooled to room temperature. The solvent was evaporated and the reaction mixture was partioned between ethyl acetate (50 mL) and water (50 mL). The products were extracted into ethyl acetate (3 x 30 mL). The organic layer was washed once with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 10 % ethyl acetate in hexanes as eluent afforded 10.29 g of **73** (quant.). ^{1}H NMR ($CDCl_3$) δ 7.75 (d, 2 H, J = 6.7), 7.34 (d, 2 H, J = 7.9), 7.18 – 7.22 (m, 3 H), 7.04 – 7.17 (m, 1 H), 3.18 (t, 2 H, J = 7.7), 3.00 (t, 2 H, J = 7.4), 2.44 (s, 3 H) ^{13}C NMR ($CDCl_3$) δ 147.6, 145.5, 133.6, 132.7, 130.5, 129.9, 128.14, 128.12, 127.1, 122.5, 34.4, 21.6, 2.9.

Synthesis of alcohol 76

Potassium carbonate (8.60 g, 0.062 mol, 3.2 equiv) was added to a 0 °C solution of 2-hydroxyphenylacetic acid (2.97 g, 0.195 mol, 1 equiv) in DMF (20 mL) and MeOH (10 mL). Benzyl bromide (8mL, 0.673 mol, 3.4 equiv) followed by sodium iodide (cat.) was added to the resulting suspension. The reaction mixture was warmed to room temperature, then heated at 85 – 90 °C for 43 hours. The reaction was quenched with water (75 mL) and the products extracted into ethyl acetate (3 x 50 mL). The organic layer was washed once with brine (60 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 10 % ethyl acetate in hexanes as eluent afforded 4.57 g of dibenzylated product with some impurities. To a solution of this material (4.75 g, 0.137 mol, 1 equiv) in toluene (35 mL) at - 78 °C was added a solution of diisobutylaluminum hydride in toluene (1.5 M in toluene, 40 mL, 0.060 mol, 4.3 equiv). The reaction was quenched after 2.5 hours at –78 °C with a solution of sodium/potassium tartrate (0.5 M, 300 mL). The mixture was warmed to room temperature and stirred overnight. The products were extracted into ethyl acetate (3 x 100 mL). The organic layer was washed once with brine, dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 10 – 30 % ethyl acetate in hexanes as eluent afforded 3.093 g of **76** (70 % overall yield). ^{1}H NMR ($CDCl_3$) δ 7.17 – 7.44 (m, 7 H), 6.90 – 6.95 (m, 2 H), 5.08 (s, 2 H), 3.85 (t, 2 H, J = 6.4), 2.96 (t, 2 H, J = 6.4); ^{13}C NMR ($CDCl_3$) δ 156.7, 137.0, 131.0, 128.6, 127.9, 127.8, 127.3, 127.2, 126.9, 120.9, 111.8, 70.0, 62.8, 34.2.

Mitsonobu procedure for the synthesis of 77

To a solution of alcohol **76** (0.0563 g, 0.247 mmol, 1 equiv) in tetrahydrofuran (5 mL) was added sequentially Binol (0.0715 g, 0.249 mmol, 1.01 equiv), triphenyl phosphine (0.0696 g, 0.265 mmol, 1.08 equiv) and diethylazodicarboxylate (40 μL, 0.254 mmol, 1.03 equiv). The reaction mixture was stirred for 10 hours at room temperature after which triphenyl phosphine (0.0320 g, 0.122 mmol, 0.49 equiv) and DEAD (20 μL, 0.127 mmol, 0.51 equiv) were added and the reaction mixture stirred overnight. The volatile material was evaporated and the residue was purified by column

chromatography on silica gel using 2 % ethyl acetate in toluene to afford 0.1143 g of **77** (93 %). ^{1}H NMR ($CDCl_3$) δ 7.79 – 7.94 (m, 4 H), 7.04 – 7.40 (m, 14 H), 6.86 (d, 1 H, J = 8.2), 5.02 (s, 1H), 4.92 (s, 1 H), 4.16 – 4.26 (m, 2 H), 2.89 – 2.91 (m, 2 H), 1.66 (bs, 1 H); ^{13}C NMR ($CDCl_3$) δ 156.5, 155.2, 151.2, 137.1, 134.0, 133.8, 131.2, 130.7, 129.6, 129.3, 129.1, 128.6, 128.0, 127.9, 127.8, 127.6, 127.5, 127.1, 126.2, 125.0, 124.9, 123.9, 123.1, 120.7, 117.5, 115.8, 115.3, 115.1, 111.3, 69.9, 68.6, 30.5.

Synthesis of diol 72b

Palladium (II) hydroxide on carbon (0.060 g) was added to a solution of alcohol **77** (0.1135 g) in ethanol (10 ml) in a Schlenk flask fitted with a hydrogen balloon. The flask was vacuum degassed twice. The reaction mixture was stirred at room temperature for 15 hours, then filtered through a plug of Celite and concentrated. Purification of the residue by column chromatography on silica gel using 15 – 40 % acetone in hexanes as eluent afforded 0.0599 g of **72b** (64 %). ^{1}H NMR ($CDCl_3$) δ 7.87 – 8.01 (m, 4 H), 7.16 – 7.43 (m, 7 H), 6.96 – 7.01 (m, 2 H), 6.82 (dd, 1 H, J = 7.4, 1.7), 6.69 (dt, 1 H, J = 7.4, 1.2), 6.55 (d, 1 H, J = 7.9), 5.31 (s, 1 H), 4.85 (s, 1 H), 4.13 – 4.29 (m, 2 H), 2.68 – 2.79 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 154.8, 154.3, 151.3, 133.8, 133.6, 130.9, 130.5, 130.1, 129.8, 129.2, 128.1, 128.0, 127.8, 127.3, 126.4, 125.2, 125.0, 124.5, 123.3, 120.5, 117.6, 116.9, 116.5, 115.6, 114.4, 65.8, 31.0; LRMS calcd for $C_{28}H_{22}O_3$ (M) 406, found 406.

Synthesis of sulfide 81

A solution of hydroxythiol **80** (0.0933 g, 0.308 mmol, 1 equiv) in DMF (2 mL) was added via cannula to a 0 °C suspension of sodium hydride (60 % dispersion in oil, 0.013 g, 0.325 mmol, 1.05 equiv, pre-rinsed with hexanes) in DMF (2 mL). The resulting yellow suspension was warmed to room temperature and stirred for 1.5 hours after which it was cooled to 0 °C and a solution of the iodide **73** (0.124 g, 0.308 mmol, 1.00 equiv) in DMF (4 mL) was added via cannula. The reaction mixture was stirred for 1 hour at room temperature followed by 20 hours at 80 °C. 1M HCl (15 mL) was added and the products extracted into ethyl acetate (3 x 10 mL). The organic layer was washed once with brine (10 mL), dried over Na_2SO_4, filtered and concentrated.

Purification of the residue by column chromatography on silica gel using 15 – 30 % diethyl ether in hexanes as eluent afforded 0.058 g of **81** (33 %). ^{1}H NMR ($CDCl_3$) δ 8.07 (d, 1 H, J = 8.7), 7.87 – 7.96 (m, 3 H), 7.74 (d, 1 H, J = 8.9), 7.61 (d, 2 H, 8.4), 7.46 (td, 1 H, J = 1.2, 7.4$_{avg}$), 7.03 – 7.34 (m, 11 H), 6.94 (d, 1 H, J = 8.4), 4.85 (s, 1 H), 2.94 – 3.02 (m, 2 H), 2.60 – 2.67 (m, 2 H), 2.33 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.9, 147.9, 145.4, 136.7, 133.5, 133.3, 133.2, 132.7, 131.9, 130.8, 130.3, 129.9, 129.7, 129.1, 128.9, 128.3, 128.2, 128.1, 127.8, 127.4, 127.1, 126.7, 125.8, 125.1, 124.7, 124.4, 123.5, 122.4, 117.6, 116.9, 31.9, 30.4, 21.6; LRMS calcd for $C_{28}H_{22}O_2S$ (M) 422, found 422.

Synthesis of sulfide 82

n-Butyllithium (350 μL, 0.924 mmol, 4.11 equiv) was added to a solution of **81** (0.1297 g, 0.225 mmol, 1 equiv) in toluene (4 mL). The reaction mixture was stirred for 14 hours, then quenched with 1M HCl (5 mL). The products were extracted into ethyl acetate (3 x 5 mL). The organic layer was washed once with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. Purification of the residue by column chromatography on silica gel using 30 – 50 % ether in hexane as eluent afforded 0.0812 g of **82** (85 %). ^{1}H NMR ($CDCl_3$) δ 7.79 – 7.96 (m, 4 H), 7.73 (d, 1 H, J = 8.9), 6.94 – 7.44 (m, 9 H), 6.79 (dd, 1 H, J = 7.1, 6.7), 6.65 (d, 1 H, J = 7.7), 4.94 – 5.05 (2 broad singlets, 2 H), 3.02 – 3.21 (m, 2 H), 2.80 – 2.86 (m, 2 H), 2.83 (t_{app}, 2 H, J_{app} = 7.3); ^{13}C NMR ($CDCl_3$) δ 153.5, 150.8, 137.2, 133.5, 133.3, 131.7, 130.5, 130.3, 129.6, 129.2, 128.5, 128.2, 128.1, 127.8, 127.4, 126.8, 126.5, 125.7, 125.0, 124.4, 123.5, 120.9, 117.6, 116.9, 115, 5, 31.9, 30.8; LRMS calcd for $C_{28}H_{22}O_2S$ (M) 422, found 422.

Synthesis of sulfide 84

To a room temperature solution of alcohol **76** (0.1064 g, 0.466 mmol, 1 equiv) in tetrahydrofuran (4 mL) was added diphenyl disulfide (0.1530 g, 0.701 mmol, 1.50 equiv) followed by n-tributylphosphine (180 μL, 0.721 mmol, 1.55 equiv). The reaction mixture was stirred at room temperature for 18 hours and at reflux for 15 hours after which the volatile material was removed *in vacuo*. Purification of the

residue by column chromatography on silica gel using 30% methylene chloride in hexanes as eluent afforded 0.1204 g of **84** (81 %). ^{1}H NMR ($CDCl_3$) δ 7.14 – 7.44 (m, 12 H), 6.92 – 6.97 (m, 2H), 5.11 (s, 1 H), 3.22 (dd, 2 H, J = 6.4, 4.9), 3.04 (dd, 2 H, J = 6.6, 4.9); ^{13}C NMR ($CDCl_3$) δ 156.6, 137.1, 136.6, 130.5, 128.8, 128.7, 128.6, 128.5, 127.9, 127.8, 127.3, 125.4, 120.8, 111.6, 69.9, 32.9, 31.2.

Literature procedures

Bis-oxazoline **23**, amino alcohol **34**, TADDOL derivative used to prepare titanium triflate **59b** and bis-sulfonamide **63** were prepared according to literature procedure.[5]

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