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The Design and Synthesis of C_3 Symmetric Ligands for Lanthanide Lewis Acid Catalysis of the Inverse Demand Hetero Diels-Alder Reaction

by

Laurel L. Clouston
B.Sc., University of Guelph, 1993

A Dissertation Submitted in Partial Fulfilment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY

in the Department of Chemistry

We accept this dissertation as conforming
to the required standard

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ABSTRACT

The inverse demand hetero Diels-Alder reaction has been shown to be catalysed by commercially available, air-sensitive lanthanide Lewis acid catalysts such as $Yb(fod)_3$. To date there have been no reported examples of enantioselective Lewis acid catalysed reactions of ethyl vinyl ether with crotonaldehyde, the inverse demand hetero Diels-Alder reaction of interest. This Diels-Alder reaction yields dihydropyran products which are key in the synthesis of a number of natural product target molecules, such as carbohydrates. The lack of stereospecificity achieved with known chiral NMR shift reagents has been attributed to fluxional behaviour of the ligands on the large lanthanide metal centre. This lack of conformational rigidity was proposed to be controlled by the use of sterically demanding C_3 symmetric multidentate ligand systems. By carefully designing a suitable ligand system the binding of the crotonaldehyde moiety in the Lewis acid catalysed reaction was anticipated to occur with facial selectivity, resulting in enantioselective Diels-Alder products.

It was determined that lanthanide complexes of fluorinated ß-diketone ligands with sufficiently low pKa's effectively catalyse the desired inverse demand hetero Diels-Alder reaction. These functionalities were incorporated into a multidentate, achiral, C_3 symmetric ligand system which upon lanthanide complexation was shown to be an air-stable efficient Lewis acid catalyst. Two chiral C_3 symmetric ligand systems were also prepared but were shown to be unsuitable for lanthanide substitution due to insufficiently robust functionalities present in the ligand framework, such as sulfonyl esters and

Molecular modelling studies of these ligand systems reveal that the incorporation of camphor into the ligand framework is ideal for the preparation of a facially selective aldehyde binding site. Thus, concluding work probed other possible ligand functionalities which would result in camphor containing, chiral, C_3 symmetric ligand systems that are stable as lanthanide Lewis acid complexes.

This new class of ligand promises to be of interest as chiral C_3 symmetric ligand systems for substitution on lanthanide metal centres have yet to be reported. This work summarises several useful synthetic strategies for the preparation of chiral C_3 symmetric ligands in multigram quantities. The application of these higher order symmetry ligands in enantioselective catalysis remains an important area of research.

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acac	deprotonated acetylacetone (2,4-pentanedione)
AIBN	2,2'-azobis(isobutyronitrile)
Ar	aryl
BINOL	1,1'-bi-2-napthol
CAN	ceric ammonium nitrate
CI MS	chemical ionisation mass spectrum
Cl_3acac	deprotonated 1,1,1-trichloro-2,4-pentanedione
DAST	diethylaminosulfur trifluoride
DCC	dicyclohexylcarbodiimide
de	diastereomeric excess
DMAP	4-dimethylaminopyridine
ee	enantiomeric excess
EI MS	electron impact mass spectrum
F_3acac	deprotonated 1,1,1-trifluoro-2,4-pentanedione
F_3trac	deprotonated tris(3-aza-4-methyl-6-oxo-7,7,7-trifluorohept-4-en-1-yl)amine
F_6acac	deprotonated 1,1,1,5,5,5-hexafluoro-2,4-pentanedione
FAB MS	fast atom bombardment mass spectrometry
fod	2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedionato
hatren	deprotonated tris(3-aza-4-methyl-5-(2'-phenol))amine
hfc	heptafluorocamphorato

HMPA	hexamethylphosphoramide
HOMO	highest occupied molecular orbital
IDHDA	inverse demand hetero Diels-Alder
LAH	lithium aluminum hydride
LDA	lithium di-isopropylamide
LSIMS	liquid secondary ion mass spectrometry
LUMO	lowest unoccupied molecular orbital
ms	molecular sieves
NBS	N-bromosuccinimide
OTf, triflate	trifluoromethylsulfonate
PDC	pyridinium dichromate
rt	room temperature
salen	N,N'-bis(salicylidene)-1,2-ethylenediamine
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS-CF_3	trifluoromethyl-trimethylsilane
Tp	tris(pyrazolyl) borate
trac	deprotonated tris(3-aza-4-methyl-6-oxo-hept-4-en-1-yl)amine
tren	tris(2-aminoethyl)amine
y	yield

ACKNOWLEDGEMENTS

The people to thank are many; to them all I owe a debt of gratitude. This learning experience has included so much more than chemistry . . . I am thankful for the many lessons. In particular I wish to thank my supervisors Dave Berg and Claude Spino for providing the opportunity. Support, both academic and moral, has been invaluable and the list of thanks is long here. In particular I want to thank my husband John Clouston and my parents Bill and Kathy Schafer; my friends Lynn Cameron and Liz MacKay; UVic faculty members Cornelia Bohne and Tom Fyles; fellow researchers Sarah Monahan, Lawrence Lee, Patrick Shao and Mark Kleinman; and UVic staff Susanne Reiser, Chris Greenwood and Dave Berry. And finally, this work would not have been possible without the financial support of NSERC and the University of Victoria. This list is abbreviated, very abbreviated . . . to the many who remained unnamed, you are certainly not forgotten.

After all is said and done, I understand why they call it a doctor of philosophy.

CHAPTER 1: Introduction

1.1 Lanthanides in Organic Synthesis

1.1.1 General Properties of Lanthanides

The lanthanides are the 14 elements which follow lanthanum in the periodic table, from cerium (58) to lutetium (71). They are commonly known as the f-block elements, since they possess 4f electrons which distinguish them from the transition metals. Both yttrium and lanthanum, although technically members of group 3, are informally considered to be included in this class of compounds because of their similar physical characteristics such as available oxidation states and ionic radii.[1]

All of these elements are most stable in a +3 oxidation state, with the +2 and +4 states being available to some elements, such as europeium, samarium, ytterbium (+2) and cerium (+4). The redox properties of the various metals are mostly due to electronic factors imparted by the partially filled f orbitals. However, oxidation behaviour of the various metals can be somewhat influenced by the ligands attached to the element, as well as solvent media.[2]

The sequential filling of the 4f valence orbitals imparts some unique properties to the lanthanides which distinguish them from the transition elements. In particular, the poor radial extension of the 4f orbitals, beyond the filled 5s and 5p shells results in very little covalent overlap with ligand orbitals and essentially ionic bonding. This bonding

description is supported by spectroscopic and magnetic evidence, where for a given lanthanide ion these properties do not vary substantially with the nature of the ligand.[3]

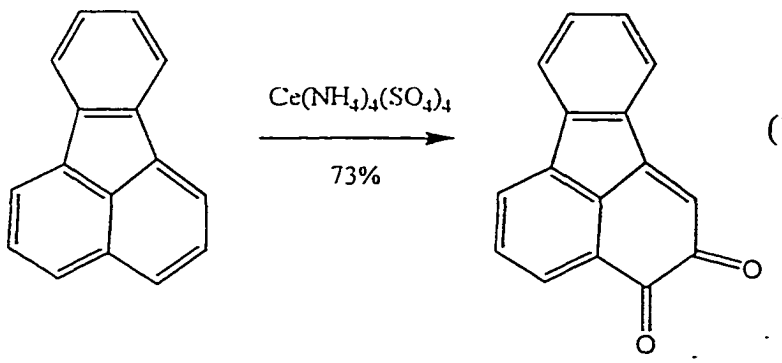
The ionic radii of the lanthanides are larger than those of the d-block transition elements, resulting in coordination numbers of up to 12 with 7 to 9 ligand binding sites being the most common. The poor screening of the nuclear charge by the 4f electrons causes the "lanthanide contraction" where the ionic (atomic) radius decreases as the atomic number increases across the series (La^{3+} = 1.17 Å to Lu^{3+} = 1.00 Å with a coordination number of 6).[2] Therefore, within the lanthanide series there is a wide range of size dependent chemistry and structures available for trivalent ions.

Lanthanides, along with yttrium and lanthanum are collectively called the "rare earths", although this is a clear misnomer as they are abundant in the earth's crust. For example, cerium (the most abundant) is more abundant than cobalt, tin and zinc while thulium (the least abundant) is more abundant than silver. They are found in many ores around the world. Each element is separated on an industrial scale to make the lanthanides commercially available as metallic powders, oxides and other salts at moderate prices.

Another interesting feature of the lanthanides is their extremely low toxicity, making them excellent candidates for catalysis, even on a commercial scale. It has been established that lanthanide salts display levels of toxicity similar to sodium chloride. Clearly the incorporation of these compartively inexpensive metals into improved organic synthetic methodologies would be an improvement from the commonly used heavy metals.

1.1.2 Lanthanides in Synthesis

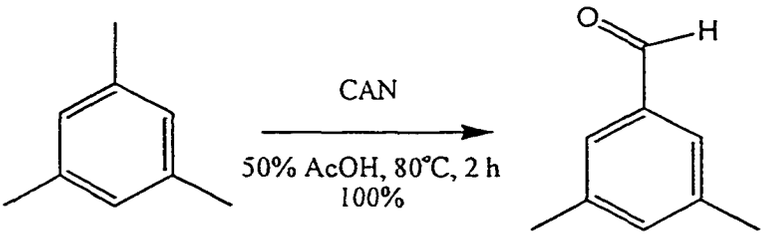
Lanthanides are useful for both functional group transformations and carbon-carbon bond forming reactions. The different physical and chemical properties of the lanthanides permits their use in a wide range of synthetic protocols where their efficiency is unmatched by other methodologies. These advantages have encouraged an explosive growth in the area of lanthanide mediated organic chemistry in the past 15 years. In response to this surge in research efforts, a number of excellent reviews on various aspects of lanthanide chemistry applied to organic synthesis have appeared.[2, 4, 5] Here, a general overview of the usefulness of lanthanides for a variety of functional group transformations and carbon-carbon bond forming reactions will be presented, including a more detailed account of the usefulness of lanthanide Lewis acid catalysts in the Diels-Alder reaction.



(1)

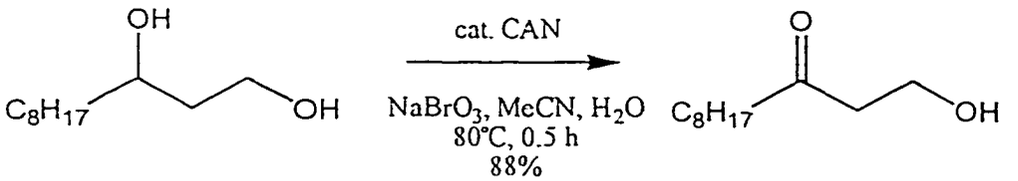
Within the scope of functional group transformations, lanthanides, and more specifically cerium (IV) salts, (such as ceric ammonium nitrate (CAN) and ceric ammonium sulfate) have been used extensively for a variety of oxidative transformations.[6] Newer developments in oxidative chemistry using the lanthanides have established milder

protocols using alternative cerium salts in catalytic amounts.[4] The oxidation of unsubstituted aromatic molecules with Ce(IV) provides an efficient route into quinones (eq 1),[6, 7] while substituted arenes undergo selective side chain oxidation yielding aldehyde or ketone substituted arenes (eq 2).[8-10]



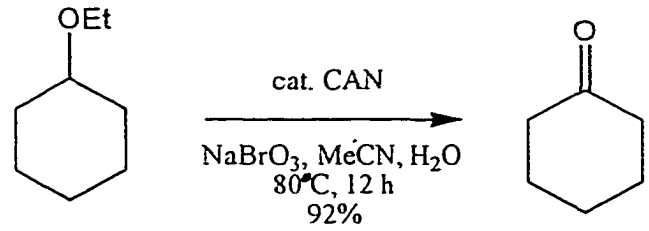
(2)

Alcohol oxidation products are exceedingly dependent on substrate structure with typical primary alcohols being virtually unreactive in the presence of Ce(IV) oxidants. Consequently, cerium reagents exhibit exceptional selectivity in the oxidation of secondary alcohols in the presence of primary alcohols (eq 3).[11, 12]



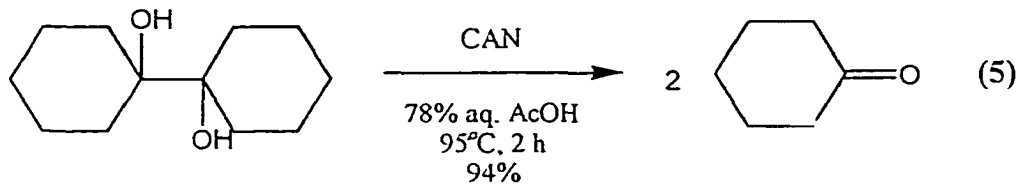
(3)

The oxidation of simple ethers results in direct conversion to aldehydes or ketones with catalytic amounts of CAN in the presence of sodium bromate (eq 4).[13]

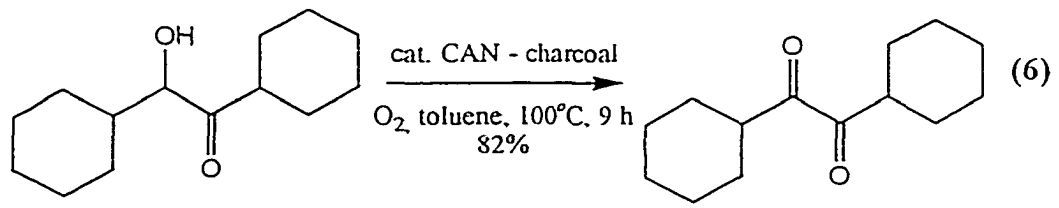


(4)

Both *cis* and *trans* vicinal diols undergo effective oxidative cleavage in the presence of Ce(IV) (eq 5),[14] while α-hydroxy ketones are oxidized to vicinal dicarbonyl products, without cleavage (eq 6).[4]

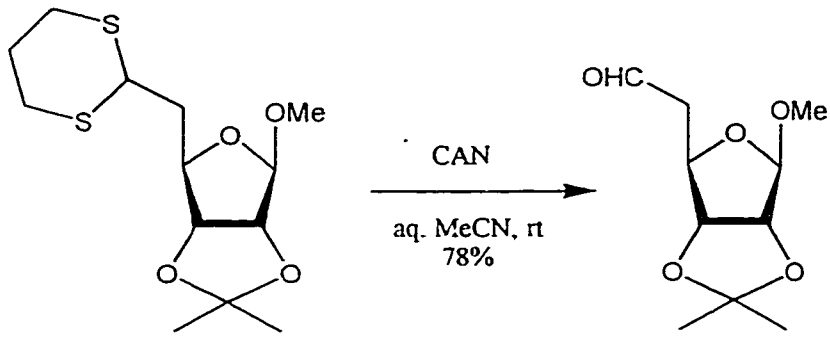


(5)



(6)

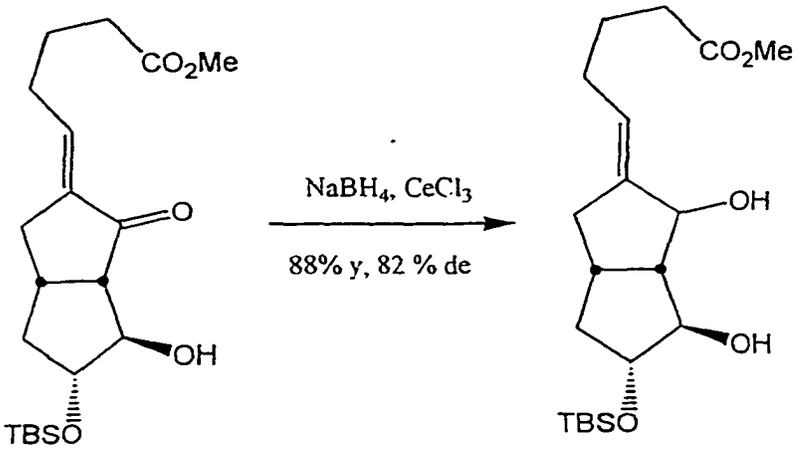
Another area where the selectivity of the cerium salts is advantageous is in the deprotection of 1,3-dithianes. These compounds can be deprotected to yield the desired carbonyl group without affecting other sensitive functionalities, such as acetals (eq 7).[15]



(7)

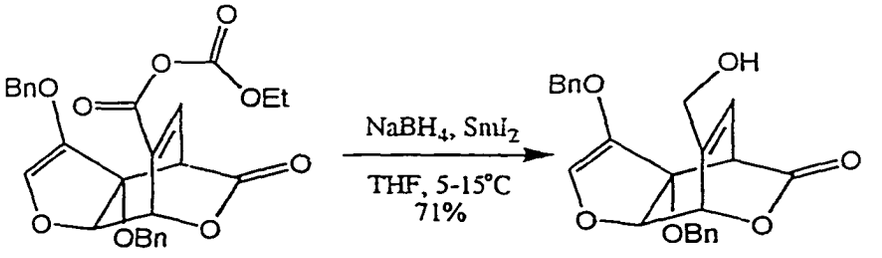
Selective, mild catalytic oxidation is an ongoing area of research interest with other lanthanide metals as well, where both ytterbium and samarium salts have been used in isolated examples.[5] Equations 1-7 are just a few interesting examples of lanthanide mediated oxidations that display unique and important selectivity for organic synthesis.

Lanthanide metals and metal salts have also been used effectively as selective reducing agents, often under very mild reaction conditions. One of the first practical uses of lanthanide reductants, such as ytterbium, was in dissolving metal reductions.[16] In this case ytterbium metal is used as an alternative to alkali metals as an electron source for Birch-type reductions. Although the lanthanides displayed no unique reactivity, the ease of handling the metals and the avoidance of strongly basic hydroxides in the workup were viewed as practical advantages.[4] Also, samarium diiodide has been established as a mild, ether soluble one electron reducing agent with many reduction applications (*vide infra*).[2, 4, 5]



(8)

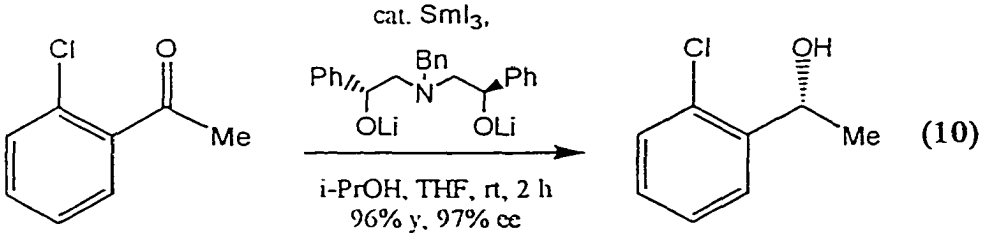
Among the most widely used lanthanide reduction methodolcgies is the Luche protocol for the selective reduction of conjugated aldehydes and ketones to allylic alcohols (eq 8).[17-19] As is shown in Equation 8, the Luche procedure exhibits excellent chemoselectivity, even in the presence of a variety of sensitive functional groups.[4] Further selectivity is exhibited where ketones and conjugated aldehydes are reduced in preference to saturated aldehydes, and under appropriate reaction conditions, the combination of lanthanide salts and hydride reducing agents is useful for selective reduction of anhydrides (eq 9) and carboxylic acid chlorides.[20, 21] Even with saturated ketones the Luche procedure often provides improved yields and/or diastereoselectivies over other reduction protocols.[4]



(9)

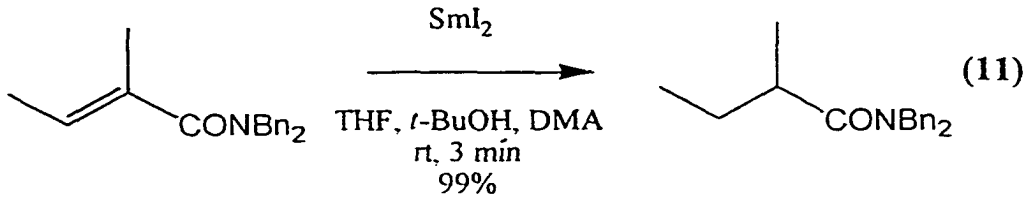
Samarium(II) itself provides considerable chemoselectivity, where carboxylic acids and esters remain unaffected while aldehydes react very rapidly to yield primary alcohols. Because ketones react more slowly, selective reduction of aldehydes in the presence of ketones is readily achieved.[22] Stereochemical control of these reductions is a keen area of interest and ongoing research.

Lanthanide alkoxides have been shown to be effective catalysts for Meerwein-Pondorf-Verley type reductions (*vide infra)*. The lanthanide reduction protocol is very mild and tolerant of a wide range of functional groups, while displaying catalytic activity up to 1000 times more efficient than known aluminum alkoxide catalysts .[23] There has also been effective enantioselective versions of this reduction reported for a limited number of substrates (eq 10) using the *in situ* generation of a chiral samarium catalyst.[24]



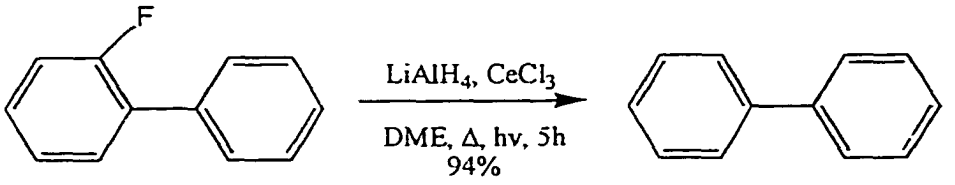
(10)

Samarium diiodide, in the presence of a proton source is also very selective for conjugate reduction of α,ß-unsaturated carboxylic acids, esters and amides (eq 11).[22]



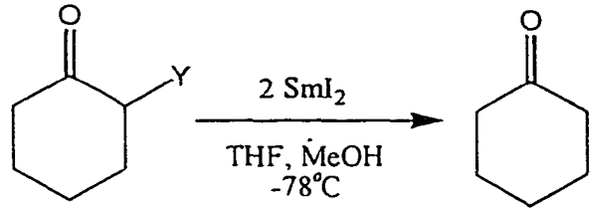
(11)

Several different lanthanide-based systems have been developed for the reduction of organic halides. Alkyl and aryl halides, including fluorides, are readily reduced by $LiAlH_4/CeCl_3$ (eq 12), providing corresponding hydrocarbons in high yields,[25] while alkyl halides are readily reduced by SmI_2.[4]



(12)

α-Haloketones are readily reduced to unsubstituted ketones in aqueous media by treatment with cerium(III) sulfate and NaI,[26] while SmI_2 can reduce a wide range of α-heterosubstituted ketones under extremely mild conditions (eq 13).[27, 28] Even hydroxyl groups are reductively cleaved under these conditions, providing a useful entry to unsubstituted ketones.[29, 30]

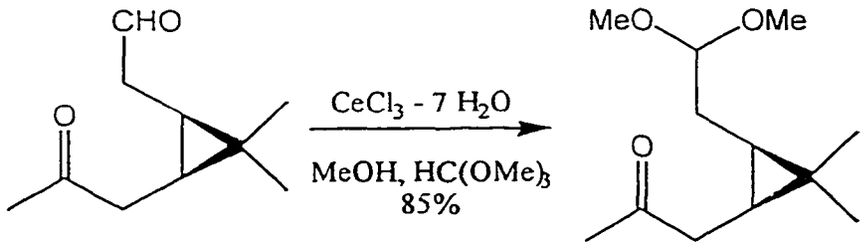


(13)

Y = Cl, SPh, S(O)Ph, SO_2Ph
yields 100 - 64%

Clearly samarium diiodide possesses a broad reduction spectrum with interesting and useful selectivity. Equations 8 - 13 outline some of the more synthetically diverse examples of lanthanides within organic synthesis, and only represent some of the potential applications of lanthanides to date. A noticeable absence within these examples is the development of enantioselective protocols. Another point of interest is the fact that for all sited examples, the reactions and reagents are of undefined mechanism and structure as they are prepared *in situ*.

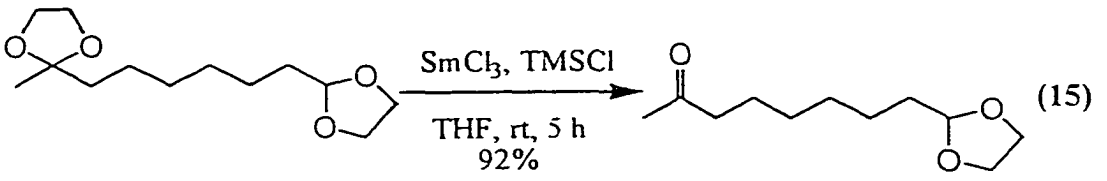
In addition to redox functional group transformations, several lanthanide Lewis acid catalysed reactions have been established. Among the most commonly used is the lanthanide salt promoted acetalization reactions. These procedures boast mild reaction conditions, excellent stereoretention (when chiral substrates are used) and chemoselectivity (eq 14) with minimal side reactions.[4]



(14)

In a similar manner, thioacetals are also easily generated using lanthanide salt catalysis.[31]

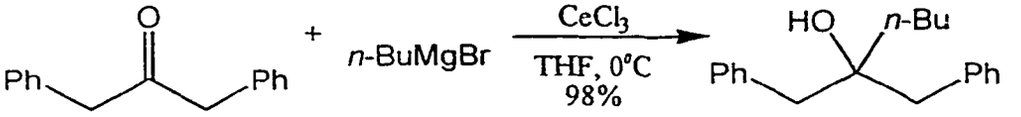
With respect to cleavage of protected carbonyl units, lanthanide salts have been used in conjunction with chlorotrimethylsilane to promote selective cleavage of ketals, even in the presence of acetals (eq 15).[32]



(15)

Another significant advantage to this protocol is the fact that other acid labile protecting groups are not affected by the reaction conditions required.

Lanthanide reagents have been used extensively in selective carbon-carbon bond formations. In particular, lanthanides have been established as extremely useful in many types of carbonyl addition reactions. Organocerium reagents react efficiently with aldehydes and ketones, providing alcohols in yields that are often superior to those reported utilizing Grignard or organolithium reagents. Particularly impressive is the ability of organocerium reagents to effect carbonyl addition to highly enolizable substrates (eq 16).[4] Organocerium reagents have been shown to be very helpful in highly hindered systems where traditional organomagnesium or organolithium reagents show reduced yields.[33, 34]

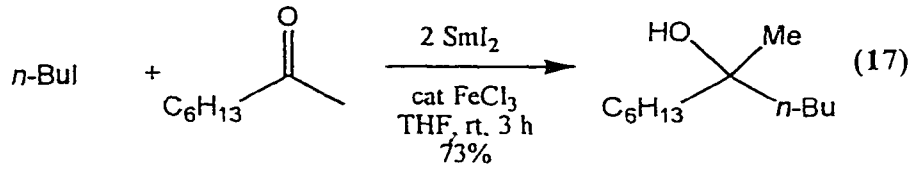


(16)

Generally organoceriums provide higher yields of 1,2-carbonyl addition products in reactions with conjugated aldehydes and ketones than their lithium and magnesium counterparts. In fact, it is rare to find functionalized ketones or aldehydes for which organoceriums do not provide higher yields of carbonyl addition products, regardless of the nature of the substrate.

Stereoselective versions of cerium mediated nucleophilic additions to carbonyl groups have been carried out,[35, 36] but the sense and magnitude of achievable diastereoselectivities has not been systematically investigated. However, it is clear that asymmetric induction is highly dependent upon both the electrophilic and nucleophilic substrates, as is observed with corresponding organolithiums or organomagnesiums. Organoytterbium triflates display even further enhanced diastereoselectivies with respect to chiral aldehydes and ketones, and are among the highest reported for addition of any organometallic reagent to carbonyl substrates.[37]

Samarium(II) complexes have proven highly effective for promoting Barbier-type reactions between aldehydes or ketones and a variety of organic halides.[2, 4, 5] Typically these reactions required heating for 8 to 12 hours, but here the use of SmI_2 with $FeCl_3$ in catalytic quantities promotes addition reactions that proceed through to completion at room temperature within a few hours (eq 17).[4]

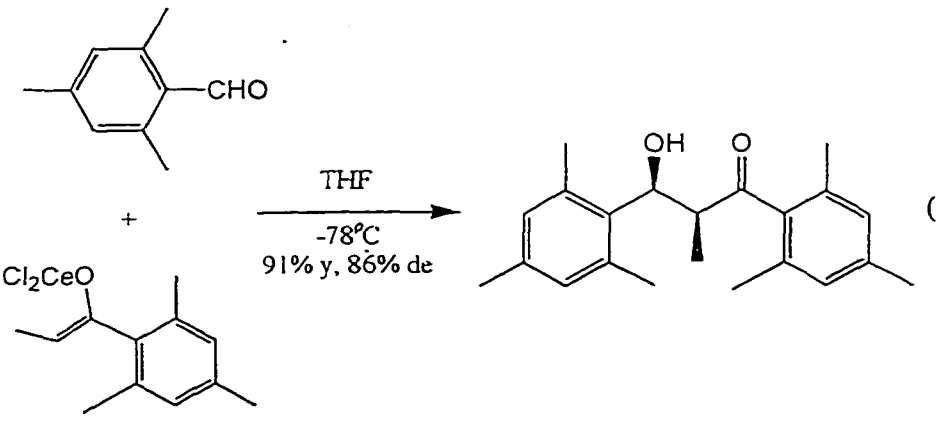


(17)

Dicyclopentadienylsamarium also permits efficient Barbier coupling reactions with very mild conditions, even for substrates which are only moderately successful with the SmI_2 protocol.[38]

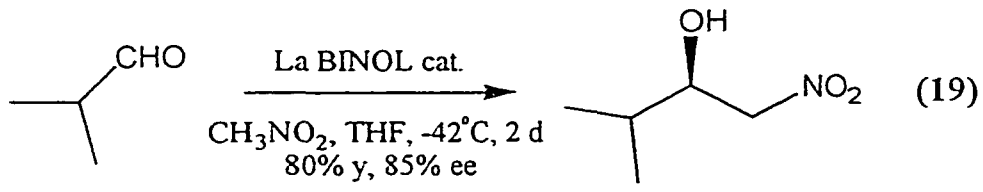
The samarium(II) promoted Barbier type reactions have been carried out in an intramolecular fashion as well, leading to bicyclic and/or multifunctionalized products.[4] Unfortunately the sense and magnitude of stereoselectivity achievable by employing SmI_2 as a reductant with other substrates is fairly unpredictable and must be determined for each individual class of substrates.

Lanthanides play a key role in several different aldol and Reformatsky-type protocols. In one of the earliest reported methods, cerium enolates derived from lithium enolates and $CeCl_3$ were found to undergo aldol condensations with sterically demanding aldehydes and ketones (eq 18).[4, 39]



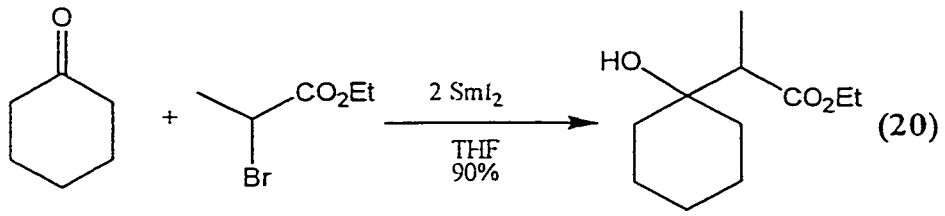
(18)

Ketone electrophiles incapable of undergoing aldol reactions with lithium ester enolates produce the desired products in nearly quantitative yields when a cerium enolate is employed.[40] More recently lanthanide triflates have been reported to be useful as water-tolerant Lewis acids for the aqueous aldol reaction of silyl enolates with aldehydes.[41-43] Lanthanides have also been used for the *in situ* generation of chiral catalysts (using BINOL as a chiral ligand) for the asymmetric nitroaldol reaction (eq 19).[44, 45]



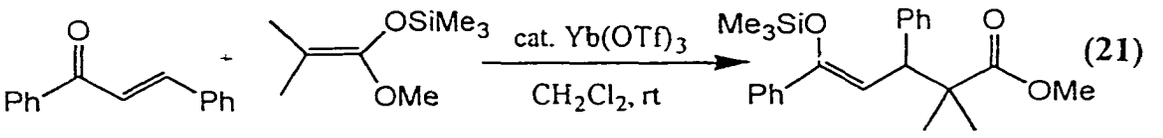
(19)

Reformatsky-type coupling reactions can be carried out between α-halo esters and ketone electrophiles when mediated by SmI_2 (eq 20).[22] This reaction appears to provide a useful alternative to the usual heterogeneous medium of Zn-promoted Reformatsky reactions.



(20)

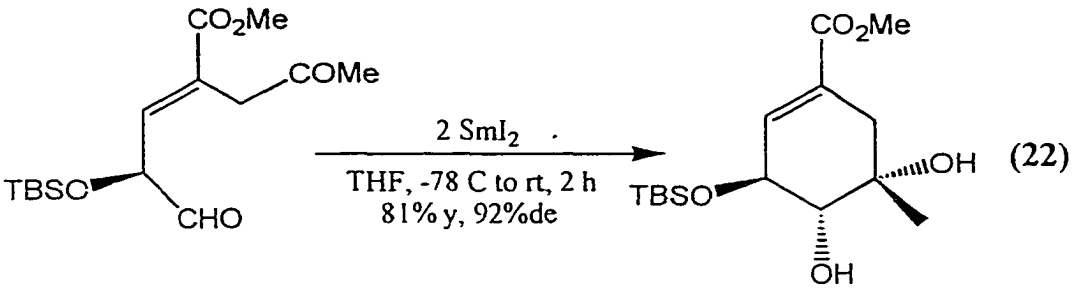
Lanthanide triflates have also been shown to promote effective Michael additions of silyl enolates to α,ß-unsaturated ketones (eq 21), where the Lewis acid catalyst can be recovered and reused without loss of activity.[43, 46]



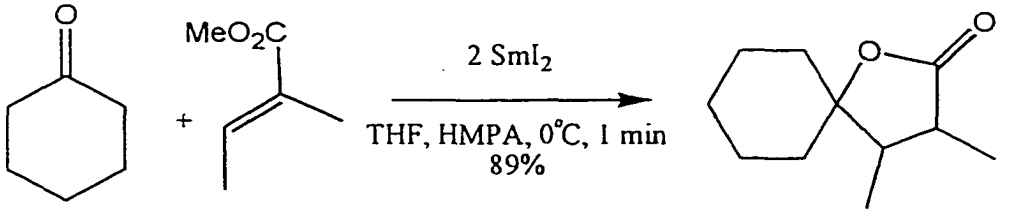
(21)

In addition to adding effectively to carbonyls, organolanthanides provide a useful alternative for nucleophilic addition reactions to carbon-nitrogen multiply bonded electrophiles.[4]

Samarium(II) species are particularly useful for reductive coupling reactions, including pinacol coupling (eq 22),[47] ketone-olefin coupling (eq 23)[48, 49] as well as radical additions to carbon unsaturated systems (eq 24).[50] Pinacol coupling reactions are carried out with excellent yields and have proven to be very useful in the assembly of highly functionalized cyclic products from intramolecular reactions. However, pinacol cross coupling reactions are not readily promoted by lanthanide reagents.



(22)



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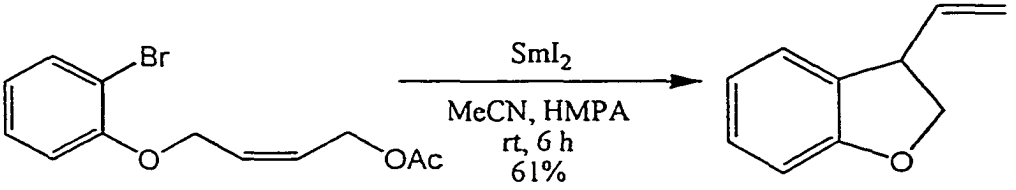
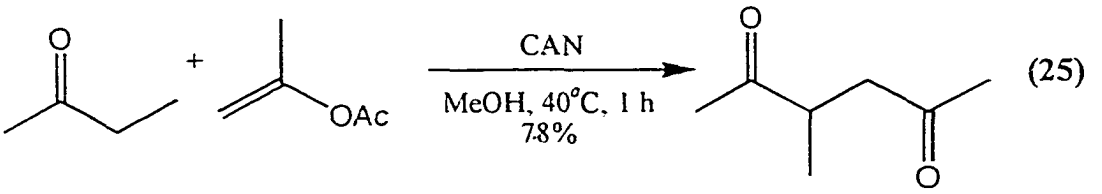


(24)

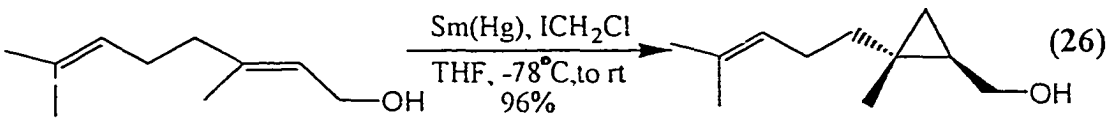
Samarium diiodide has proven effective for various radical addition reactions and in many cases the protocol provides significant practical advantages. In particular, workup is much easier in lanthanide promoted reactions over more traditional radical initiation procedures which are generally promoted by tin reagents.

Cerium(IV) has dominated oxidative coupling reactions due to enhanced reactivity and general superiority over the more traditional Mn(III) salts.[4] 1,4-Dicarbonyl compounds are readily synthesized by CAN promoted reactions (eq 25).[51]



(25)

The samarium-promoted route to cyclopropanes works very well for allylic alcohols, providing a chemoselective alternative to the Simmons-Smith procedure for cyclopropanation (eq 26).[52, 53] In contrast to the zinc-mediated reaction, no byproducts resulting from cyclopropanation of the isolated olefin are detected.[4]



(26)

Lanthanides have been used extensively as Lewis acid catalysts for a range of reactions including the aldol and Michael reactions (*vide supra*), Friedel Crafts reaction,[4] and most notably the Diels-Alder reaction. Numerous lanthanide complexes have served as highly selective catalysts for Diels-Alder reactions of many types. These catalysts are of extreme synthetic interest due to their demonstrated mildness and efficiency for acid sensitive Diels-Alder substrates. Indeed, the development of new lanthanide complexes which function as Lewis acid catalysts for the inverse demand hetero Diels-Alder reaction has been the focus of this work. Consequently, a more detailed review of the known examples of lanthanide catalysts for the Diels-Alder reaction is presented in the following section.

1.1.3 Lanthanide Lewis Acid Catalysis of the Diels-Alder Reaction

The Diels-Alder reaction is a concerted 4 + 2 cycloaddition of a diene with a dienophile to yield cyclohexene derivatives.[54] The reaction of the HOMO of the diene with the LUMO of the dienophile, as shown in Figure 1, results in the simultaneous formation of 2 carbon-carbon bonds, as well as the fixation of the relative stereochemistry of 4 carbon centres.

There are two possible stereochemical orientations of the dienophile with respect to the diene, called *endo* and *exo*. The *endo* transition state is the more sterically congested, but kinetically preferred, due to the interaction of the dienophile substituent(s) and the π electrons of the diene. The reaction is also highly regioselective in the case of asymmetrically substituted dienes and dienophiles due to strong electron substituent effects. Therefore, the well established regioselectivity and relative stereospecificity arising from a concerted mechanism makes the Diels-Alder reaction a very useful and important synthetic tool for the preparation of substituted 6-membered rings.[54, 55]

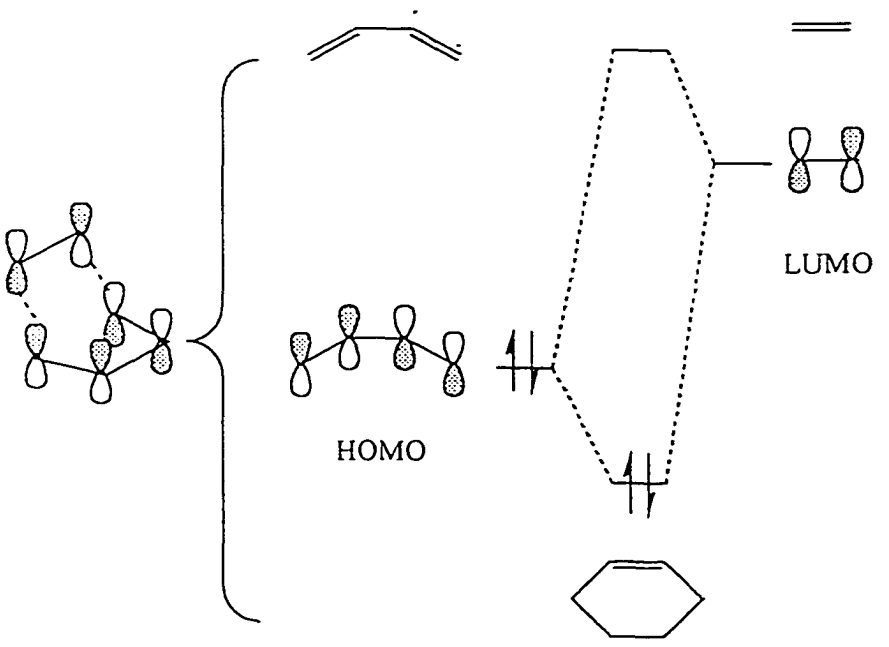
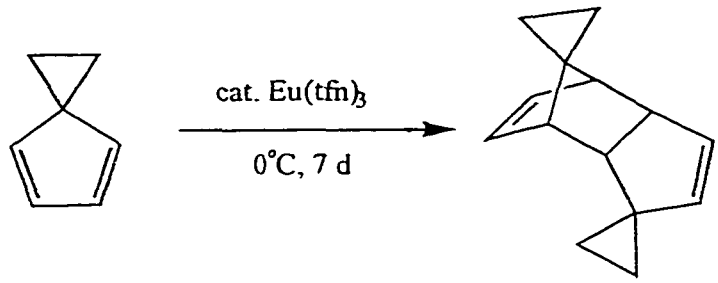


Figure 1: Cycloaddition of an alkene and a diene, showing interaction of LUMO of alkene with HOMO of diene.

In cases where there is not sufficient interaction of the frontier orbitals of the diene and dienophile, Lewis acid catalysis can promote the reaction. In this case the LUMO of the dienophile is sufficiently lowered through an interaction with the Lewis acid to promote reaction with the HOMO of the diene.[54] Lanthanide Lewis acids were first noted to effect this transformation in the example shown in Equation 27, where in the absence of the europium(III) salts (an NMR shift reagent), no dimerization took place.[56]



(27)

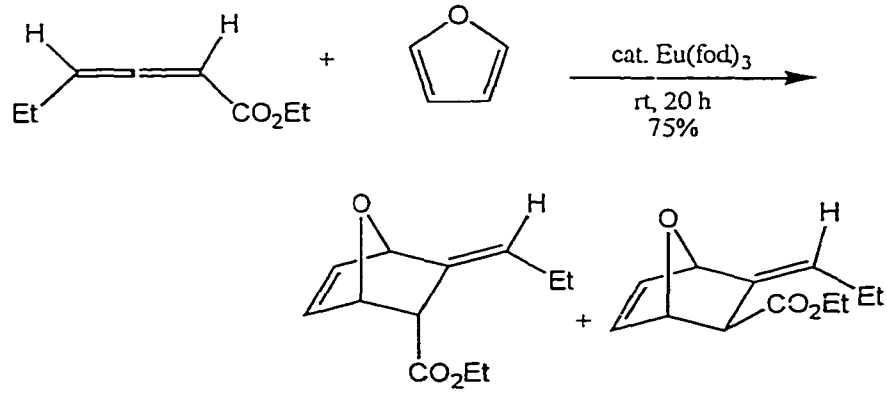
Lanthanide catalysts provide a useful alternative to other stronger Lewis acids, such as aluminum and titanium for the following reasons:[2]

1) Reactions are catalysed even when there are no oxygen functional groups in the molecules.

2) The reactions occur under mild conditions, and therefore acid-sensitive functional groups remain unaffected.

3) Good to high regio- and stereoselectivities are observed, *endo* adducts being major products in most cases.

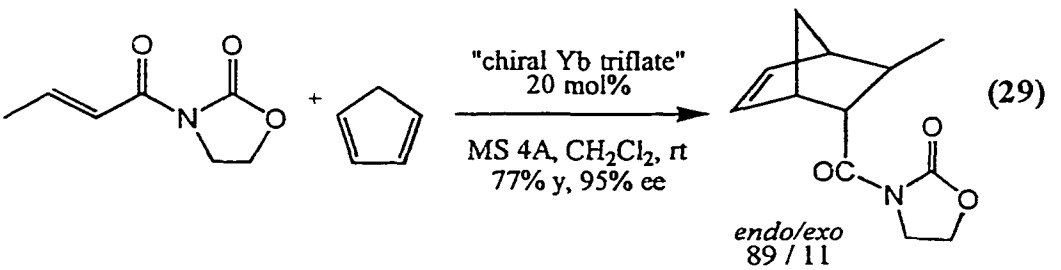
Equation 28 gives an example of a very acid sensitive Diels-Alder reaction which is enhanced in both yield and stereoselectivity with the use of a lanthanide catalyst.[57]



(28)

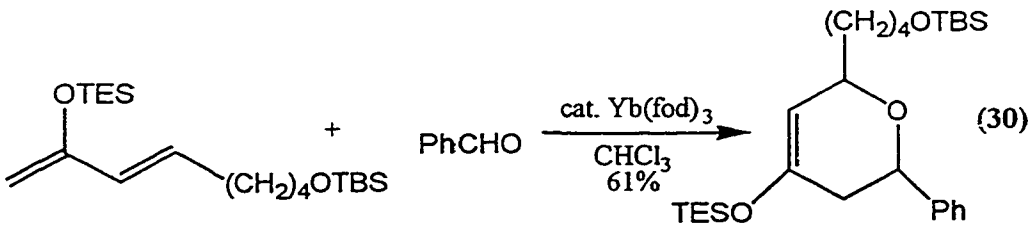
89 : 11

Lanthanide sulfonamides,[58] and lanthanide triflates, reuseable water-tolerant lanthanide Lewis acids, have also been used for the homo Diels-Alder reaction (meaning the carbon-carbon bond forming Diels-Alder reaction).[43] Most importantly, the lanthanide triflate Lewis acids have been chirally modified with BINOL resulting in the catalysis of highly enantioselective Diels-Alder reactions (eq 29).[59, 60, 61] The exact nature of the catalyst and the interactions which result in enantioselectivity are poorly understood as the lanthanide complex is prepared *in situ* and the structure of the catalyst is unknown.[59]



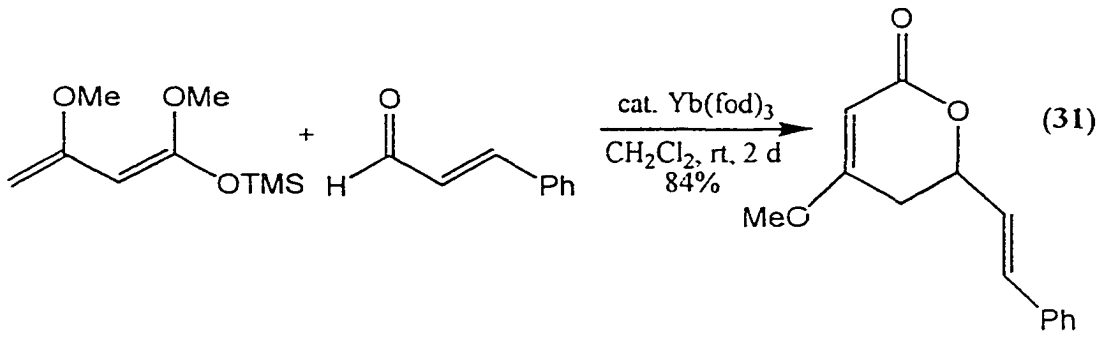
(29)

Perhaps the most dramatic examples of lanthanide Lewis acid catalysis have resulted from applications of the hetero Diels-Alder reaction.[62] This methodology has provided unprecedented entries to highly substituted, stereodefined dihydropyran derivatives (eq 30).[634]



(30)

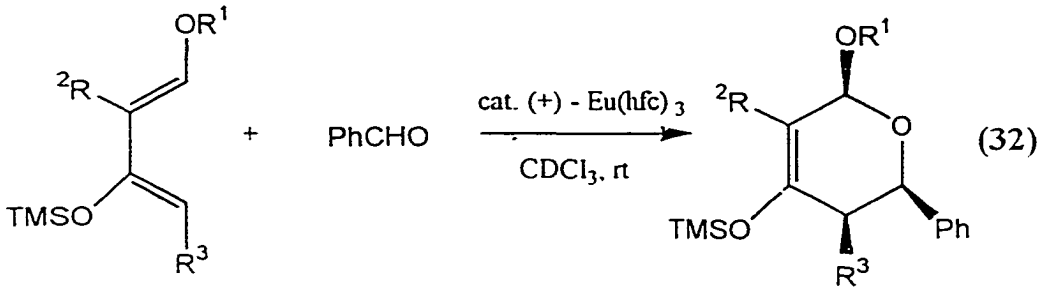
Remarkably, unsaturated aldehydes can be used as heterodienophiles, with a single regioisomeric product resulting from the addition of the carbonyl as the dienophile, with the alkene moiety remaining unaffected (eq 31).[4]



(31)

Lanthanide catalysts in the hetero Diels-Alder reaction have been used to enhance yields under mild conditions, promote reaction of sensitive substrates and also to assist in stereochemical control. These systems have been noted to promote *endo* selectivity in a number of diverse systems.[64] Similar reactivity and selectivities have been established for Diels-Alder reactions promoted by samarium diiodide.[65]

Further enhanced selectivities have been achieved by using the commercially available chiral shift reagent, $Eu(hfc)_3$, as a chiral catalyst (eq 32).[66, 67]



(32)

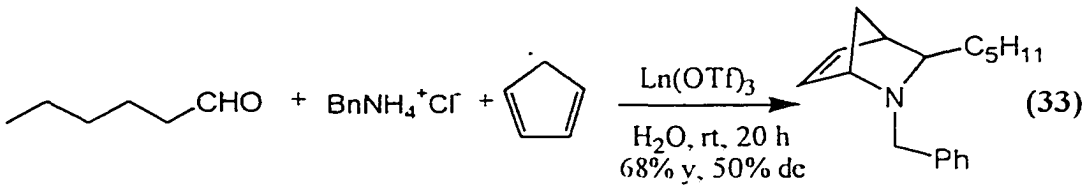
R^1 = Me, R^2 = H, R^3 = H : 18% ee
R^1 = *i*Pr, R^2 = H, R^3 = H: 28% ee
R^1 = *t*Bu, R^2 = H, R^3 = H: 38% ee

R^1 = Me, R^2 = Me, R^3 = H : 15% ee
R^1 = Me, R^2 = Me, R^3 = Me: 36% ee
R^1 = *t*Bu, R^2 = Me, R^3 = Me: 42% ee

The use of a chiral auxillary, in the R^1 position, combined with a chiral lanthanide catalyst yielded enantioselectivies of up to 95%.[68, 69] These remarkable enantioselectivities have established lanthanide Lewis acid catalysis as an important protocol in the stereoselective syntheses of carbohydrates.[67-69]

Not surprisingly, the interaction of the lanthanide complex with hetero Diels-Alder substrates has been shown by NMR studies to occur via carbonyl complexation.[70] However, observed enantioselectivites, even in the presence of the same chiral lanthanide catalyst as above, have been shown to be substrate dependent with some systems exhibiting modest or negligible asymmetric induction.[67, 71] A more recent attempt at asymmetric catalysis of the hetero Diels-Alder reaction used a bidentate chiral sulfonamide ligand to prepare a lanthanide catalyst of unknown structure which displayed modest enantioselectivities (<55%).[72]

It should also be noted that lanthanide Lewis acids are effective in the catalysis of non-oxygen hetero Diels-Alder reactions. Aza Diels-Alder reactions[73, 74] and imino Diels-Alder reactions[75] have been catalysed efficiently by lanthanide triflates to yield aza sugar derivatives (eq 33) and pyridine/quinoline derivatives respectively.



(33)

As mentioned previously, lanthanide catalysts often permit reactions of dienes and dienophiles containing sensitive functional groups. A particularly good example of this is the inverse demand hetero Diels-Alder reaction between α,ß-unsaturated aldehydes and vinyl ethers.[71] In the inverse demand case, an electron poor dienophile reacts with an electron rich diene, resulting in cyclohexene derivatives (Figure 2). The use of lanthanide catalysts promotes stereoselective reactivity with the only products resulting from *endo* addition, as is seen in the case of crotonaldehyde addition to ethyl vinyl ether (Figure 2, eq 34).[71]

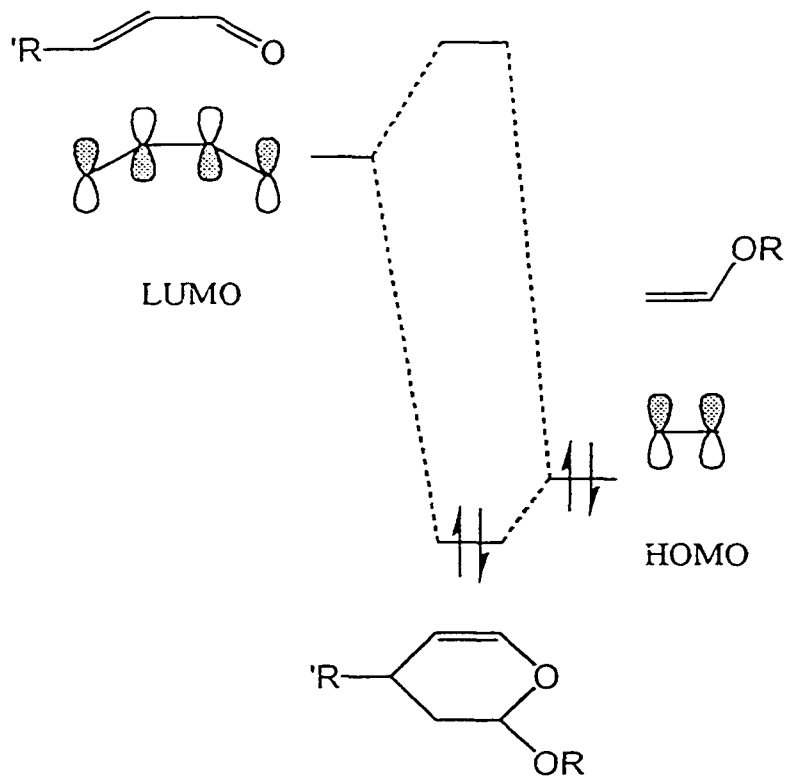
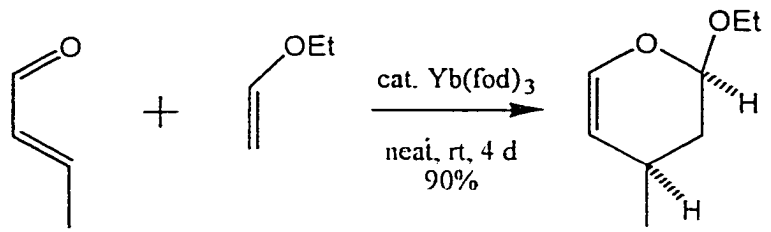


Figure 2: Simplified frontier orbital diagram of inverse demand hetero Diels-Alder reaction.

In the absence of catalyst this reaction only proceeds at 175°C in sealed tube conditions to give 87% of cycloadducts[76] or under high pressure conditions (15 kbar, 75°C, 24 h) to give 89% of the *endo* product.[77, 78] Other Lewis acids, such as $ZnCl_2$ or BF_3-Et_2O, promote the cycloaddition as well as the polymerisation of the starting materials, resulting in low isolated product yields (46% and 12% respectively).[79]



(34)

By using a combination of lanthanide catalysis and high pressure conditions, Scheeren and Vandenput demonstrated that it is possible to prepare highly functionalized dihydropyrans.[80]

There is great interest in this methodology as dihydropyrans are contained in a number of natural compounds such as sugars and polyether antibiotics. To date, no examples of enantioselective inverse demand hetero Diels-Alder reactions have been reported. The use of commercially available chiral NMR shift reagents, even when combined with chiral auxiliaries, resulted in negligible ee's.[80] Clearly, the development of enantioselective lanthanide Lewis acid catalysts suitable for the inverse demand hetero Diels-Alder reaction would represent a significant contribution to organic synthetic methodology.

1.1.4 Summary

The unique properties of the lanthanide metals have resulted in interesting and diverse selectivities when applied to organic synthesis. Lanthanide mediated organic reactions ranging from redox functional group transformations to selective carbon-carbon

bond formation has established lanthanide protocols as an essential tool of today's organic chemist. Unfortunately, these reaction mechanisms (and consequently the resulting selectivities) are poorly understood in almost all cases. Most reaction procedures have been established by preparing reagents of unknown structure *in situ*, with reaction conditions being optimised for each new set of substrates. As the organic chemist continues expanding the limits of chemo and stereoselective reactions, it becomes increasingly important to understand the fundamentals of lanthanide mediated processes. With a better understanding of the reaction chemistry at hand, one advances toward the possibility of rationally designing lanthanide reagents that display desired selectivity. The plethora of organic reaction chemistry mediated by lanthanide reagents of ill-defined structure and mechanism exemplifies the need for a methodical and systematic investigation of lanthanide complexes and the role this class of metals play in select organic transformations.

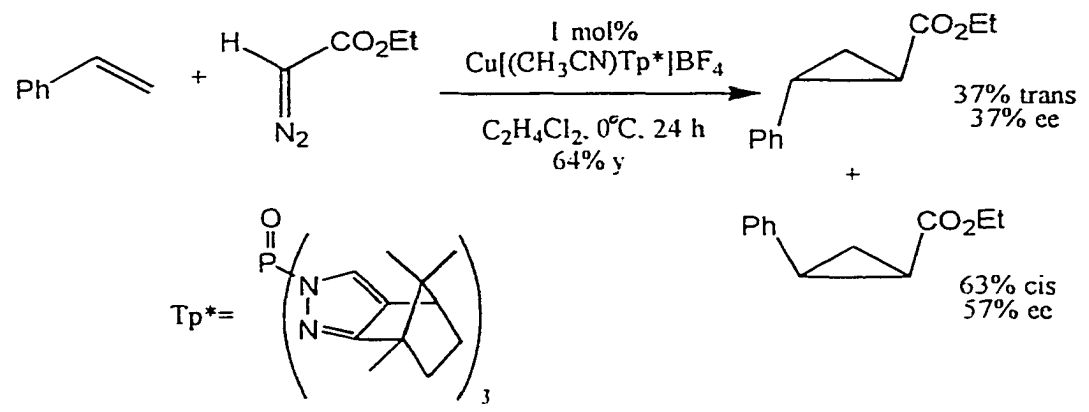
1.2 C_3 Symmetric Ligands

Chiral elaboration of C_3 symmetric ligand systems provides a route into chiral metal complexes. The possible applications of these high symmetry chiral compounds with respect to asymmetric catalysis is a topic of much current interest.[81] Despite the great success with C_2-symmetric ligands in the stereocontrol of a variety of transition metal mediated processes, chiral ligands possessing elements of higher symmetry have largely remained unexplored.[82] However, it has been suggested that multidentate ligands

with higher order rotational symmetry may be even better at promoting asymmetric reactions. C_3 symmetric ligands would have greater steric interactions resulting from the presence of three stereogenic centers in a metal complex (rather than 2 in C_2 systems) while 3 binding sites in these complexes are rendered symmetry equivalent.[83]

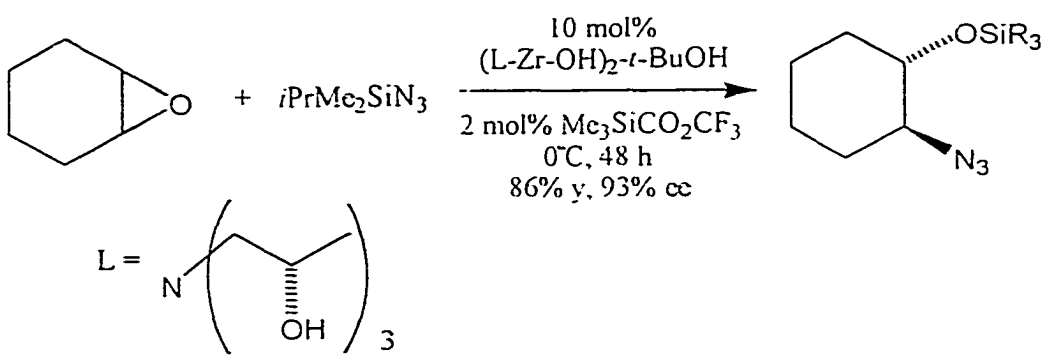
To this end there has been significant synthetic efforts devoted toward the efficient synthesis of chiral C_3 symmetric ligands.[81, 84] The preparation and subsequent applications of these compounds with respect to supramolecular self-assembly and chemical selectivity are of interest to many groups.[81] For asymmetric synthesis a host of chiral C_3 symmetric ligands have been prepared which are suitable for metal complexation; including phosphanes,[82] amines (Figure 1),[84, 85] pyrazolyls (*vide infra*) and alcohols (*vide infra*).[86, 87]

An example of the potential application of these types of ligand systems is given in Scheme 1 where catalytic asymmetric cyclopropanation was carried out with a chiral C_3 symmetric Cu(I) complex. The resulting moderate enantiomeric excess of ≈60% was viewed as a promising indication of the useful applications of 3-fold symmetric complexes toward asymmetric synthesis.[83] The modified chiral elaboration of a variety of tris(pyrazolyl) ligands resulted in the successful preparation of a series of well characterised C_3 symmetric complexes of Cu(II), Zn(II), Ni(II), and Co(II).[88,89]



Scheme 1: Chiral C_3 symmetric Cu complex for asymmetric catalysis.

Nugent and co-workers have demonstrated excellent enantioselectivities for the asymmetric cleavage of meso epoxides that is catalysed by a poorly characterised oligomeric Zr species.[87] Although the exact nature of the catalyst is not well understood, the use of a C_3 symmetric ligand imparted significant enantioselectivities (Scheme 2).



Scheme 2: Chiral Zr complex of a C_3 symmetric ligand for asymmetric catalysis.

Although there are examples of efficient asymmetric induction using C_3 symmetric ligand systems, the anticipated effective application of these ligands to a variety of enantioselective metal mediated transformations has not been reported.[81, 89, 90] With significant synthetic efforts being directed toward the preparation of chiral C_3 symmetric ligands, it is disconcerting to note the lack of reports regarding their use in efficient asymmetric catalysis. Consequently, there is considerable debate about the advantages of higher order symmetry catalysts in metal mediated organic synthesis. Clearly, further experimentation is necessary to determine the ideal applications of C_3 symmetric systems, and for a number of reasons, the lanthanides are perfect candidates for these investigations.

As stated earlier, the lanthanides can accommodate a coordination sphere of up to 12 donors, with 7 to 9 donors being preferred. Thus, the preparation of discrete, well characterised lanthanide(III) complexes requires a well defined ligand environment which is sterically congested about the metal centre, thereby limiting access to potential coordination sites. For example, a low coordination number of 3 can be achieved when suitably bulky ligands systems are chosen; as in the monomeric, crystalline compounds $Ln(N(SiMe_3)_2)_3$.[91] In the absence of sterically demanding ligands, lanthanides are prone to form bridging interactions, leading to the formation of coordination oligomers and polymers, usually of ill-defined structure. Therefore the design of new ligand systems suitable for lanthanide complexation must incorporate steric bulk as a desirable ligand feature.

Complex stability is substantially enhanced when multidentate ligands are used. Due to entropic factors, a multidentate ligand is less likely to dissociate from the metal centre than a monodentate ligand. With this in mind, a tripodal ligand array which lends itself to the formation of a -3 anion is ideally suited for lanthanide(III) substitution. Further elaboration of a tripodal ligand with chiral substituents would provide the steric bulk necessary for the preparation of monomeric, chiral, C_3 symmetric complexes.

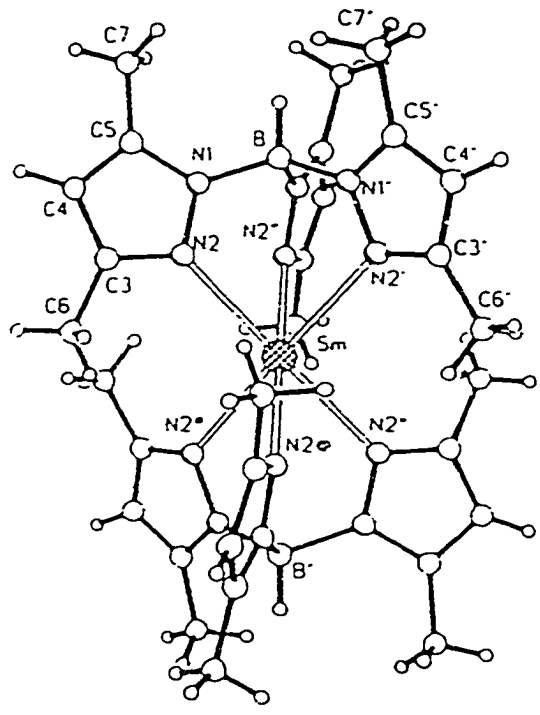


Figure 3: ORTEP drawing of Bis [Tris(pyrazylol)Borate] Samarium Complex

Several achiral, multidentate, C_3 symmetric ligand systems have been substituted effectively on lanthanide metals. For example, tris(pyrazolyl) borate ligands (Figure 3) and the heptadentate trac ligands[92, 93] (Figure 4) have been used in the preparation of stable lanthanide complexes. These compounds have been fully characterised by X-ray crystallography and are monomeric, crystalline solids. These materials indicate that appropriately designed tripodal systems are well suited for the preparation of highly symmetric monomeric lanthanide complexes.

With respect to chiral lanthanide complexes, there have been several recent advances in the application of C_2 symmetric chiral ligands suitable for enantioselective

protocols.[24, 44, 45, 59-61] However, the role of chiral, C_3 symmetric ligands with respect to lanthanide mediated organic methodologies has not been investigated.

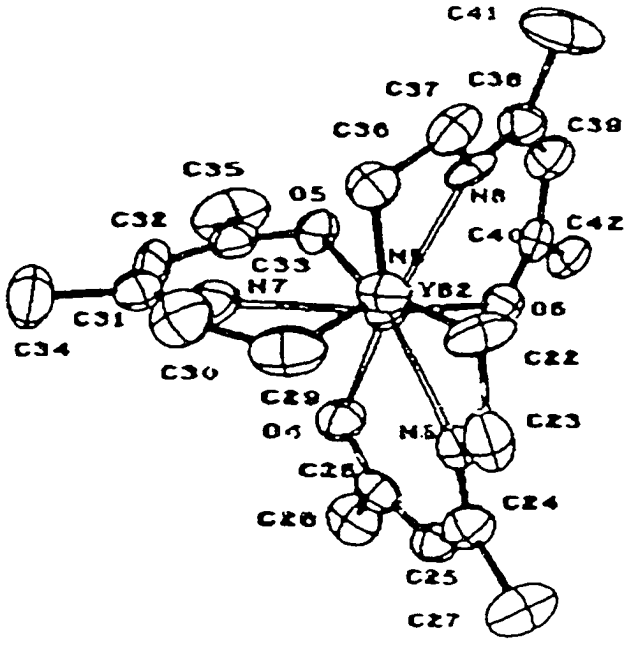


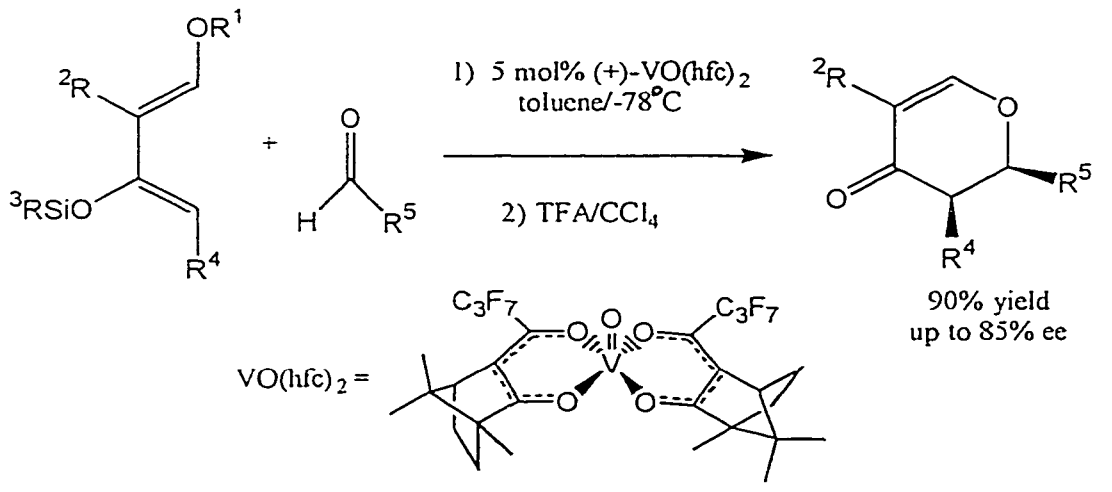
Figure 4: ORTEP drawing of Yb(trac) complex.

As stated above, the lanthanides are well suited toward tripodal substitution for a number of reasons including their +3 oxidation state, enhanced stability with multidentate ligands and need for a sterically demanding environment about the metal centre. Therefore, the lanthanides are excellent candidates for further research regarding the effectiveness of C_3 ligand systems in enantioselective catalysis. A chiral C_3 symmetric ligand system that results in monomeric, crystalline lanthanide complexes would provide important information about the effect of high symmetry ligands for stereoselective metal mediated organic reactions. Also, these new systems would assist in the elucidation of the mechanistic role of the lanthanide metal centre.

1.3 Enantioselectivity in the Hetero Diels-Alder Reaction

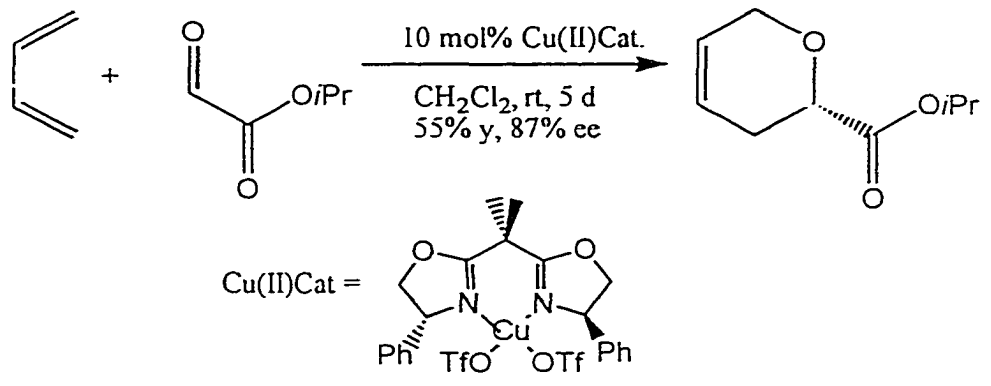
In recent years there have been significant advances in enantioselective Lewis acid catalysis, including those examples previously discussed that involve lanthanides. Additionally, it is important to note the many promising developments using transition metals. To demonstrate the need for further research in this area a brief summary of these results for enantioselective hetero Diels-Alder and inverse demand hetero Diels-Alder reactions will be given.

One of the first well characterised chiral metal complexes known to catalyse the hetero Diels-Alder reaction was an oxovanadium(IV) species (Scheme 3). This reagent was shown to promote the cycloaddition reaction between an activated diene and aldehyde with excellent enantioselectivies (up to 85%).[94, 95]



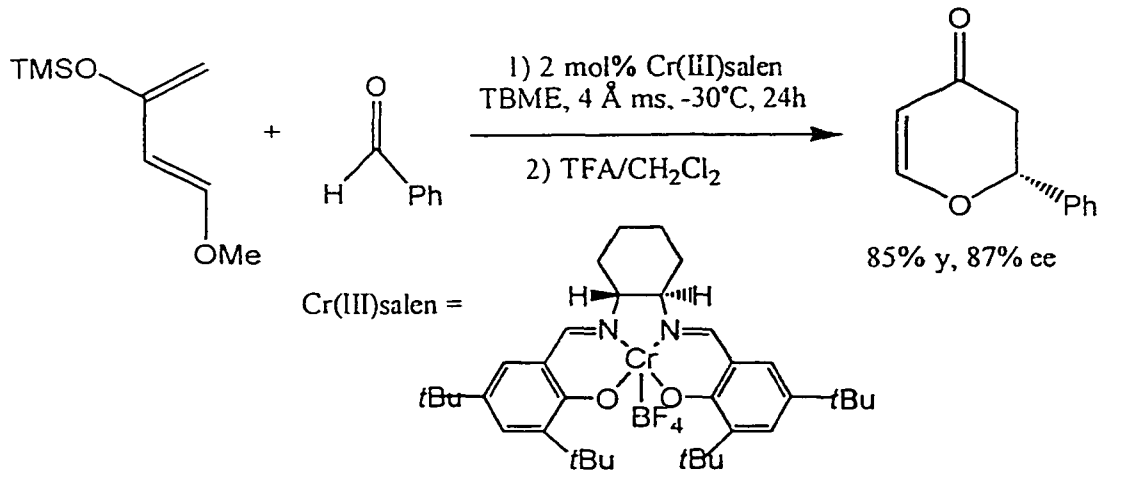
Scheme 3: Chiral oxovanadium complex as a catalyst for the hetero Diels-Alder reaction

C_2 symmetric chiral Cu(II)bis(oxazoline) complexes have been used for asymmetric Diels-Alder[96, 97] and aldol[98, 99] reactions with high selectivities. They have also been established as efficient catalysts for the hetero Diels-Alder reaction.[100] This catalyst promotes the cycloaddition of dienes and glyoxylates (Scheme 4) in high enantioselectivities (87%), with modest yield (55%) due to side products resulting from the ene reaction.



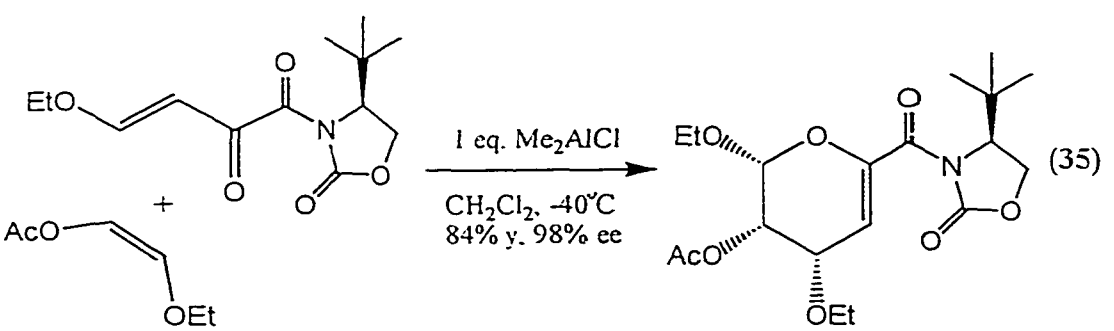
Scheme 4: Chiral Cu catalyst for the hetero Diels-Alder reaction.

Other C_2 symmetric systems which have had extensive success in a variety of metal mediated asymmetric reactions are the salen complexes of Jacobsen.[101-103] More recently salen chromium(III) complexes were determined to be effective catalysts for the hetero Diels-Alder reaction.[104] A number of catalyst derivatives and Diels-Alder substrates were screened to determine the optimised system shown in Scheme 5. All reported examples of the hetero Diels-Alder reaction, in the presence of the catalyst shown, proceed in good yields (>65%) with good to excellent enantioselectivities (70 - 93% ee's).[104]

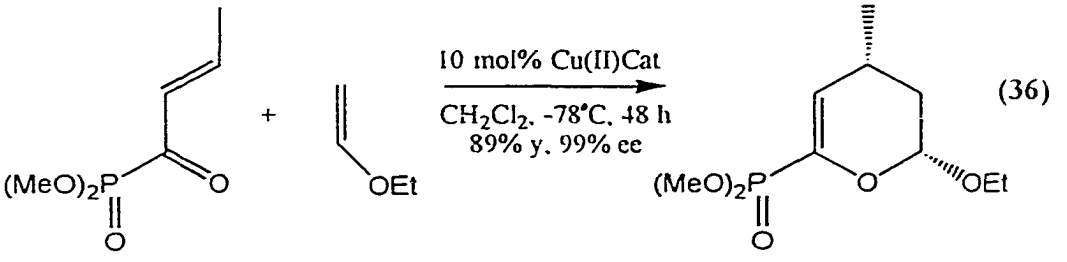


Scheme 5: Cr salen catalyst for the hetero Diels-Alder reaction.

Examples of asymmetric induction in the inverse demand case are few and rely upon auxiliaries in the Diels-Alder substrates. One example uses a chiral auxiliary and achiral aluminum catalyst to achieve the desired compound in 84% yield with 98% ee (eq 35).[105]

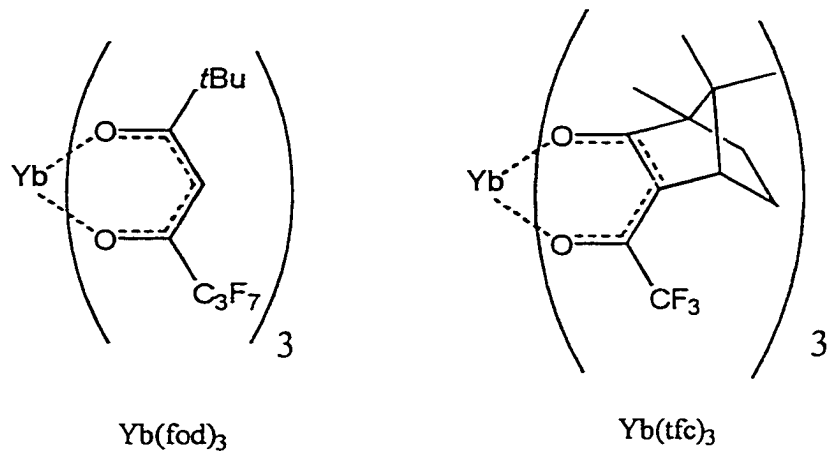


A second example uses an achiral, chelating auxiliary in combination with the chiral Cu(II)bis(oxazoline) complex shown in Scheme 4.[106] The Diels-Alder adduct is obtained in excellent yield (89%) and enantioselectivity (99%) as shown in Equation 36.



Although Equations 35 and 36 are examples of highly enantioselective inverse demand hetero Diels-Alder reactions, they are not examples of synthetically efficient transformations.[107] The use of auxiliaries requires the subsequent removal of the auxiliary, meaning further synthetic steps resulting in loss of yield and time, as well as the wasteful use of reagents. Clearly, the development of enantioselective catalytic systems which directly promote the inverse demand hetero Diels-Alder reaction would represent a significant methodological improvement into dihydropyran derivatives.

As was demonstrated in section 1.1, the lanthanides with their unique physical properties offer important and selective protocols for organic synthesis. Of all the potential applications of lanthanides within organic methodology one of the most interesting lanthanide promoted reactions is the inverse demand hetero Diels-Alder reaction between crotonaldehyde and ethyl vinyl ether (eq 34). This reaction has only been reported to proceed at room temperatures and pressures in the presence of lanthanide NMR shift reagents, such as $Yb(fod)_3$ and its chiral analogue $Yb(tfc)_3$ (Figure 5).[71]



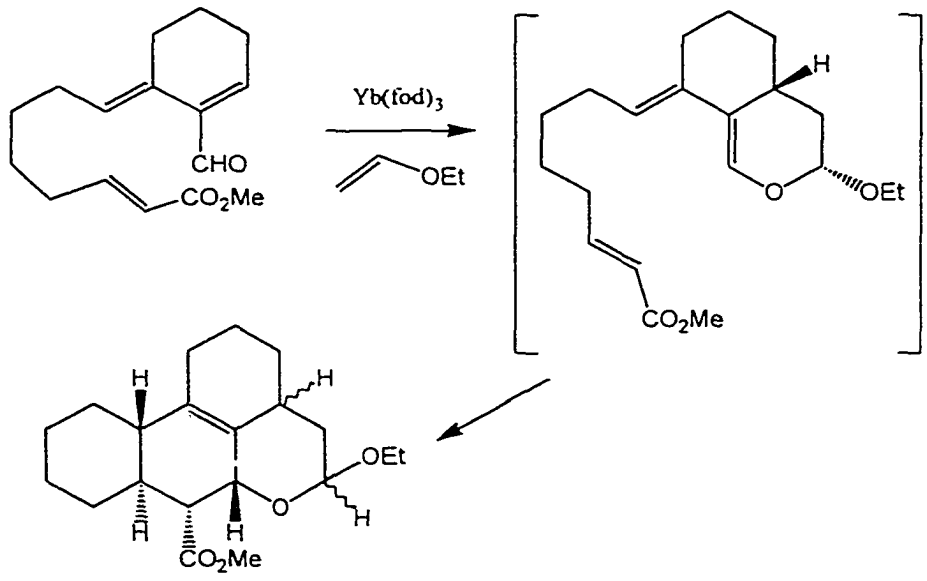
$Yb(fod)_3$ $Yb(tfc)_3$

Figure 5: Commercially available NMR shift reagents / Lewis acid catalysts.

It has been demonstrated that these catalysts are very mild and tolerant of a wide range of acid sensitive functional groups, making them ideal reagents for total syntheses of natural products.

The Diels-Alder reaction of crotonaldehyde with ethyl vinyl ether results in the preparation of dihydropyran structures, which are important intermediates in the synthesis of carbohydrates as well as polyether antibiotics.[62] Here at the University of Victoria these lanthanide reagents have been used in the key step of a diene-transmissive Diels-Alder strategy which assembles three rings and six chiral centers in a single step (Scheme 6)[108, 109] The selectivity of the lanthanide promoted reaction could be further enhanced by preparing a chiral catalyst which would exhibit enantioselectivity. To date there are no

efficient examples of chiral lanthanide catalysts which exhibit significant enantioselective inverse demand hetero Diels-Alder reactivity.



Scheme 6: Lanthanide Lewis acid catalyst in Diene-transmissive Diels-Alder strategy in the synthesis of natural products.

It has been demonstrated in the "normal" demand hetero Diels-Alder reaction that the role of the lanthanide is to act as a Lewis acid catalyst by binding to the aldehyde.[70] In this manner, the aldehyde LUMO is lowered in energy permitting it to better interact with the HOMO of the

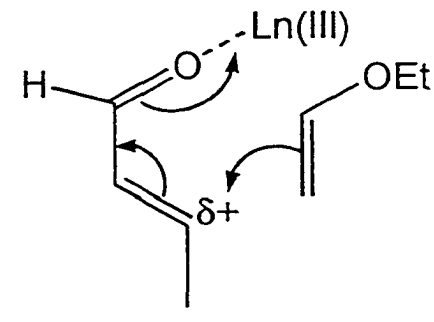


Figure 6: Simplified view of Lewis acid catalysis.

dienophile. A simplified view of the role of the Lewis acid upon carbonyl coordination is shown in Figure 6. Thus, by chirally elaborating the ligand environment about the lanthanide metal centre one would anticipate facial selectivity in the approach of the dienophile, resulting in an enantiospecific reaction.

In effect this general approach has been attempted where the chiral lanthanide shift reagent $Yb(tfc)_3$ has been used. However, this chiral reagent only resulted in modest enantioselectivities (<55%) for the hetero Diels-Alder reaction[66] and negligible enantioselectivities for the inverse demand case.[80] Clearly, the development of an enantioselective protocol for the inverse demand hetero Diels-Alder reaction would result in a generally applicable asymmetric Lewis acid catalyst, as the IDHDA reaction has proven to be the most challenging case.

The observed poor chiral induction when using the camphorato ligand was proposed to be due to a lack of defined ligand conformation about the metal centre. Because the large lanthanides have ionic bonding character, and consequent lack of bonding directionality, the three independent ß-diketonate ligands have fluxional behaviour about the metal centre. Therefore, there would not be a well defined coordination site, but rather a host of possible active sites where the carbonyl coordination could take place. This problem was proposed to be remedied by the preparation of a sterically demanding ligand system which would define a Lewis acid "active site" which could be chirally modified. The tethering of three anionic ligands in a tripodal array would yield a sterically congested multidentate ligand system leading to new C_3 lanthanide complexes.

1.4 Project Proposal

Therefore the defining objective of this research project is the design and synthesis of C_3 symmetric ligand systems suitable for the preparation of monomeric, well defined lanthanide complexes which can be used as catalysts for the IDHDA reaction of crotonaldehyde and ethyl vinyl ether. The preparation of these high symmetry ligands and their chiral analogues represent a new class of ligand suitable for lanthanide complexation. Although we are interested in the enantioselective catalysis of an important carbon-carbon bond forming reaction, these complexes display behaviour which could be useful in the preparation of lanthanide contrast agents for magnetic resonance imaging.[110]

The preparation and investigation of this new class of ligands and their lanthanide complexes are presented as follows. In Chapter 2, achiral lanthanide complexes provide important and useful information regarding the relationship between ligand structure and catalyst function.[79, 111] This investigation assisted in the design of second generation chiral, tripodal ß-diketone ligands, whose synthetic routes are presented in Chapter 3. In Chapter 4, the synthesis, characterisation and potential applications of a new family of alcohol ligands are discussed. The results and conclusions regarding the preparation of C_3 symmetric ligand systems, their chiral analogues and metal complexes are summarised in Chapter 5, along with several proposals for related future work. Finally, Chapter 6 provides full experimental detail pertaining to the synthesis and characterisation of the ligands and their metal complexes discussed throughout this work.

CHAPTER 2: Achiral Systems:

Investigations of Ligand Structure and Catalyst Function

2.1 Introduction

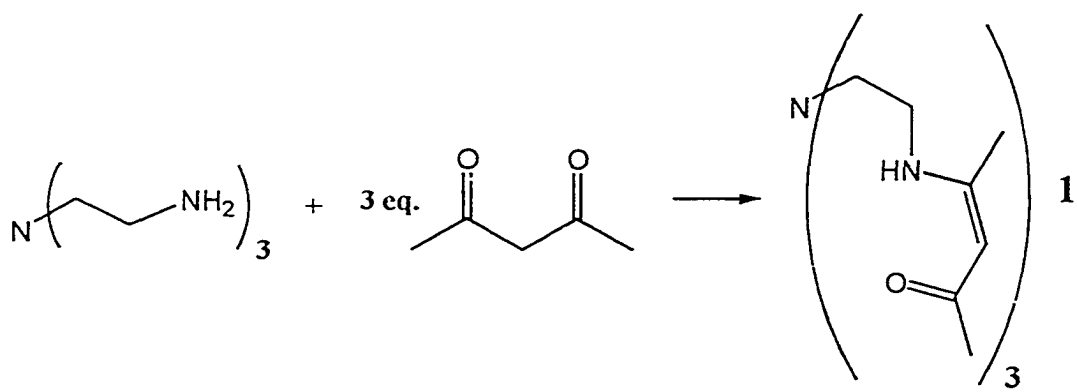
The initial goal of the project was to prepare an effective achiral, monomeric lanthanide catalyst which would lend itself to future chiral elaboration. First, by investigating the ligand structure/catalytic function relationship, it was determined what functional groups must be incorporated into a useful ligand design. Second, the challenging synthetic methodology necessary for the preparation of C_3 symmetric ligand systems could be established in the absence of complicated chiral substituents.

The most effective catalysts known for the inverse demand hetero Diels-Alder reaction, as described in Chapter 1, are those with fluorinated ß-diketonate ligand systems of ytterbium.[66, 71] These commercially available NMR shift reagents have been shown to effectively catalyse the desired reaction while leaving other acid sensitive functional groups untouched.[108] Other Lewis acid catalysts have been shown to promote the reaction in poor yields due to starting material and product decomposition.[111] The reasons for the effectiveness of the lanthanide Lewis acids in contrast to the limited usefulness of the latter had not been investigated. Also, effective alternatives to the commercially available catalysts had never been reported in the literature. Therefore, the preparation of a variety of achiral lanthanide coordination complexes and an investigation of their

usefulness as Lewis acid catalysts for the inverse demand hetero Diels-Alder reaction was undertaken.

2.2 Trac Ligand Systems

A series of monomeric lanthanide complexes of ß-diketonate derivatives have been previously reported in the literature.[93] They are easily prepared using a Schiff base condensation of tren with acac (Scheme 7) to yield a multidentate ligand which has been given the acronym H_3trac **1**.



Scheme 7: Preparation of H_3trac ligand (1).

As is shown in the simplified view of trac lanthanide complexes in Figure 7, this series of compounds possess a number of desirable features including their heptadentate binding mode and C_3 symmetric ligand system. Because one apical site is blocked with the

coordinating tertiary nitrogen, there is only one possible site accessible for coordination of the incoming heterodiene, crotonaldehyde. Therefore, a "chiral pocket" ideal for enantioselective catalysis can be built by placing chiral substituents about the site of diene complexation. Thus, the selection of a chiral ß-diketone starting material would provide an efficient route into a multidentate, chiral C_3 symmetric catalyst.

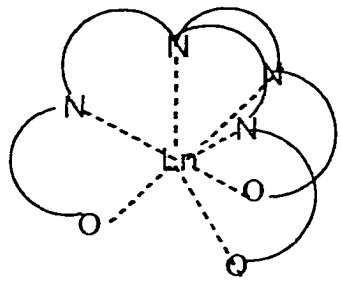


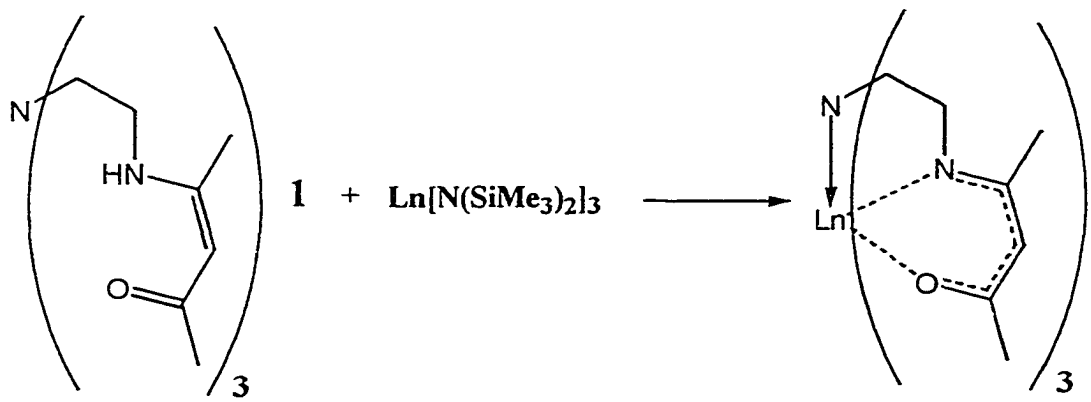
Figure 7: Simplified Trac Complex

First, the usefulness of trac complexes as Lewis acid catalysts needed to be established. Therefore, initial investigations focused on the preparation of achiral trac complexes and their potential as Lewis acid catalysts for the inverse demand hetero Diels-Alder reaction.

Ligand **1** was prepared as shown in Scheme 7 and its NMR spectra were compared with literature data.[93] The ligand was purified by silica gel column chromatography using 1:1 chloroform/methanol as eluent to give an orange semi-solid in excellent yield (95%). The ligand was dried and stored over molecular sieves at -30°C.

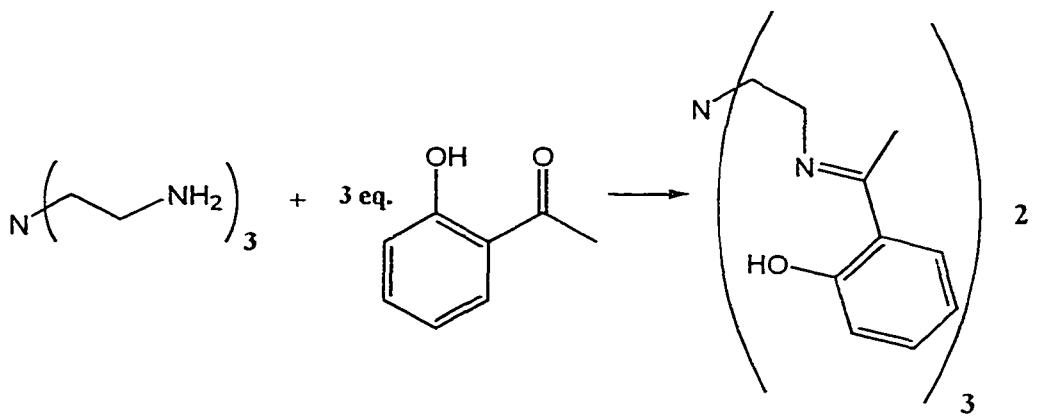
The lanthanide complexes of the H_3trac ligand were prepared using the reaction shown in Scheme 8. The side product $HN(SiMe_3)_2$ was removed in vacuo to leave the desired products as pale coloured, moisture-sensitive powders that could be purified by sublimation under vacuum. Both the yttrium and the ytterbium analogues were prepared and characterised by NMR spectroscopy for the diamagnetic species and by IR for the

paramagnetic analogue.



Scheme 8: Preparation of lanthanide complexes of ligand 1.

Using a similar synthetic strategy, a second ligand system H_3hatren was prepared (Scheme 9).[92, 93] Here the Schiff base condensation of 2-hydroxyacetophenone with tren gives the tripodal H_3hatren, as a flaky yellow solid, in excellent yield. This ligand was substituted onto ytterbium using $Yb[N(SiMe_3)_2]_3$ as the metal containing starting material. The ligand was characterised by NMR spectroscopy and compared with literature data, while the Yb(hatren) complex was characterised by IR.[92, 93]



Scheme 9: Preparation of Ligand H_3hatren

It should be noted that throughout this work there was an emphasis on Y complexes as well as Yb. Yttrium is diamagnetic and can be probed by NMR while Yb, a paramagnetic species, has fewer characterisation options available. It was anticipated that the Y and Yb would display very similar catalytic behaviour due to their very similar ionic radii of 1.04 Å and 1.01 Å (with a coordination number of 6) respectively.[112] Therefore, with several lanthanide complexes in hand, the purified compounds were analyzed for their potential as Lewis acid catalysts.

The test reaction of interest, as described in Chapter 1, is the hetero Diels-Alder reaction between crotonaldehyde and ethyl vinyl ether yielding cis-2-ethoxy-4-methyl dihydropyran as product (eq 34). In order to follow the progress of the catalytic reaction a GC assay was developed.

The known protocol for the IDHDA reaction using $Yb(fod)_3$ as catalyst[71] is described below, with a summary of the GC results. First, the catalytic product was prepared in a 10 mL round bottom flask using 2 mol % of the commercially available

achiral catalyst, $Yb(fod)_3$, in 5.0 mL of freshly distilled ethyl vinyl ether with 0.2 mL of crotonaldehyde delivered by syringe. The reaction was tightly capped and stirred for up to 4 days. Aliquots for GC analysis were removed by syringe every 4 hours, diluted to 0.5 mL with ether and injected (0.5 μL) onto the GC column to monitor the progress of the reaction. The appearance of the product peak and the simultaneous reduction in the crotonaldehyde peak was clear, as is shown in Figure 8. Therefore, the progress of the reaction could be easily followed by comparing the integrations of the crotonaldehyde peak to the product peak.

Upon reaction completion the desired product was isolated from the reaction mixture as a pale yellow oil which could be further purified by column chromatography. This product was characterised by NMR for comparison with literature data,[77] and provided a retention time standard (5.5 minutes) for the GC monitoring of all other catalyst screening assays.

The identical methodology was used in all catalysis analyses, where 2 mol % of the alternative catalysts were tried in three repetitive trials. In the case of both yttrium and ytterbium trac complexes little catalysis was observed (10 % by GC) after 4 days, with both metals demonstrating the same sluggish catalysis. The Yb(hatren) complex was completely ineffective as a catalyst with no product formation detectable after 4 days. This was somewhat disappointing as the trac and hatren ligands possessed chelating structures similar to those of the known lanthanide catalysts. However it was noted that all known effective catalysts possessed specifically fluorinated ß-diketonate ligands. Therefore, the preparation of a fluorinated trac complex was undertaken.

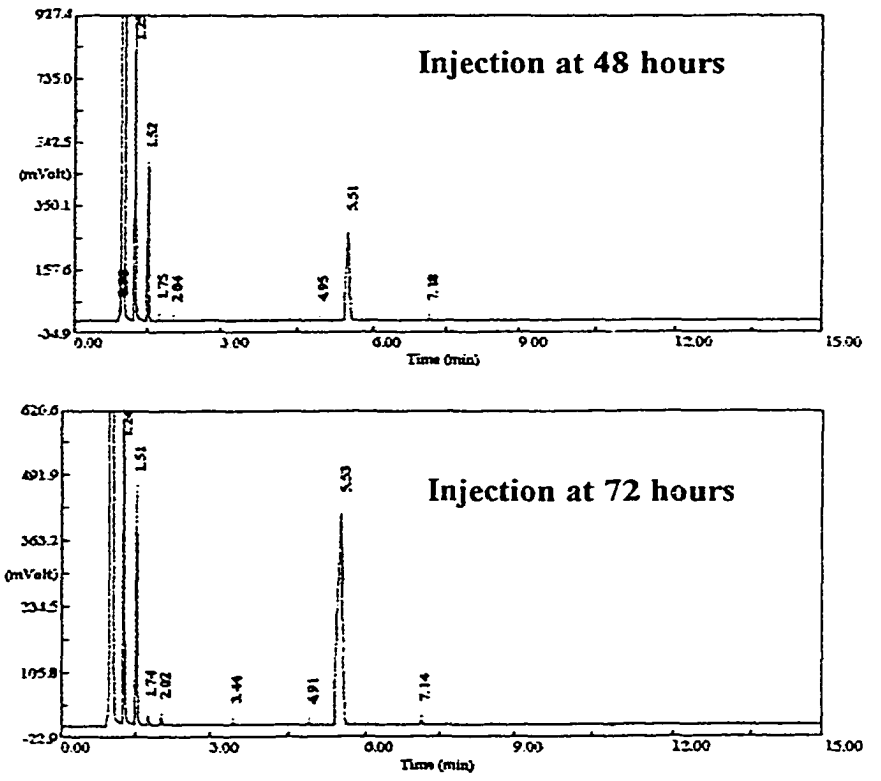
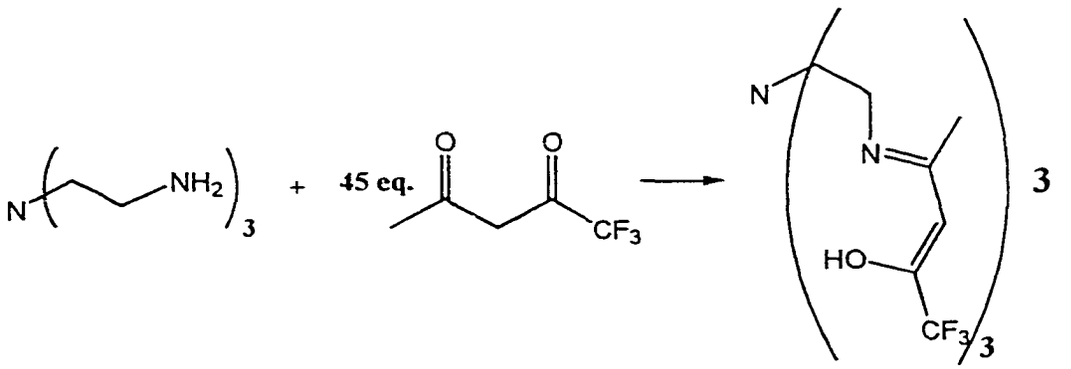


Figure 8: Example GC traces demonstrating reaction progress where 1.2 min. retention time corresponds to unreacted crotonaldehyde, 1.5 min. is an internal standard and 5.5 min. corresponds to product

The H_3F_3trac ligand **3** could be prepared from a large excess of distilled trifluoroacac and tren as shown in Scheme 10. Due to the strong electron-withdrawing character of the trifluoromethyl group, the starting material trifluoroacac exists almost entirely in the enol form. Therefore, when subjected to nucleophilic attack by the amine, the site of attack is always at the carbonyl distal to the trifluoromethyl group.[113]



Scheme 10: Preparation of H_3F_3trac ligand.

This ligand was substituted onto yttrium using $Y[N(SiMe_3)_2]_3$ as starting material in the reaction analogous to Scheme 8. The product was isolated as a creamy white powder which could be recrystallised from warm toluene as colourless brick-like crystals. The X-ray crystal structure of this solid is shown in Figure 9.

Comparison of the bond lengths and angles of Y(F_3trac) complex with Yb(trac)[93] reveals a very similar bonding structure with the ligand adopting a heptadentate binding mode. All M-X bond lengths are approximately 0.03 Å longer in the Y case, due to the difference in ionic radii of the metal centres. Surprisingly, the trifluoromethyl group does not affect the M-X (X = O, N) bond lengths in any significant way. Also, the trifluoromethyl group induces little change in the bond localization within the imine subunit, as in both the trac and F_3trac cases the C-C(N) bond lengths were 1.44 Å while the C-C(O) bond lengths were 1.37 Å.[93]

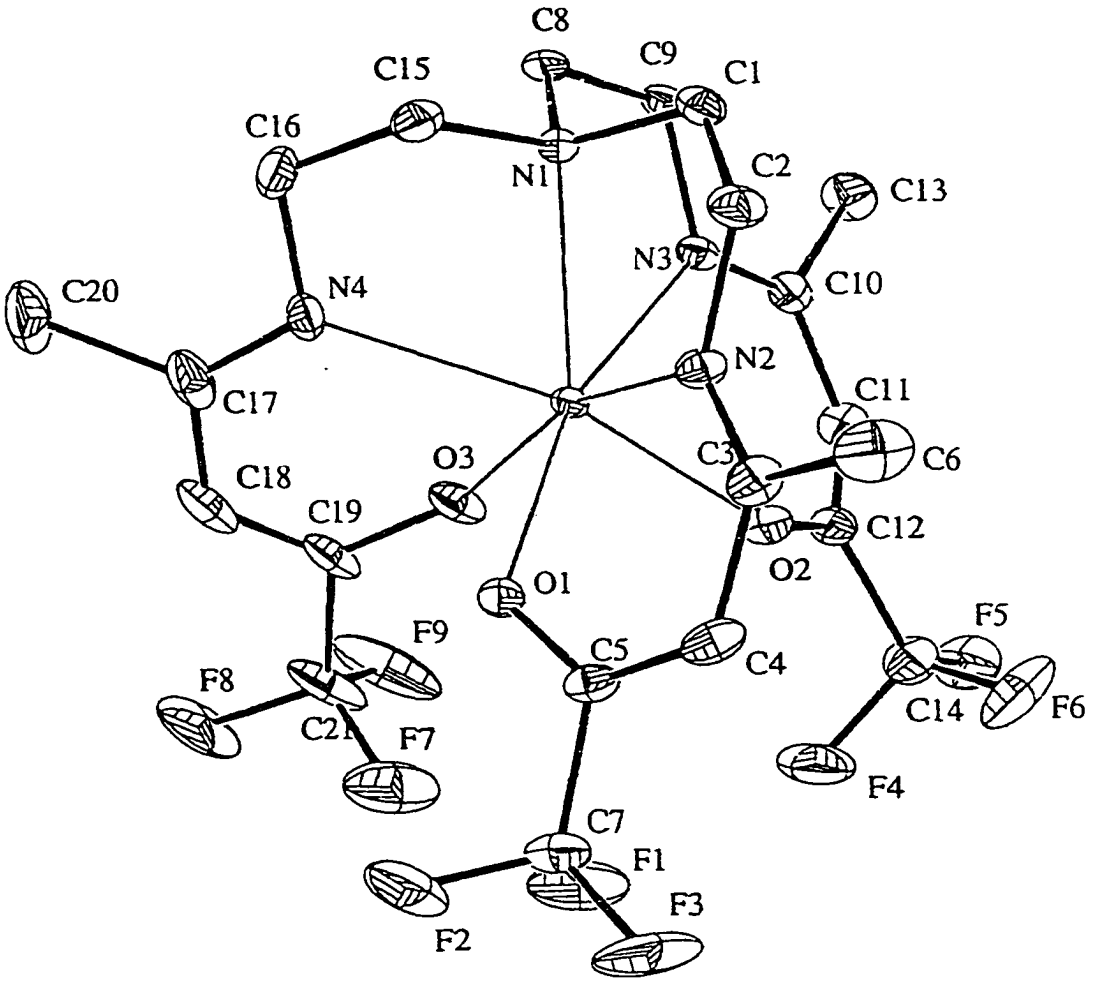


Figure 9: ORTEP of Y(F_3trac) crystal structure.

Surprisingly, when evaluated for catalytic potential, the YF_3trac complex was also ineffective for the hetero Diels-Alder reaction. In fact, the presence of the trifluoromethyl substituents did not influence the catalytic behaviour at all, as 4 days of catalysis yielded only 8% of the desired product, as determined by GC.

Therefore, the lack of sufficient activity of all the trac systems investigated indicated the importance of the ligand environment surrounding the lanthanide metal

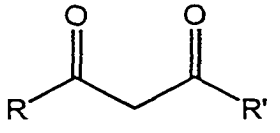
centre. Previously, there was little known about the necessary features of an effective lanthanide Lewis acid catalyst for the hetero Diels-Alder reaction, with the only two known examples being the commercially available NMR shift reagents described previously. At this point, it became clear that a methodical investigation of the relationship between ligand structure and catalyst function would be an integral factor in future ligand design.

2.3 Effect of Ligand Structure and Acidity on Catalytic Function

In order to probe a wide range of ligand structures, simple tris complexes of commercially available ligands, or previously prepared lanthanide complexes were screened for catalytic function. The mixed hetero-atom chelating ligands of the trac ligand systems did not promote useful catalysis. Yet, oxygen diketonate chelate complexes are known to be effective catalysts for the IDHDA reaction. Therefore, it was desirable to investigate a variety of chelating ß-diketone ligands to determine the necessary ligand features in a functioning catalyst. Also, of key interest was the possibility of determining a non-chelating ligand which would exhibit the desired catalysis.

2.3.1 Oxygen Donor Ligands

An investigation of a range of diketone chelating systems was important to establish what types of diketones promoted this reaction. The examination began by preparing a range of tris chelates of a series of ß-diketone type ligands (Figure 10).



4 a $R = R' = CH_3$
b $R = CH_3$, $R' = CF_3$
c $R = R' = CF_3$
d $R = t\text{-}Bu$, $R' = C_3F_7$
e $R = CH_3$, $R' = CCl_3$

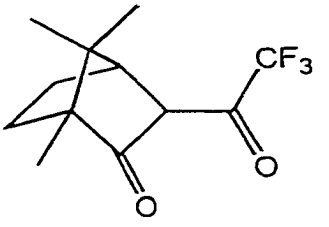


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Figure 10: Various ß-diketone type ligands probed.

Ligands **4a-c** are all commercially available and were purified by distillation prior to preparation of the yttrium and ytterbium tris chelates. These complexes were easily prepared under anhydrous conditions using the $Ln[N(SiMe_3)_2]_3$ starting materials described earlier. Although acac tris chelates of the lanthanides are readily-accessible from aqueous solution, leading to hydrated compounds,[114] literature precedence for well characterised anhydrous tris-chelates is sparse.[115] It has been shown that while the stoichiometry and room temperature NMR spectrum of the yttrium tris-acac complex are consistent with a six-coordinate monomeric formulation, in fact it exists in both the solution and the solid state, as an aggregated formula best described as $[Y(acac)_3]_n$.[115,114]

This tendancy to form oligomers excludes the possibility of preparing X-ray quality crystals, or obtaining meaningful mass spectral data in most instances. Consequently, there were significant challenges in obtaining characterisation data for the various acac type ligand complexes of the lanthanides. However, the yttrium complexes of ligands **4a-c** were all characterisable by NMR, while the molecular ions of the ytterbium complexes were observable by EI mass spectrometry (Figure 11).

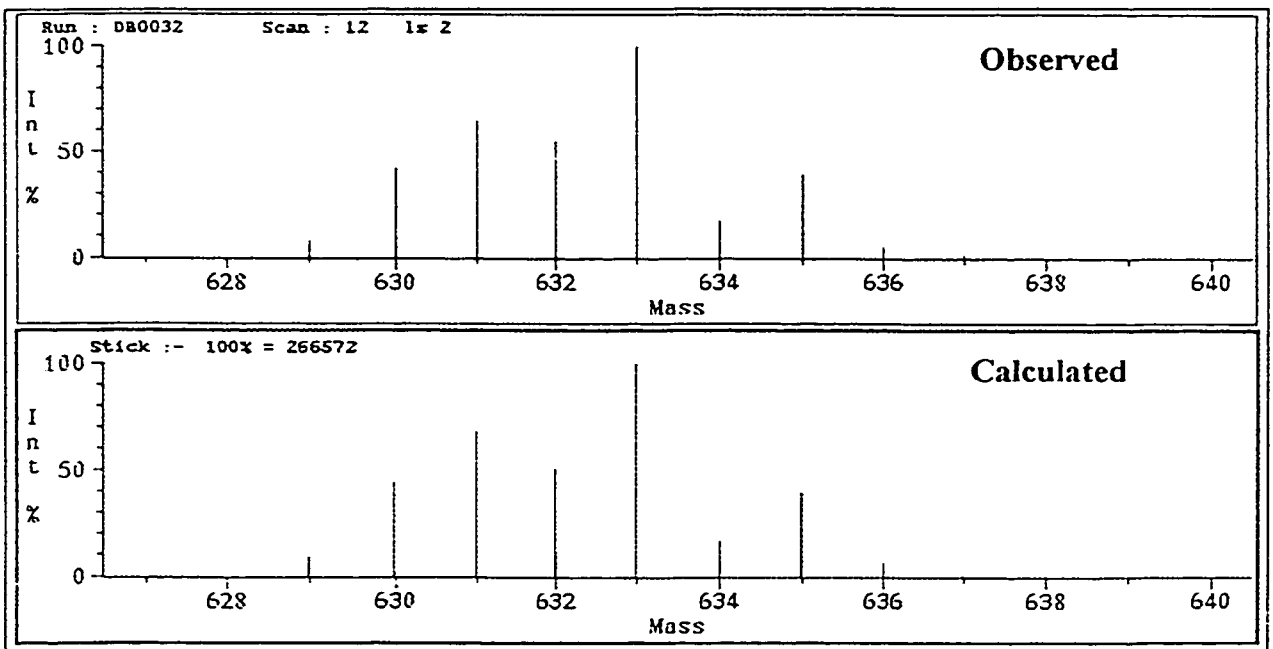
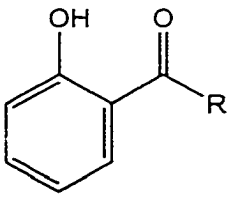


Figure 11: EI Mass Spectra of $Yb(F_3acac)_3$.

In addition to yielding the desired molecular ions, the calculated and observed isotope patterns for these complexes were well matched (as shown in Figure 11) indicating the presence of ytterbium. The ytterbium complexes of ligands **4d** and **5** were purchased, handled under a stream of argon and used without further purification. The ligand **4e** was prepared as described by Morris and Koob,[116] and was substituted onto yttrium using

previously described reaction conditions to obtain an orange solid.[115] However, the yttrium complex was not meaningfully characterisable by MS, due to trichloroacetylacetonate's propensity for unpredictable rearrangement and reduction in the gas phase,[116] nor was it characterisable by NMR due to complex oligomer formation in solution.

Various substituted phenols can be considered ß-diketone type ligands, where the diketone backbone is in the enol tautomeric form. Thus, commercially available ligands **6a** (salicaldehyde), and **6b** (2-hydroxyacetophenone) (Figure 11) were substituted onto ytterbium to probe their ability to promote catalysis at the lanthanide metal centre. These complexes were pale yellow and bright yellow respectively and were of low solubility, indicating their probable oligomeric structure. There is no literature precedence for the characterisation of anhydrous lanthanide complexes of either ligand **6a** or **6b**. Meaningful mass spectral data could not be obtained while their low solubilities excluded the possibility of NMR characterisation. Although the nature of the lanthanide complexes of **4e, 6a** and **6b** cannot be discussed, the materials isolated after reaction completion were solids that were different colours from the starting materials and contained no unreacted reagents. What can be determined with certainty is the impact the various ligand environments had upon the catalytic function of the lanthanide metal centre.



6 a R = H
b R = CH_3

All of the complexes of the ligands discussed above were evaluated using the GC assay described in 2.2. The results of these tests are presented in Table 1.

Table 1: Reaction of crotonaldehyde with ethyl vinyl ether as catalysed by different lanthanide complexes.

Ligand	Metal(s)	Yield (%)[a]
4a	Y, Yb	19
4b	Y, Yb	86
4c	Y, Yb	86
4d	Yb	90
4e	Y	17
5	Yb	88
6a	Yb	21
6b	Yb	6

[a] As measured by GC after 4 days, average of three trials.

This investigation of a variety of acac type ligands revealed that efficient catalysis relies on having a fluoro substituted acac ligand. Also, an important point established during this investigation was the fact that either yttrium or ytterbium had comparable catalytic results and it is a reasonable simplification for subsequent catalyst development to focus on the preparation of yttrium complexes. In addition to investigating chelating ligands several non-chelating oxygen bound lanthanides were screened for catalysis.

In particular two monomeric, well characterised yttrium complexes of ligands 7[117] and 8[118] (Figure 12) were readily available by following literature preparations.

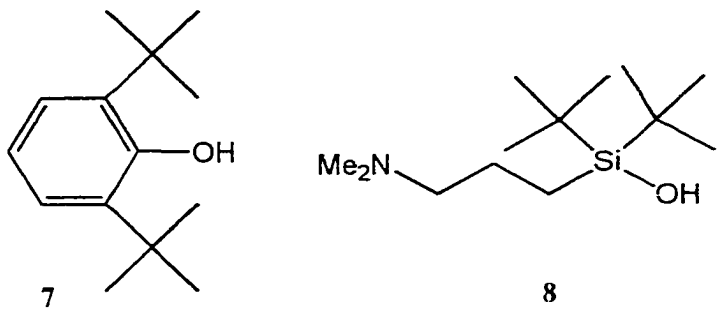


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Figure 12: Alcohol type ligands

The yttrium tris-alkoxide complexes of both of these ligands were soluble under catalysis conditions, but exhibited no product formation in the hetero Diels-Alder reaction as observed by GC. The unreacted starting materials were observed to remain unaffected for up to 4 days.

Upon examining the catalytic results obtained up to this point a trend seemed to appear: as the pKa of the ligand went down, the catalytic activity of the metal centre increased. A reorganisation of the data obtained up to this point in Table 2 demonstrates this trend nicely.

Table 2: Catalytic activity of metal complexes and its relationship to ligand pKa.

Ligand	pKa	Ref.	Metal(s)	Yield (%)
8	13.6	[119]	Y	0
1	12	a	Y, Yb	9
7	>11	b	Y	0
2	11	a	Yb	0
6b	10	[120]	Yb	6
3	9	a	Y	8
4a	9	[120]	Y, Yb	19
4e	8.5	c	Y	17
6a	8.2	[120]	Yb	21
4b	6.3	[120]	Y, Yb	86
5	6	b	Yb	88
4d	5.1	[121]	Yb	90
4c	4.5	[122]	Y, Yb	86

a Estimated from known trends.[123]
b Estimated from similar compounds.[120]
c Measured in 40% dioxane/water.[124]

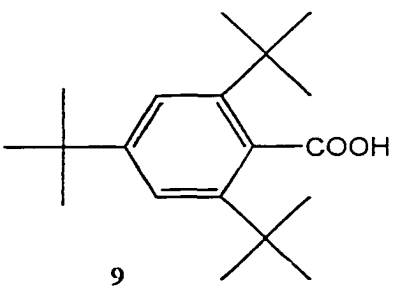
The ligand pKa's were obtained from the literature wherever possible, with the appropriate references given in the table. In the case of trichloroacac it was necessary to determine the ligand pKa experimentally and it was measured in a 40% dioxane/H_2O solution using a standard titration method.[124] Yet other ligands, such as the trac ligand

systems, which have various acidic and basic sites within the same ligand, were estimated from trends established by similar well known ligand systems such as salen.[123]

The trend apparent in Table 2 makes intuitive sense when one considers how the ligand environment can in turn "tune" the metal environment. In effect, ligands of low pKa, that stablize negative charge effectively, do not contribute large amounts of electron density to the electropositive metal centre when compared with ligands of higher pKa. Using this analogy it could be considered that by lowering ligand pKa we are increasing the Lewis acidity of the metal centre.[125] From the data in Table 2 it would appear that the ligand must possess a pKa value of approximately 7 or less to yield an effective Lewis acid centre. This conclusion needed to be tested and consequently the preparation of carboxylic acid derivatives, with pKa's within the desired range was undertaken.

2.3.2 Carboxylic Acid Ligands

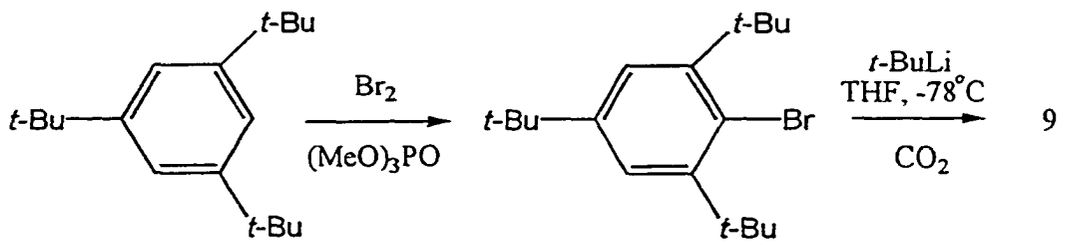
In our effort to prepare monomeric, well-characterised lanthanide catalytic reagents we designed target molecule **9** as a ligand possessing many desirable features. The bulky t-butyl substituents were incorporated into the ligand for two important reasons: First, lanthanide carboxylates are known to form oligomeric materials and the placement of the bulky substituents in the *ortho* position would promote monomer formation; second, the t-butyl groups would ensure complex solubility. Most importantly, this carboxylic acid has a calculated pKa of 6.25;[126] a value well matched with the active



9

catalysts previously prepared. Because of the host of readily available chiral amino acids, a carboxylic acid ligand yielding an active catalyst was an attractive goal.

Ligand **9** was prepared by monobromination of 1,3,5-tri-t-butylbenzene[127] followed by lithium-halogen exchange with n-butyllithium in THF and quenching with gaseous carbon dioxide (Scheme 11).[128]

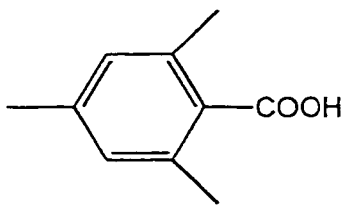


Scheme 11: Preparation of Ligand 9

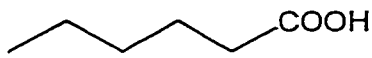
Ligand **9** was isolated as a white crystalline solid in 35% yield and was dried in *vacuo* before reacting with the $Ln[N(SiMe_3)_2]_3$. In both the yttrium and the ytterbium case a soluble white powder was obtained in good yield (75%). The complexes were characterised by NMR spectroscopy and the metal content of a known amount of sample was determined by titration.[129] The sharp signals apparent in the ^1H NMR, as well as the metal content data, were consistent with a monomeric formulation.

When evaluated for catalysis, complexes of ligand **9** demonstrated no catalysis and only starting material crotonaldehyde was recovered. In an investigation attempting to probe the Lewis acidity of the metal centre[130] trans-crotonaldehyde, in the presence of the complex of ligand **9** was observed to undergo cis-trans isomerism. In the absence of a

Lewis acidic species this isomerism takes place at a much slower rate in solution. Although isomerisation was observed, indicating a complex-crotonaldehyde interaction of some sort, there was not the anticipated chemical shift changes (eg. $\Delta\delta$ 1.2 ppm for BF_3) which have been documented for other Lewis acids in the presence of crotonaldehyde.[130] A possible problem in ligand design was the presence of the very bulky *t*-butyl groups, which may have caused too much steric congestion about the metal centre, thereby inhibiting effective metal-crotonaldehyde interaction. Thus, ligands **10** and **11** were identified as useful ligands to test this new hypothesis.



10



11

CF_3SO_3H

12

Ligand **10** and the yttrium complex of ligand **11** were commercially available. The calculated pKa of **10** is 5.25,[126] while hexanoic acid is known to have a pKa of 4.8.[120] Once again, these target ligands had pKa values in the desired range, and were anticipated to "tune" the Lewis acidic nature of the metal centre appropriately. Another commercially available lanthanide Lewis acid, the reagent derived from triflic acid **12**, was also probed for catalysis. This ligand has a very low pKa value of <-6[131] and its complexes have already been shown to be active Lewis acid catalysts for a variety of Diels-Alder reactions, although there have been no reports of an inverse demand hetero Diels-Alder reaction.[43, 60, 75]

The yttrium complex of ligand **10** was prepared using the general procedure, with the desired product isolated as a white powder in adequate yield (54%). It was characterised by NMR spectroscopy, which revealed the complex as being consistent with a monomeric formulation. The complexes of ligands **11** and **12,** which are known to be oligomeric, were handled under a stream of argon and used without further purification.

The attempts to use either the complexes of ligands **10** and **11** were fruitless. Using the same GC assay for product detection, no product formation and no detectable side products were observed. The starting materials remained intact and unreacted for 4 days. It was clear that carboxylic acid functional groups, although in the correct pKa range, did not promote Lewis acidic catalysis at the lanthanide. Clearly, there are more factors to consider in effective ligand design than just ligand pKa, although these factors remain unclear.

When the complex of ligand **12** was tested, it provided an interesting result for the inverse demand hetero Diels-Alder reaction; it polymerized the starting materials within seconds of addition to the reaction vessel. This result indicates that for the inverse demand case, where starting materials are sensitive to Lewis acids, there is an important balance between enough Lewis acidic nature to catalyse the reaction, but not so much that decomposition of the starting materials occurs.

These investigations provided useful information for the design of future catalytic systems. First, we established that the use of the diamagnetic metal yttrium is a reliable alternative to the previously reported paramagnetic ytterbium. Second, it became clear that ß-diketone ligands represent an important functional feature which must be incorporated into future ligand design, as the only efficient catalysts which we observed

possessed ligands of this type. Last, the ß-diketone ligand must be of sufficiently low pKa to promote efficient catalysis, and this target pKa range is best achieved using perfluoromethyl substituted ß-diketones.

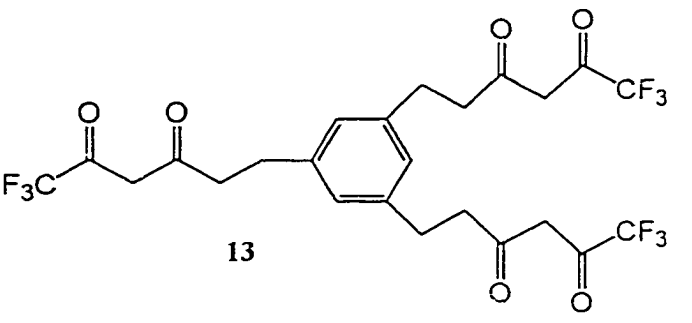
The reason for the effectiveness of ß-diketone ligands of sufficiently low pKa versus the lack of activity exhibited by catalysts with carboxylic acid ligands of equally low pKa has been the topic of much discussion. One possible explanation is a hinging mechanism in the ß-diketonate case that would improve accessibility to the metal centre, thereby promoting catalysis. This mechanism proposes a partial dissociation of one arm where a bidentate ligand would become monodentate, and has been identified as a key step in the intramolecular rearrangements of aluminum and gallium acac complexes.[132, 133] However, given the significant size difference between the lanthanides and aluminum and the lack of steric congestion imposed by ß-diketonates on lanthanides, a hinging mechanism does not seem necessary to promote access to the metal centre. A change in mechanism due to size has already been investigated in the case of titanium[134] where a twist mechanism (*via* a trigonal prism) for ligand rearrangement has been established rather than a hinging process. Although a hinging mechanism would help to explain a functional difference between ß-diketonate ligands versus carboxylate ligands (which do not have improved access to the metal centre when invoking a hinging argument), it does not seem a likely pathway for catalysis.

A more important feature of the ß-diketonate ligand system is its delocalised electron density between the two chelating carbonyls,[114] which may impact the binding/donor mode of the oxygen-metal interactions. This rather unique electronic arrangement with respect to the metal centre may significantly impact the Lewis acidity of

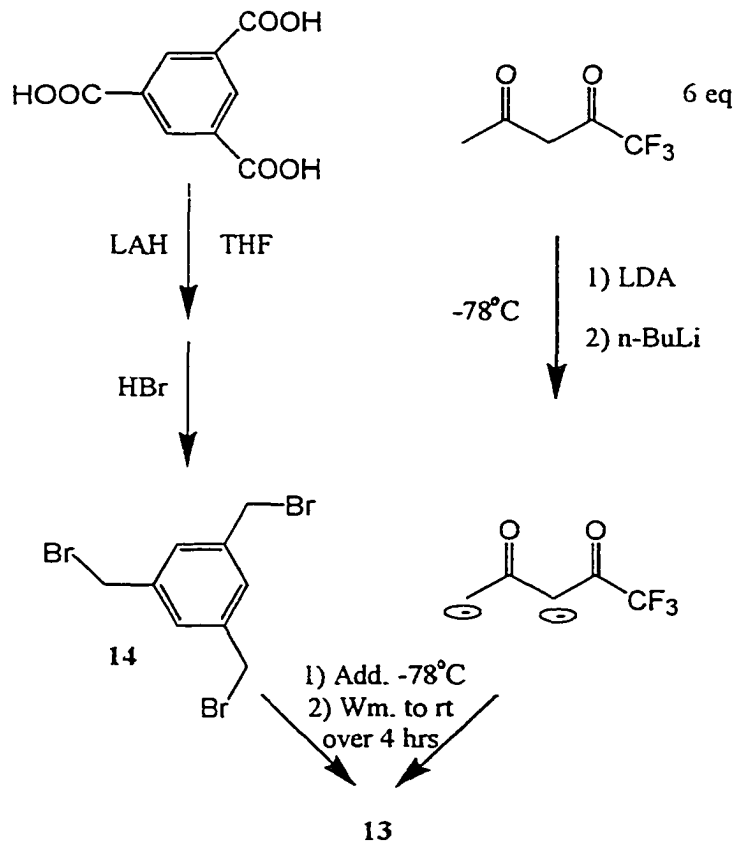
the metal centre. Attempts to measure the Lewis acidity of the metal centre[130] by NMR proved to be impossible due to the low solubilities of the complexes in non-coordinating solvents. A second computational method for the determination of Lewis acidities at metal centres[135] was considered, but was not possible due to the lack of semiempirical parameters for the lanthanides. Regardless of the theoretical premise, it was clear from our investigations that fluorinated ß-diketone functionalities must be incorporated into the design of a ligand system suitable for efficient catalysis.

2.4 Achiral Catalyst

The results of the ligand structure/catalyst function investigation revealed the necessity of chelating fluorinated ß-diketones as ligands for an active lanthanide Lewis acid catalyst. The desire for monomeric lanthanide complexes led to the design of multidentate ligand **13**. This ligand possesses the required features while incorporating the initial scheme of restricted access to the metal centre; where in this case the benzene cap blocks a potential coordination site, while providing a tethering site for the three chelating arms. The strategy for the preparation of **13** is outlined in Scheme 13 where the key step requires the generation of the dianion of trifluoroacetylacetone and its subsequent attack of the capping group, tribromomesitylene **14**.[111]

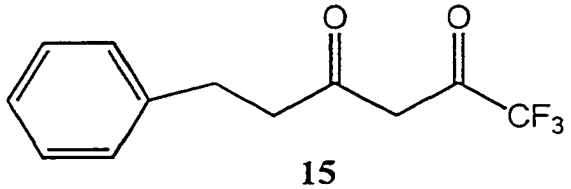


13



Scheme 12: Preparation of achiral multidentate ligand 13

The generation and reaction of dianions of non-fluorinated ß-diketones is well established[136] while the fluorinated case had not been discussed in the literature. Therefore, initial efforts focused on the development of methodology for the reaction of the dianion with benzyl bromide to yield the model compound **15**.



15

The preparation of **15** provided valuable insight into the generation and handling of the dianion of trifluoroacac which only reacted reliably with benzyl bromide at -78°C. Also, a purification procedure was established where the final product could be easily separated from decomposition products by following the initial work-up with base extraction of the deprotonated product into the aqueous layer, followed by acidification and isolation. The model compound was isolated in 62% yield (not optimised) and was characterised by ^{1}H NMR spectroscopy where the appearance of two triplets, centred at δ 2.96 and 2.74 respectively, indicated the successful nucleophilic attack by the dianion on benzyl bromide. With reaction conditions and a purification procedure established the preparation of tripodal ligand **13** was pursued.

The first synthetic challenge was the efficient preparation of α,α',α"-tribromomesitylene, **14**, a strong lachrymator. Compound **14** can be prepared by NBS bromination of mesitylene,[137, 138] but this was found to be an inefficient route to the desired product. The reaction provided a mixture of mono, di and tribrominated products which were only separable by repeated recrystallisations from hot cyclohexanes, resulting in poor yields (<20%). Attempts to force the reaction to go to completion with longer reaction times, higher reaction temperatures and large excesses of the brominating agent did not improve isolated product yield significantly.

An alternative route for the preparation of **14** is outlined in Scheme 12. In this case the LAH reduction of benzene 1,3,5-tricarboxylic acid yielded lithium/aluminum salts of the intermediate tris alcohol. Isolation of the alcohol is very difficult and requires extensive soxhlet extraction of the above mentioned salts. However, the alcohol product does not need to be isolated, but rather the salts can be dried in *vacuo* and reacted directly

with a large excess of 48% HBr in benzene, to give the desired product in excellent yield. The crystalline solid **14** was further purified by recrystallisation from hot cyclohexane and the compound was isolated as off white needles in 80% yield.

With the brominated capping compound in hand and the methodology established in the preparation of model compound **15**, ligand **13** was prepared as shown in Scheme 12 (p 63). The crude product was a viscous golden oil from which beige crystals could be obtained in a dry THF/hexanes mixed solvent system with cooling. To further purify and eliminate any moisture the product was sublimed at 140°C at 10^{-2} Torr and gave crystalline product in 40% yield.

The ^{1}H, ^{13}C and ^{19}F NMR spectra are shown in Figures 14, 15 and 16. The carbon spectrum is most informative with the clear fluorine-carbon coupling of the CF_3 substituent and its adjacent carbon. The significant chemical shift difference of >20 ppm between the ketone carbon and the enol carbon is indicative of the enol tautomeric structure of the ligand. The simple pattern of all the spectra are indicative of formation of the C_3 symmetric tripodal ligand and was confirmed by high resolution mass spectrometry.

The multidentate ligand, after vacuum sublimation, was taken into the glove box and could be reacted with $Y[N(SiMe_3)_2]_3$ using the standard procedure to yield a white solid which was insoluble in non-coordinating solvents and highly soluble in coordinating solvents. Spectroscopic studies of the complex in d_8-THF showed a non-C_3 symmetric system implying either an oligomeric structure or an incorporation of solvent into the coordination sphere that destroys symmetry. Variable temperature studies of the complex did not indicate significant changes in complex symmetry. This observation combined

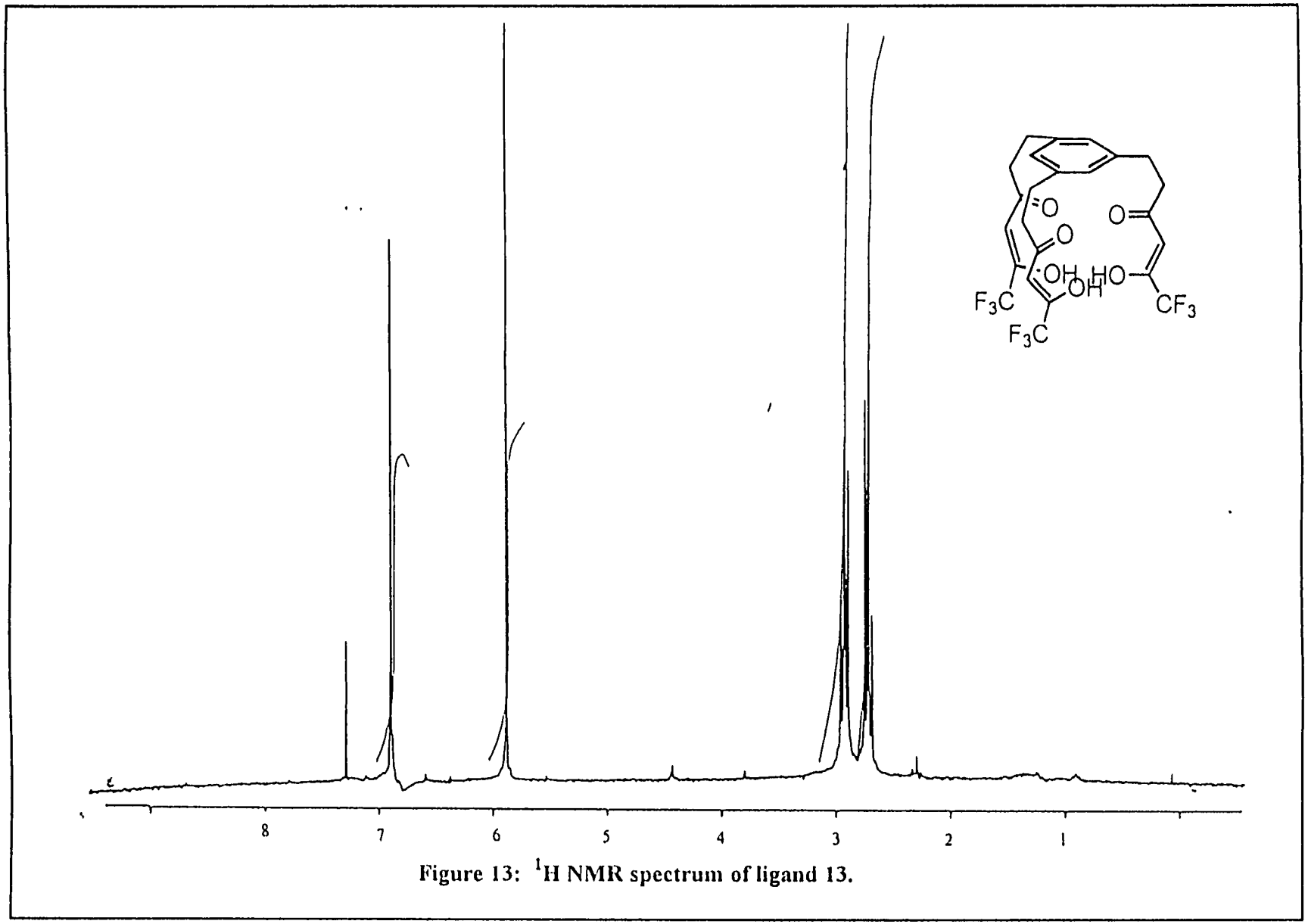


Figure 13: ^{1}H NMR spectrum of ligand 13.

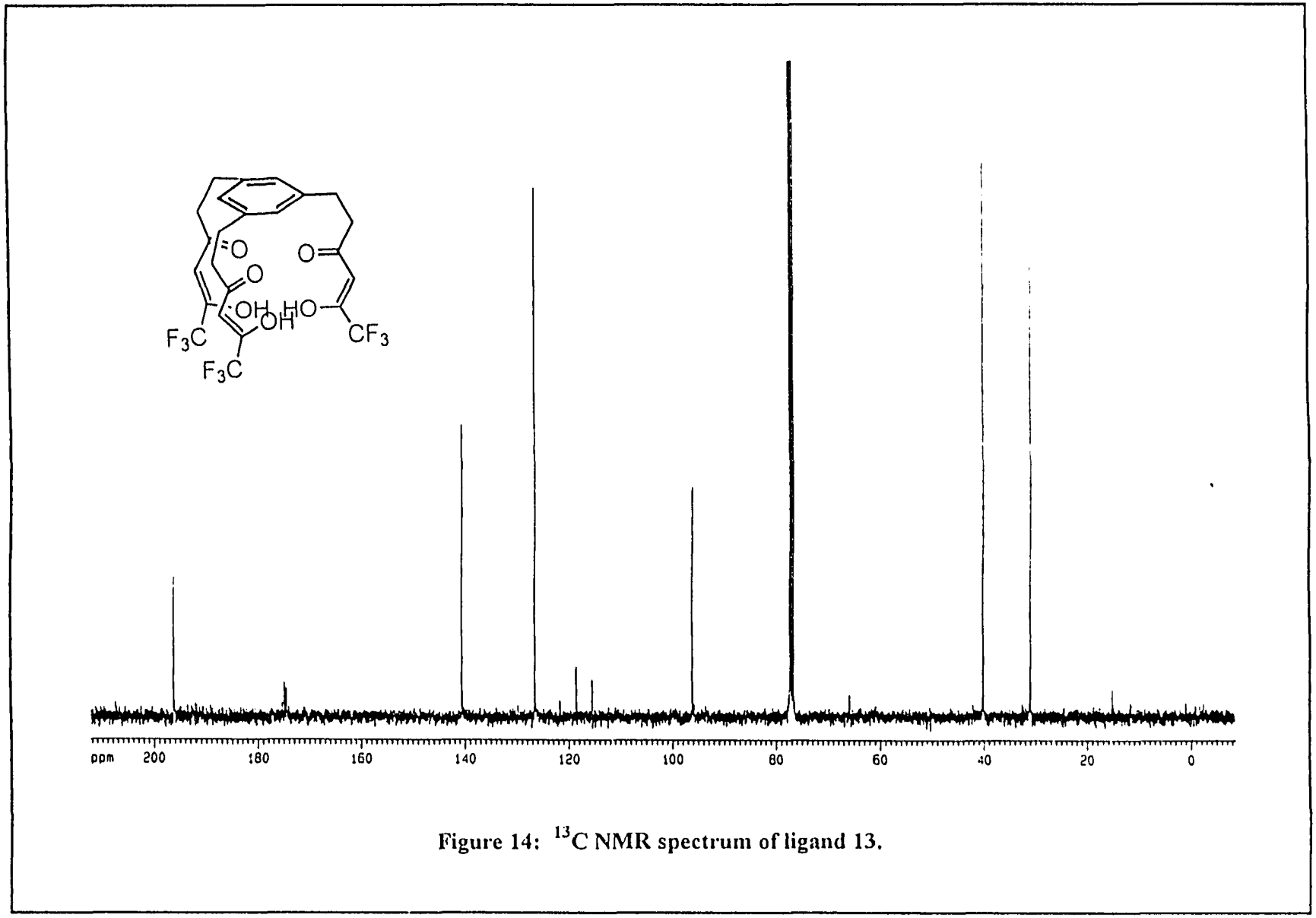


Figure 14: ^{13}C NMR spectrum of ligand 13.

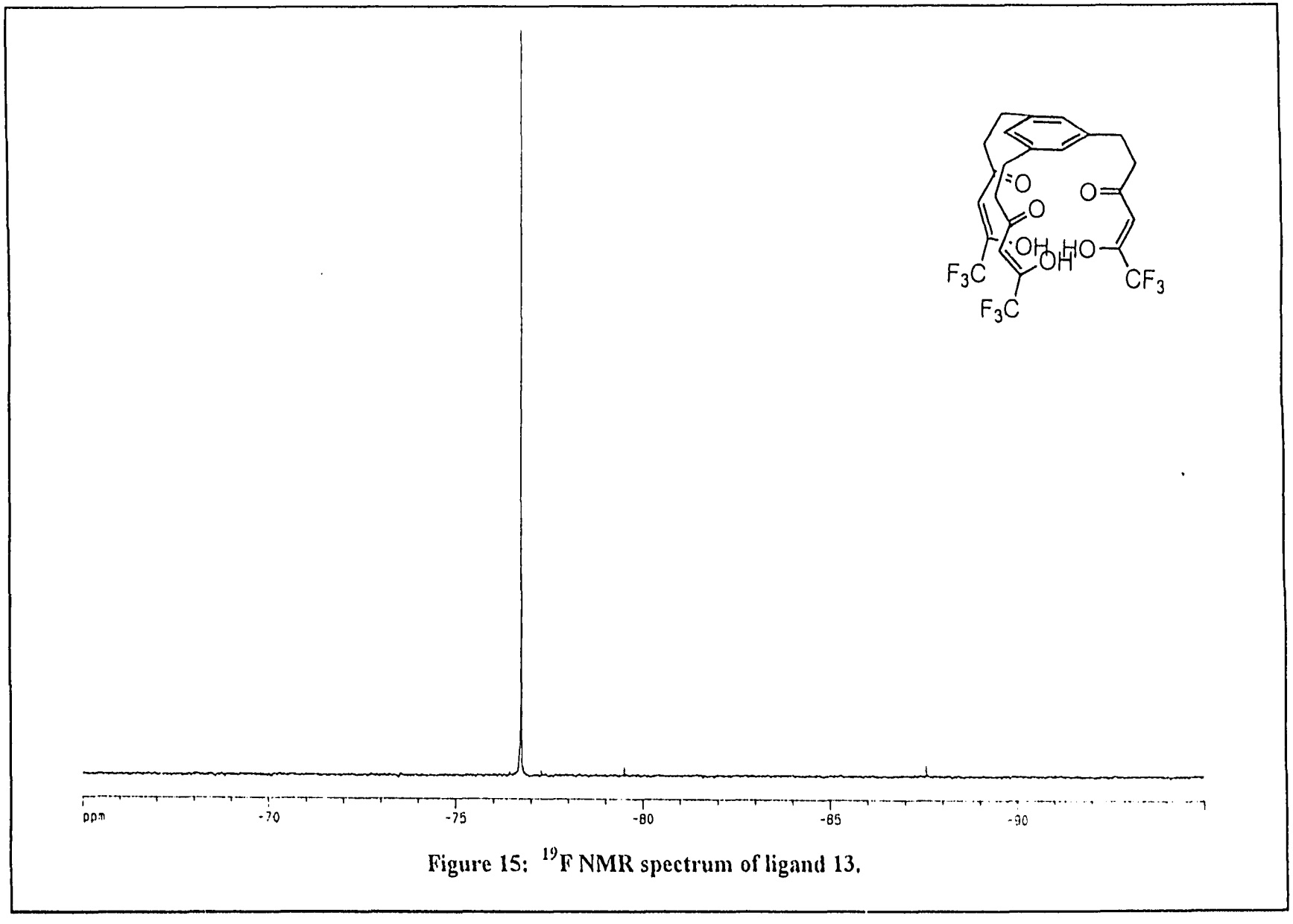


Figure 15: ^{19}F NMR spectrum of ligand 13.

with the solubility behaviour is indicative of an oligomeric structure. However, by preparing the complex using THF as solvent it is possible to isolate a somewhat benzene soluble C_3 symmetric complex which included one molecule of THF (as determined by ^1H NMR integration) as is shown in Figure 16. Other interesting features of the spectrum are the upfield shift of the aromatic protons $\Delta\ \delta$ 0.45 ppm. This significant shift away from the aromatic region might indicate a disruption of the aromatic ring current, indicative of a possible metal interaction with the π system of the benzene ring. The tripodal, C_3 symmetric structure was further confirmed by ^{19}F (Figure 17) and ^{13}C NMR spectroscopy while the yttrium complex was observable by high resolution mass spectrometry (calc. 662.0018, found 662.0000). Unfortunately, repeated attempts in many solvent systems did not yield conditions suitable for the growth of X-ray quality crystals.

The yttrium complex of ligand **13**, whether isolated as an oligomer or as a monomer was an effective catalyst for the hetero Diels-Alder reaction with the desired product appearing in up to 96% yield (as determined by the GC assay). In fact, the complex prepared in the absence of coordinating solvent yielded the most active catalyst, presumably due to the lack of solvent occupying the anticipated crotonaldehyde coordination site.

The effect of potential donors on product yield was further demonstrated by the use of dioxane as an internal standard for GC yield determinations. The use of this donating solvent slowed product formation slightly (80% after 4 days) for two possible reasons. First, the presence of the donor solvent lowers Lewis acidity of the metal centre, thereby lowering catalytic activity. Second, the donor solvent is in a competitive equilibrium with crotonaldehyde for access to the metal centre, which consequently slows

the rate of product formation. It is likely that both of these mechanisms play a role in the reduction of catalyst performance.

During the course of our investigation it was discovered that the complex exhibited remarkable stability when exposed to air, as formation of insoluble hydrated yttrium oxides was not observed and the appearance of protonated or decomposed ligand was not seen in NMR studies. In fact, the achiral ligand complex continued to display catalytic behaviour after prolonged bench top storage of up to 3 months. The catalysis was shown to be marginally slower for the air-exposed complex (90 % after 4 days) and this is believed to be due to the complexation of atmospheric moisture. The notable stability of the complex was demonstrated by suspending the complex in water (it is not soluble), and re-isolating the complex by extraction to yield a functioning catalyst. This moisture-stability is a significant practical improvement over the commercially available $Yb(fod)_3$ catalyst which decomposes upon exposure to air and must be handled using air-sensitive techniques. The air-stability is presumably due to the multidentate nature of the catalyst.

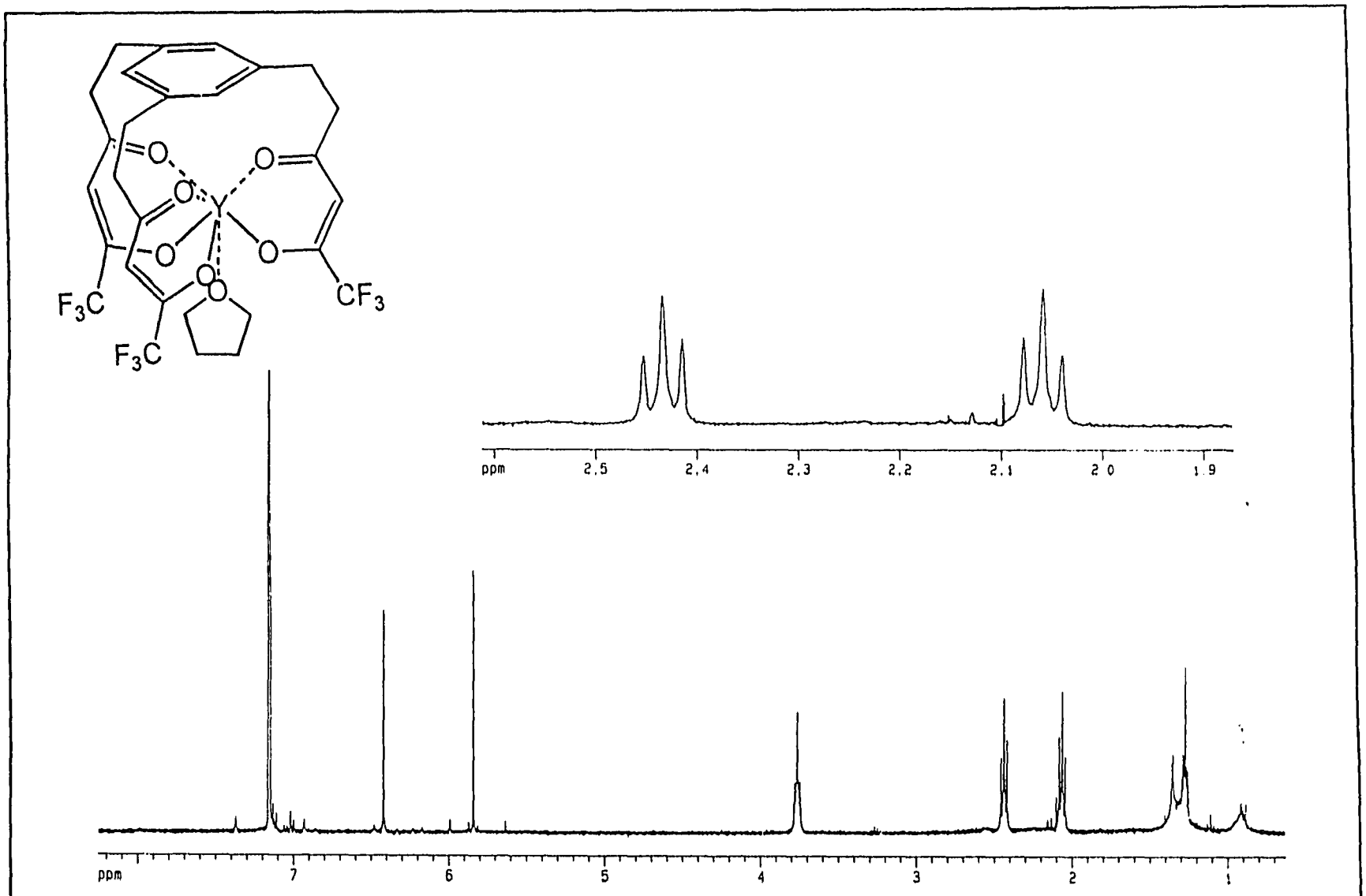


Figure 16: ^{1}H NMR spectrum of the Y complex of ligand 13.

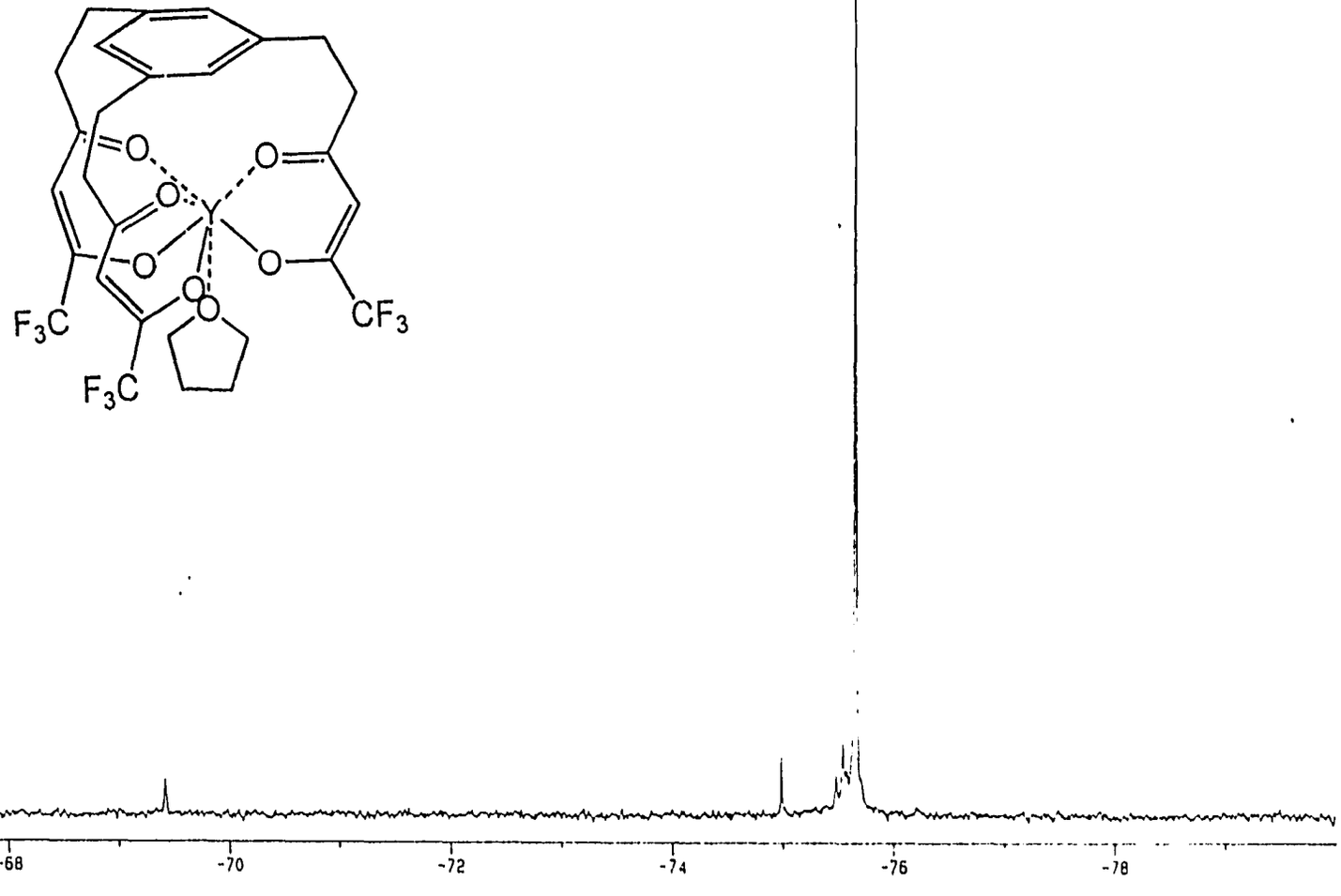


Figure 17: ^{19}F NMR spectrum of the Y complex of ligand 13.

2.5 Conclusions

We have prepared an effective air-stable achiral lanthanide catalyst which provides a solid model from which to design future chiral catalysts. The ligand structure/catalytic function investigation of a variety of lanthanide coordination complexes provided important information regarding necessary ligand features to yield effective lanthanide catalysts. It was determined that ß-diketone type ligands of sufficiently low pKa were required. We also established the usefulness of yttrium as a catalytic metal centre. The incorporation of these functional groups into a multidentate ligand design yielded a complex which is resistant to decomposition.

CHAPTER 3: Chiral ß-Diketone Ligand Syntheses

3.1 Introduction

The achiral, multidentate yttrium catalyst provided an excellent model system for the preparation of chiral catalysts. We established the design features which needed to be incorporated into all target ligand systems during the ligand structure/catalyst function studies. It was also recognised that rarely does rational chiral catalyst design lead to optimised enantiomeric excesses, and a strategy for the preparation of a variety of chiral catalysts would need to be adopted. Therefore a generalised route into chiral catalytic systems was maintained as an ideal approach.

One such possibility was the preparation of a host of chirally substituted, fluorinated ß-diketones which could then be attached to the benzene capping system using established methodologies. A second, more modular strategy, involved the preparation of a fluorinated benzene capping system which could be coupled with chiral ketones. During the course of these investigations the many synthetic challenges of α-fluoroketones were discovered.

Ultimately, the design of target ligand systems was guided by literature precedence and new chiral ligand systems were prepared using well established methodologies. The ligand complexes were explored through molecular modelling to determine their potential as enantioselective catalysts.

3.2 Chiral ß-Diketones

The preparation of chirally substituted ß-diketones (Figure 18) would permit the facile assembly of C_3 symmetric chiral ligands using the dianion methodology established during the preparation of the achiral, multidentate yttrium catalyst. Addition of the chiral substituent is possible using a number of C-C bond forming reactions including Michael additions and direct alkylations.

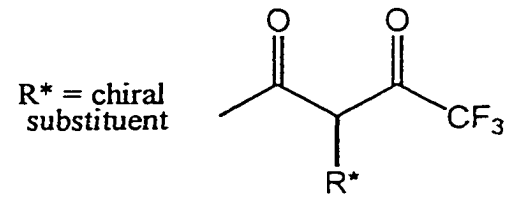
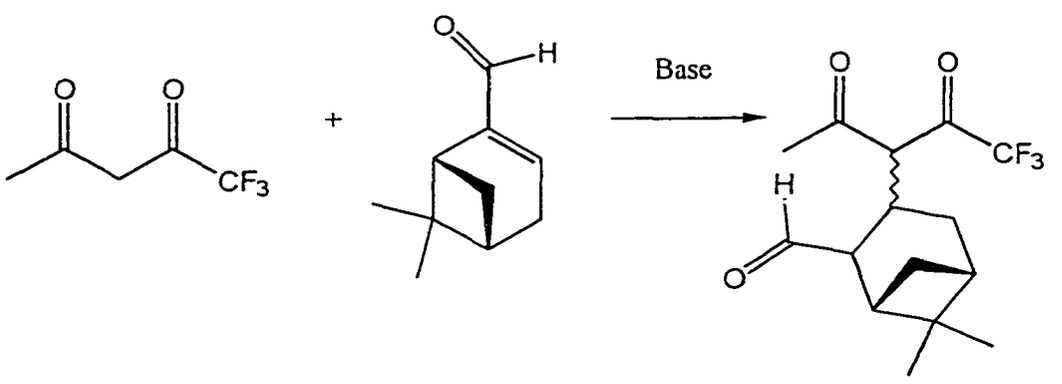


Figure 18: Generalised chiral fluorinated ß-diketone

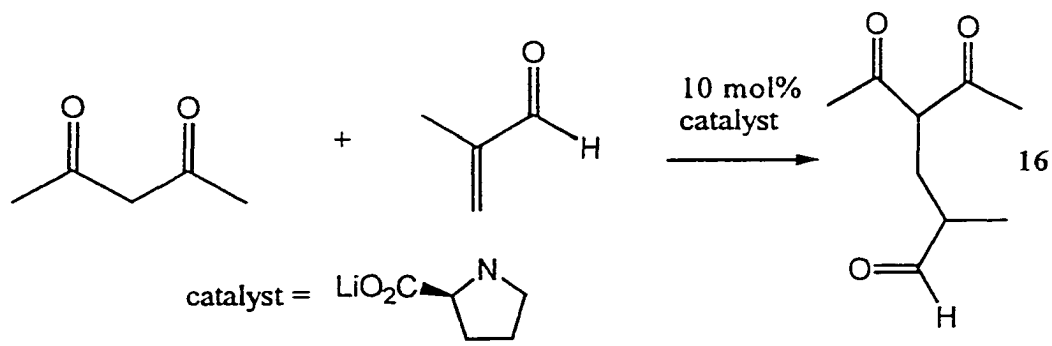
3.21 Michael Additions

The Michael addition is an effective, mild C-C bond forming reaction which is well established for the addition of α,ß-unsaturated carbonyls to ß-dicarbonyls.[151-153] We were interested in using this methodology to effect the addition of commercially available chiral α,ß-unsaturated aldehydes, such as myrtenal, to trifluoroacetylacetone (Scheme 13). One recognised challenge of this strategy was the choice of an α,ß-unsaturated aldehyde as the Michael acceptor, as reaction control is difficult with few successful examples in the literature.[154]



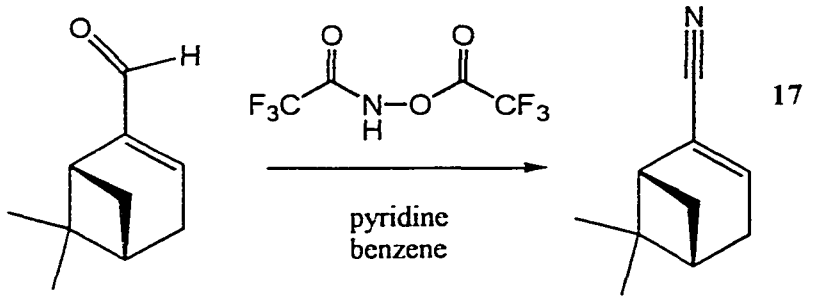
Scheme 13: Michael addition of myrtenal to trifluoroacetylacetone.

Thus, initial efforts focused on the preparation of model compound **16** by the route outlined in Scheme 14. The preparation of **16** was catalysed by the lithium salt of the amino acid proline[154] in methanol, where the crude product could be purified by column chromatography to a diastereomeric mixture of the desired product in 20% yield (not optimised). The successful preparation of **16** indicated the usefulness of the proline lithium salt in promoting the Michael addition of diketones to α,ß-unsaturated aldehydes. Furthermore, literature precedent indicated improved yields for ß-substituted unsaturated aldehydes, such as myrtenal, over the acrolein model system.[154]



Scheme 14: Model system using proline lithium salt as catalyst.

Although successful Michael additions could be induced when using acetylacetonate as the nucleophile, attempts to carry out the target reaction outlined in Scheme 13 were fruitless. The trifluoroacetylacetone proved to be a poor Michael donor, even in the presence of the proline lithium salt, undoubtedly due to the enhanced stability of the trifluoroacetylacetonate anion. Because the Michael donor was inherently poor, it therefore became necessary to improve the nature of the Michael acceptor. It had been shown that even poor nucleophiles can be added effectively to unsaturated nitriles under weakly basic conditions.[155] Consequently, the cyano derivative of myrtenal (**17**) was prepared as shown in Scheme 15.[156]

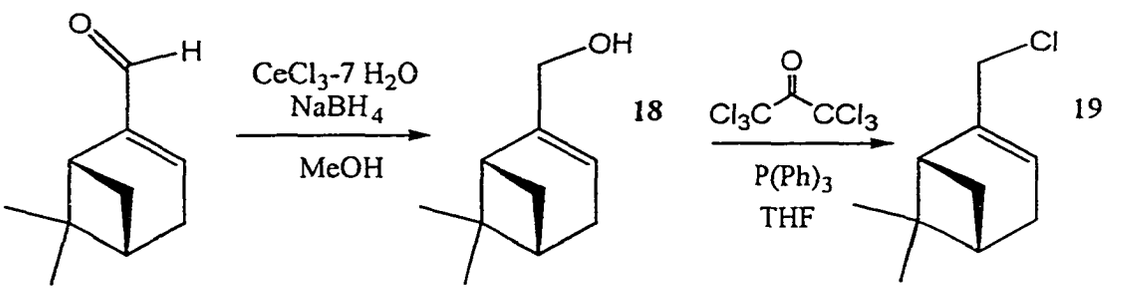


Scheme 15: Preparation of myrtenitrile.

Trifluoroacetohydroxyamic acid did effect the desired conversion to the nitrile in modest yields (27%), however the desired product was inseparable from the starting aldehyde, even by column chromatography. Therefore the entire crude product was subjected to mild reduction conditions[19] resulting in the conversion of aldehyde to alcohol while the desired nitrile remained unaffected. At this point the product mixture could be effectively separated by column chromatography, from which nitrile **17** and side product myrtenol **18** were both isolated. Unfortunately, the nitrile modification did not improve the Michael acceptor nature enough to promote the addition of the trifluoroacetoacetate. Therefore, a variety of reactions using Lewis acid catalysts for both the unsaturated aldehyde and nitrile were attempted. These included titanium tetrachloride,[157] boron trifluoride etherate complex in the presence of copper,[158] and the preparation of nitrilium salts as an enhanced Michael acceptor[159] but the very stable anion of trifluoroacetylacetone proved to be an exceptionally poor nucleophile even under forcing conditions.

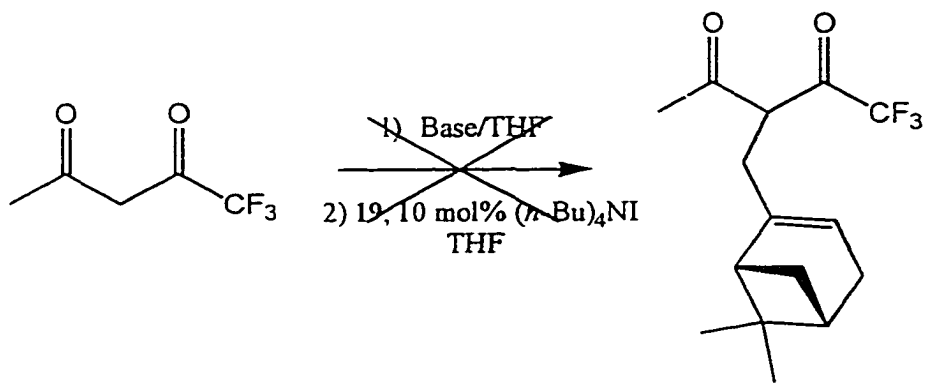
3.2.2 Direct Alkylation

As noted above, the preparation of nitrile **17** resulted in the isolation of a small amount of alcohol **18**. Myrtenol could also be prepared directly (Scheme 16) from the aldehyde using the same reduction conditions mentioned above in 95% yield.[19] This alcohol was then easily converted to the allyl chloride **19** derivative using hexachoroacetone and triphenylphosphine to give **19** in quantitative yield.[160]



Scheme 16: Preparation of myrtenol and myrtenallyl chloride.

In spite of the ease of preparing an electrophile suitable for nucleophilic displacement, all attempts to effect direct alkylation failed, as shown in Scheme 17. This was undoubtedly due to the lack of nucleophilicity of the trifluoroacac anion, as noted in the Michael addition attempts.



Scheme 17: Attempted preparation of chiral ß-diketone by alkylation.

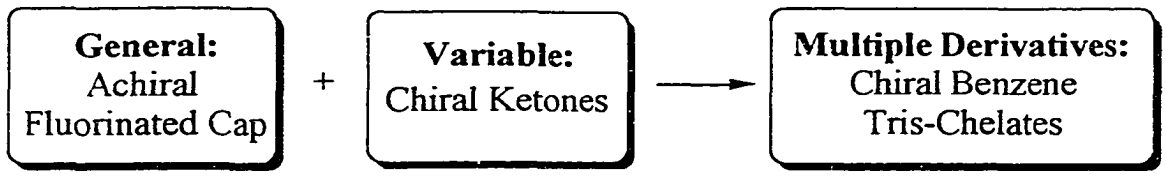
3.2.3 Summary

Although the preparation of chirally substituted ß-diketones seemed an efficient strategy in the preparation of tripodal, chiral ligands, it relied on the facile preparation of a variety of the chiral diketones. As demonstrated in both the Michael addition efforts and direct alkylation attempts, the substitution of trifluoroacac with chiral moieties was challenging at best. Further efforts using this strategy were not pursued for the following reasons. First, the placement of a chiral substituent in between the chelating oxygens would ensure that the asymmetric centre was far removed from the anticipated site of catalysis. It was questionable as to whether this distal location of the chiral moiety could impart any enantioselectivity during catalysis. Second, from a practical perspective, it had been observed that the preparation of the tripodal achiral catalyst using the dianion

approach could not be increased to gram scale without a sacrifice in yield. Even using optimised reaction conditions, a 2 fold excess of the ß-diketone was required to obtain a 40% yield of the desired achiral ligand. Therefore, when considering efficiency, it did not seem reasonable to tackle the preparation of chirally substituted ß-diketones only to consume them in huge excesses while attempting to prepare ligand. For these reasons a new strategy in the preparation of chiral ligands was pursued.

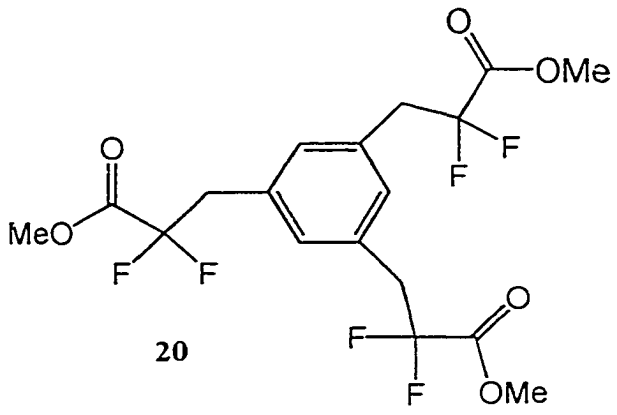
3.3 Achiral, Fluorinated Cap

New ligand designs focused on finding a way to create the desired "chiral pocket" mentioned in the introduction. The strategy described above did not meet this design criterion, and thus a new way of approaching the preparation of these ligands needed to be investigated. It was clear that the ideal chiral pocket would be built with the chiral substituents being placed furthest from the benzene capping system. A second major change in the synthetic strategy was the concept of building up the ß-diketone functionality on a tripodal framework, rather than using the dianion approach of attaching diketones to the tripodal capping system. A modular approach where an achiral carbonyl capping system that could be coupled with a range of chiral ketones was viewed as an improved generalised route into the desired ligand systems. This strategy is best summarised in the simplified Scheme 18.



Scheme 18: Modular approach for the preparation of chiral ligands.

The design of the achiral fluorinated cap **20** would incorporate the chiral substituents about the active site while accommodating the modular approach outlined in Scheme 18. The fluorinated achiral cap would permit the attachment of commercially available ketones using enolate chemistry to build up the necessary fluorinated ß-diketone ligand structure complete with chiral pocket. The resulting ligands would have a structure very similar to the efficient achiral catalyst, but with the fluorine substitution reversed with respect to the diketone framework.



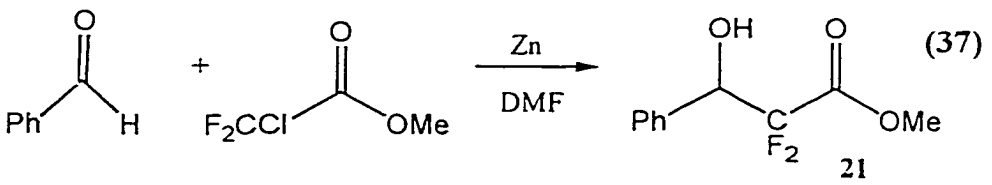
20

An evaluation of the *gem*-difluoroketone literature[161-163,164] revealed a number of potential routes, including a variety of fluorinated synthon approaches, as well as direct fluorination possibilities. This literature search also revealed the significant synthetic challenge that target molecule **20** would pose. Many groups continue to develop methodology for the preparation of *gem*-difluoroketones as existing routes lack generality

and reliability. In our case, because of the C_3 symmetric nature of the capping system, we were attempting to carry out a challenging reaction three times on the same molecule! Regardless, the possibility of accessing a general route into a host of chiral, tripodal ß-diketone ligands was extremely appealing. With this goal in mind a number of attempts to prepare **20** were pursued.

3.3.1 Fluorinated Synthon Approaches

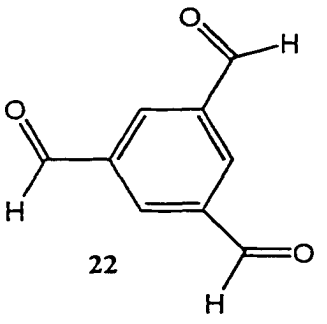
One example of the preparation of difluorocarbonyls uses the Reformatsky type reaction of chlorodifluoroacetic acid derivatives as shown in Equation 37.[165,166] The preparation of compound **21** was carried out as a model system investigation.



(37)

Although the literature yield of **21**[165] was reported to be 68%, in my hands it was considerably less successful with approximately 20% yield as estimated by NMR (not optimised). In this case the preparation of model compound **21** demonstrated the utility of the Reformatsky strategy for the synthesis of difluoroketones. Attentions were then turned toward the preparation of suitable capping molecules, such as **22** and **23**, to provide the desired tripodal framework.

Compound **22** was synthesized from the previously prepared tribromomesitylene **14** using the Sommelet reaction[167] in only 20% yield. This compound is easily prepared, however the challenge lies in its isolation as it is an unstable material which readily oligomerises. Consequently, the possibility of doing three successful Reformatsky additions to **22**, especially under Lewis acid conditions (i.e. the presence of zinc) was assessed as not being a viable synthetic route.



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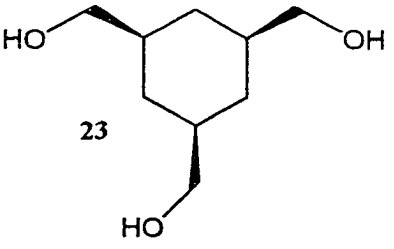
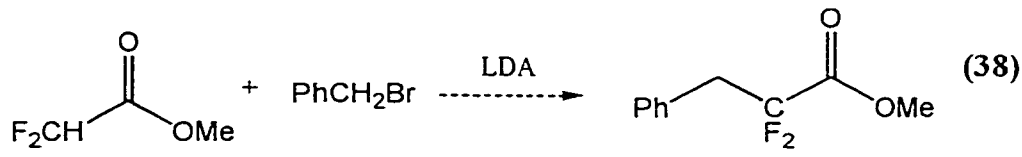


23

A different attempt to prepare a similar capping molecule, the tris-aldehyde of cyclohexane, was abandoned with the preparation of compound **23**. Using literature preparations,[168] compound **23** was prepared using a lithium aluminum hydride reduction of Kemp's triacid and was isolated in poor yield, due to difficult removal of the product from the aluminum salts.

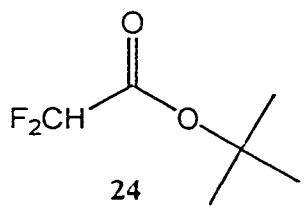
The combination of poor reaction yields in the preparation of model compound **21** and the lack of efficient routes into robust tri-functional capping molecules indicated the need to investigate other possible routes toward the desired achiral fluorinated cap **20**. New synthetic efforts continued to focus on the use of commercially available fluorinated synthons.

A search for useful fluorinated synthons resulted in the possibility of pursuing previously established enolate chemistry to build the desired achiral fluorinated cap **20** as shown in Equation 38. Difluoroacetic acid is commercially available and easily converted

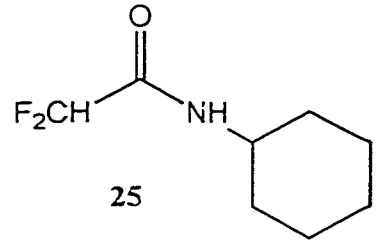


(38)

to the methyl ester shown in Equation 38 by reflux in methanol. However, repeated attempts to carry out the preparation of the model system shown resulted only in unidentified decomposition products. Although use of fluorinated carbon nucleophiles is an area of growing research,[163, 164] there are few examples in the literature of difluoroenolates,[169] with no mention of using difluoroacetic acid derivatives as potential nucleophiles. Due to the volatility of reaction decomposition products, the actual mechanism of decomposition was never determined. One could envision methyl difluoroacetate as a ketene precursor, or perhaps the enhanced electrophilic nature of the carbonyl group (in the presence of the adjacent fluorine substituents) allows lithium diisopropyl-amide to react as either a base or a nucleophile. Consequently, t-butyl difluoroacetate **24** with its increased steric bulk, was identified as a desirable starting material that would decrease the possibility of nucleophilic attack at the carbonyl. However, attempts to prepare **24** in acid catalysed conditions were unsuccessful. When room temperature esterification conditions, using DCC and DMAP in dichloromethane[170] were attempted, the only isolated product



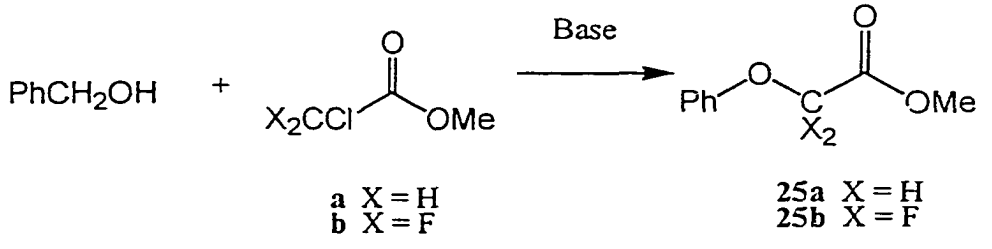
24



25

from this reaction was the crystalline side product **25** as identified by NMR and mass spectroscopy. Formation and isolation of compound **25** supports the hypothesis that difluoroketones have significantly enhanced electrophilic character; so much so that the chemistry of fluorinated versus non-fluorinated carbonyls is drastically varied. Therefore, the anticipation that previously established enolate routes into tripodal ligands could be pursued with fluorinated synthons was shown to be inaccurate.

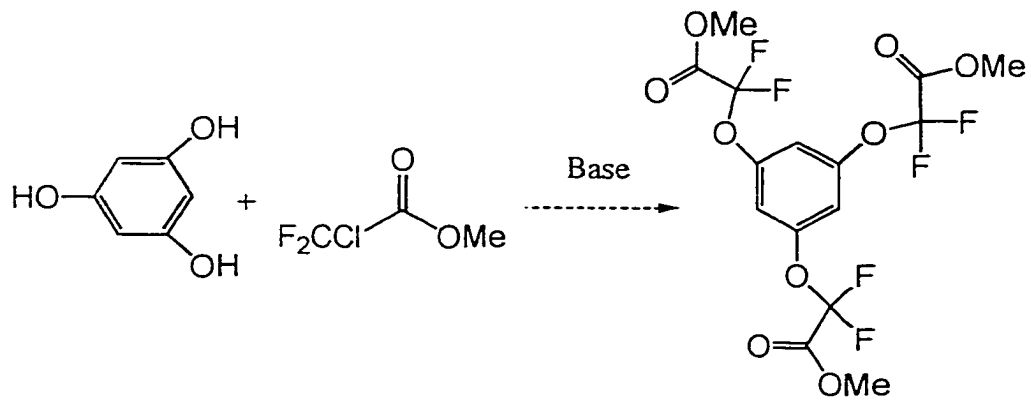
The enhanced electrophilic behaviour of the carbonyls prompted the consideration of using the difluorinated synthon as an electrophile rather than a nucleophile. The addition of phenoxide to α-chloroesters is well established and leads to the product **25a** shown in Scheme 19. Also, there was a report in the literature[171] of the successful addition of potassium phenoxide to dibromodifluoromethane. Thus the synthesis of model compound **25b** was pursued as outlined in Scheme 19.



Scheme 19: Phenoxide addition to α-chloro esters.

This synthetic strategy was an exciting option because both the required capping system, phloroglucinol, and the fluorinated synthon were commercially available. Therefore, the development of appropriate methodology would result in the straight

forward preparation of a modified achiral fluorinated capping system as shown in Scheme 20.



Scheme 20: Proposed synthesis of alternative achiral fluorinated cap.

The preparation of model compound **25b** was attempted using a variety of base catalysed protocols. The most reliable experimental procedure used K_2CO_3 in acetone with catalytic amounts of 18-crown-6. The ^{19}F NMR signal shifted while the broad alcohol signal in the ^{1}H NMR spectrum disappeared. However the ^{13}C NMR did not show any shifts while the mass spectra did not show any trace of the desired products, but did indicate a number of peaks including starting material molecular ions. These results were interpreted in the following manner. The carbon spectrum may not exhibit any significant change, as oxygen substitution on a CF_2 group may have a similar effect on chemical shift as chlorine. The lack of supporting mass spectral data was dismissed as unimportant for several reasons, including the fact that the desired product may be susceptible to decomposition in the gas phase. The shift in the fluorine NMR was interpreted to be

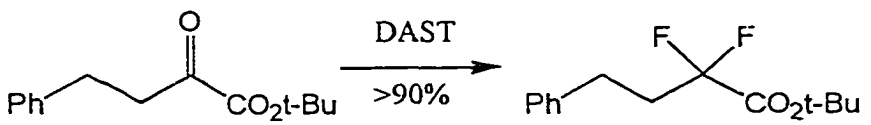
diagnostic of product formation. With this exciting observation, the full characterisation of the model compound and preparation of desired achiral capping system was vigorously pursued. These efforts revealed that curiously, the chemical shift of the ^{19}F NMR signal was not consistent between products of identical reaction conditions and could vary by up to 6 ppm, depending upon concentration of the NMR sample. It was finally established that in fact, product formation had never been achieved, but instead there was a shift in the fluorine signal due to extensive hydrogen bonding between the phenol or phloroglucinol, methyl chlorodifluoroacetate and any water which may be present after work-up.

Working with fluorinated synthons in these various synthetic strategies exemplified the challenges involved in fluorinated small molecule chemistry. Fluorine and hydrogen are of similar size (1.35 Å vs. 1.10 Å respectively), resulting in negligible effects due to steric differences. However, their drastically different electronegativities (4.0 vs. 2.1) explains their very different, and in this case troublesome, chemical behaviour. Although, monofluorination chemistry is well developed,[162, 172] it is usually not applicable to the preparation of difluorinated species. The possibility of using monofluorinated species was not investigated, as it would be necessary to effect difficult chiral monofluorinations. However, the timely appearance of the review article "Methods for the Synthesis of *gem*-Difluoromethylene Compounds"[164] (while this work was in progress), helped by outlining the expansive growth in this area of chemistry over the past decade.

3.3.2 Direct Fluorination

After having pursued the fluorinated synthon approach to build **20,** the only other avenue of investigation remaining was direct fluorination. *Gem*-difluoroketones have been classically achieved by the use of direct fluorinating reagents, involving either nucleophilic or electrophilic fluorine sources. The challenge with direct fluorinations is the frequent use of forcing and harsh conditions in the presence of very toxic fluorinating agents, such as SF_4 and HF. Recent developments in this area have focused on fluorinating agents which are easily handled using standard laboratory equipment.

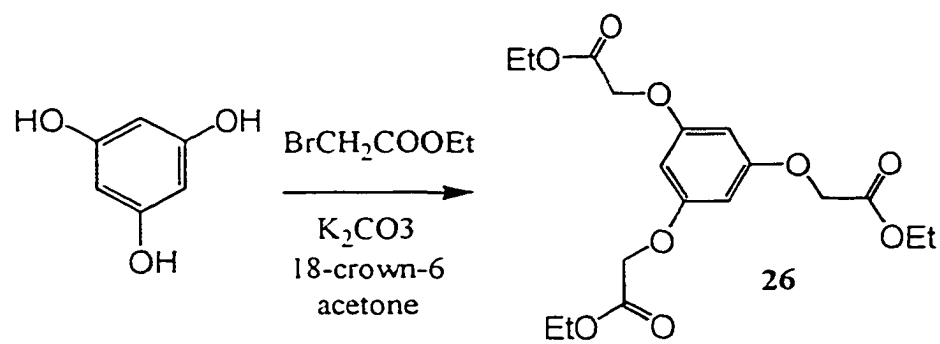
DAST (diethylaminosulfur trifluoride) is a commercially available liquid which was developed by Dupont as a safer alternative to the useful fluorinating agent SF_4.[173] It has become one of the most common and successful strategies for *gem*-difluorination of esters as shown in Equation 40.[174] This methodology, converting α-ketoesters to the desired *gem*-difluoroesters, provides the desired difluorinated product in excellent yield.



(39)

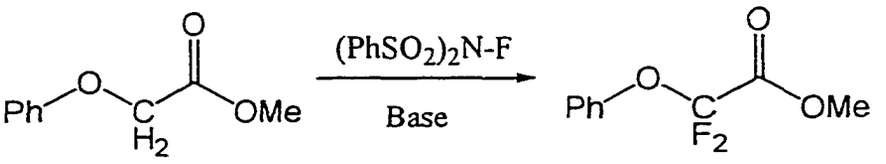
While extremely efficient in preparing exactly the functionality required for the synthesis of the achiral fluorinated cap **20**, the preparation of non-fluorinated α-ketoesters presents a different synthetic challenge. In our case, an efficient route into a tris [α-ketoester] benzene ring cap was not evident. Although many nucleophilic fluorinating agents,

including DAST and xenon difluoride, have been demonstrated to be effective in the preparation of *gem*-difluoroketones, the overall synthetic efficiency of this preparative strategy relies on accessible non-fluorinated precursors. In our case it was precisely this synthetic challenge that precluded the use of nucleophilic fluorine sources in the preparation of the achiral fluorinated cap **20**. However, one accessible non-fluorinated precursor is the tris ester **26** which is easily prepared in 70% yield from commercially available starting materials, as shown in Scheme 21.



Scheme 21: Preparation of trisester 26.

This precursor is well suited for electrophilic fluorination using enolate chemistry and a mild electrophilic fluorine source such as the commercially available *N*-fluorobenzene-sulfonamide.[175] Electrophilic difluorination was attempted on the model system as shown in Scheme 22.



Scheme 22: Electrophilic difluorination of model system.

The fluorinating agent *N*-fluorobenzenesulfonamide was initially developed for monofluorinations and it is just recently that this class of fluorinating agents has been applied to the specific demands of geminal fluorination.[164] Difluorination is most easily achieved in cases of highly acidic enol protons, such as those of 1,3-dicarbonyl compounds. In our case of a much less acidic enol proton, there was no observed difluorination, only unreacted starting material and decomposition products were isolated. A variety of reaction conditions were explored as electrophilic difluorination of enolates has been shown to be base and counterion sensitive, with highly variable yields (5 - 57%).[176, 177] In spite of literature precedence, no adequate reaction conditions were established for difluorination of our model system. In the absence of reactivity on the model system, the direct fluorination route into the desired achiral fluorinated cap **20** was abandoned.

3.3.3 Summary

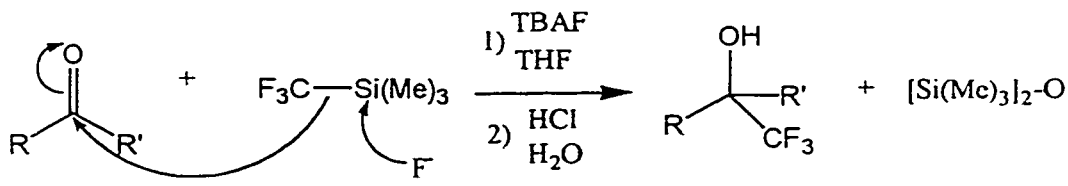
Ultimately the synthesis of achiral fluorinated cap **20** was set aside In spite of many recent developments in selective fluorination chemistry, the preparation of α,α-difluoroketones remains non-trivial, and our desire to accomplish this transformation three times over in the same molecule proved to be impossible. Regardless, this target compound and overall synthetic strategy remains the "pièce de résistance" of the project. Any significant improvements in the preparation of α,α-difluoroketones would provide an exciting development for the efficient synthesis of chiral, multidentate fluorinated ß-diketones suitable for lanthanide Lewis acid catalysis.

At this point in the project it was clear that synthetic goals needed to turn toward reliable synthetic protocols. The overall strategy of a modular approach for the preparation of the ß-diketone functionality was necessary, as shown earlier. To this end we chose existing chiral ketones (or ketone precursors) which could be attached to our capping system and trifluoroacetylated to yield the desired chiral ß-diketone framework.

3.4 Nopol Route

The extensive literature searches during the attempted synthesis of the fluorinated cap **20** revealed a reliable method for the trifluoromethylation of ketones and aldehydes.[178, 179, 180] The commercially available trifluoromethylating agent TMS-CF_3 is viewed as a

source of trifluoromethyl carbanion, suitable for nucleophilic attack of carbonyls as shown in Scheme 23.

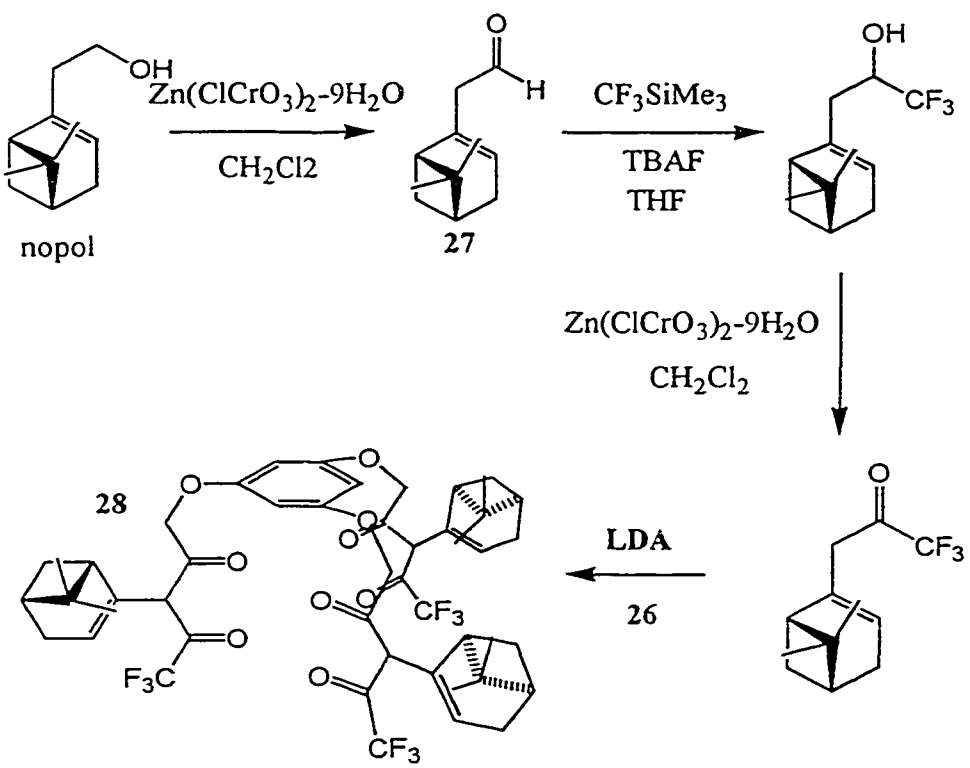


Scheme 23: Trifluoromethylation of carbonyls with TMS-CF_3.

Yields for this reaction are 80% or better, depending upon the steric accessibility of the carbonyl. The addition of trifluoromethyl carbanion to aldehydes yields secondary alcohols which can be subsequently re-oxidized to the ketone. However, initial reports in the literature indicated that this methodology cannot be used with esters, as there is no observed reaction, presumably due to the lesser electrophilic character of this class of carbonyls.[179]

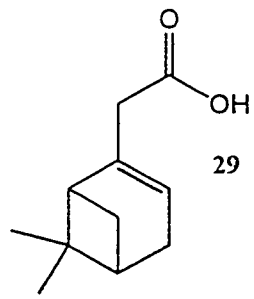
It was envisioned that this methodology could be used with a commercially available chiral aldehyde to generate a chirally substituted trifluoroacetyl group. The resulting fluorinated chiral ketone could then be reacted with the previously prepared trisester **26** to give a tripodal, fluorinated ß-diketone ligand. The advantage of this strategy lies in the preparation of a fluorinated chiral ketone, which is then attached to the tripodal framework. In this manner, the troublesome fluorine chemistry is done on one compound, which can be isolated and purified, without needing to do the fluorine substitution three times over on the same molecule.

The choice of the chiral substitutent was important as it required an aldehyde, with a methylene group α to the aldehyde. This CH_2 group is necessary as one proton will be eliminated in the C-C bond forming step in formation of the ß-diketone, while the second proton will be consumed in the formation of the lanthanide chelate complex. Thus, the chiral compound which came to our attention was nopol, which could be subsequently oxidized to its related aldehyde (nopal **27**). The proposed ligand synthesis incorporating nopol is shown in Scheme 24 (ligand **28**).



Scheme 24: Proposed synthesis of nopol chiral ligand.

The initial step of oxidizing nopol to nopal 27 proved to be quite troublesome due to an isomerization resulting in the formation of an α,ß-unsaturated aldehyde, even in the presence of mild oxidizing agents such as PDC and zinc chlorochromate nonahydrate.[149, 181] The two resulting isomeric aldehydes were formed in a 1:1 ratio as determined by NMR. Their effective separation could not be achieved by column chromatography, but the desired yellow oil could be isolated by fractional distillation under reduced pressure in adequate yield (35%) (not optimised). The difficulty encountered in nopal preparation seemed to be due largely to lengthened reaction times (10 hours). Periodic evalution of the reaction mixture as the oxidation progressed revealed that the desired product was slowly forming, but that as reaction times were increased to promote complete oxidation of the starting material, the undesired aldehyde was slowly appearing. This time dependent isomerisation is further supported by the efficient preparation of nopoic acid 29 via a rapid oxidation using Jones' reagent,[182, 183] where the desired product was isolated in good yield (60 %). In this case the desired product was formed in only 10 minutes, with no indication of bond isomerisation. Therefore, the effective preparation of 27 can probably be further optimised by a careful selection of oxidizing agent and reaction time.



29

Trifluoromethylation of nopal was attempted using literature protocol,[179] with encouraging results. The diagnostic loss of the aldehyde peak was evident, although the product was not very clean. The challenge of obtaining the necessary nopal in significant yield posed a small synthetic problem. However, the major question that was raised with respect to this ligand synthesis was the location of the chiral substituent. Once again, the chiral moiety would be located distal to the metal centre, and its ability to

impart any enantioselectivity during catalysis was questionable. These concerns were further supported by computerised molecular modelling studies (Figure 19), where molecular dynamics experiments did not locate a particular low energy conformer, but rather a series of low energy conformers. Due to these design concerns and the unexpected difficulty in obtaining the nopal starting material, the investigation of this ligand system was abandoned.

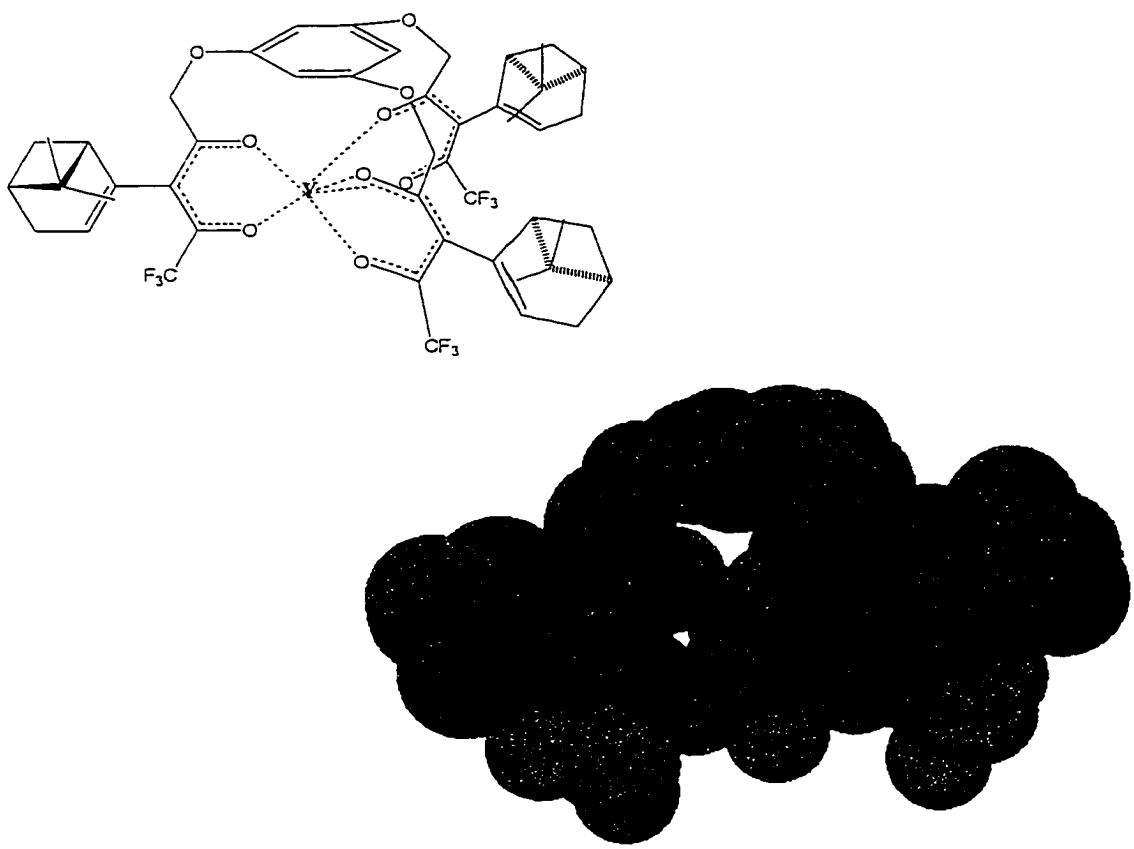
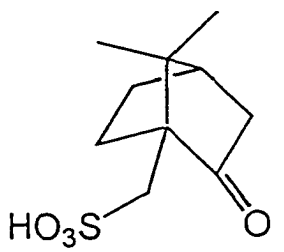


Figure 19: CAChe molecular model of the Y complex of ligand 28.

Since this time, there has been a report in the literature of a modified protocol for the trifluoromethylation of esters.[184] This development would encourage renewed efforts toward the synthesis of this ligand. It has been shown that nopoic acid **29** is easily prepared, and all that remains is simple esterification of the acid. Thus, the synthetic barriers to the preparation of **28** could be overcome. With the chiral substituent distal to the metal centre, we are faced with an intriguing question about the importance of the location of the chiral group. Other extremely successful enantioselective catalysts have chiral substituents which do not impose significant steric effects at the active site (eg. Jacobsen's Catalyst).[103, 104] Therefore the preparation of ligand **28** and its resulting complexes would provide useful information regarding the necessary features for enantioselective catalyst design.

3.5 Sulfonate Ester Chiral Ligand

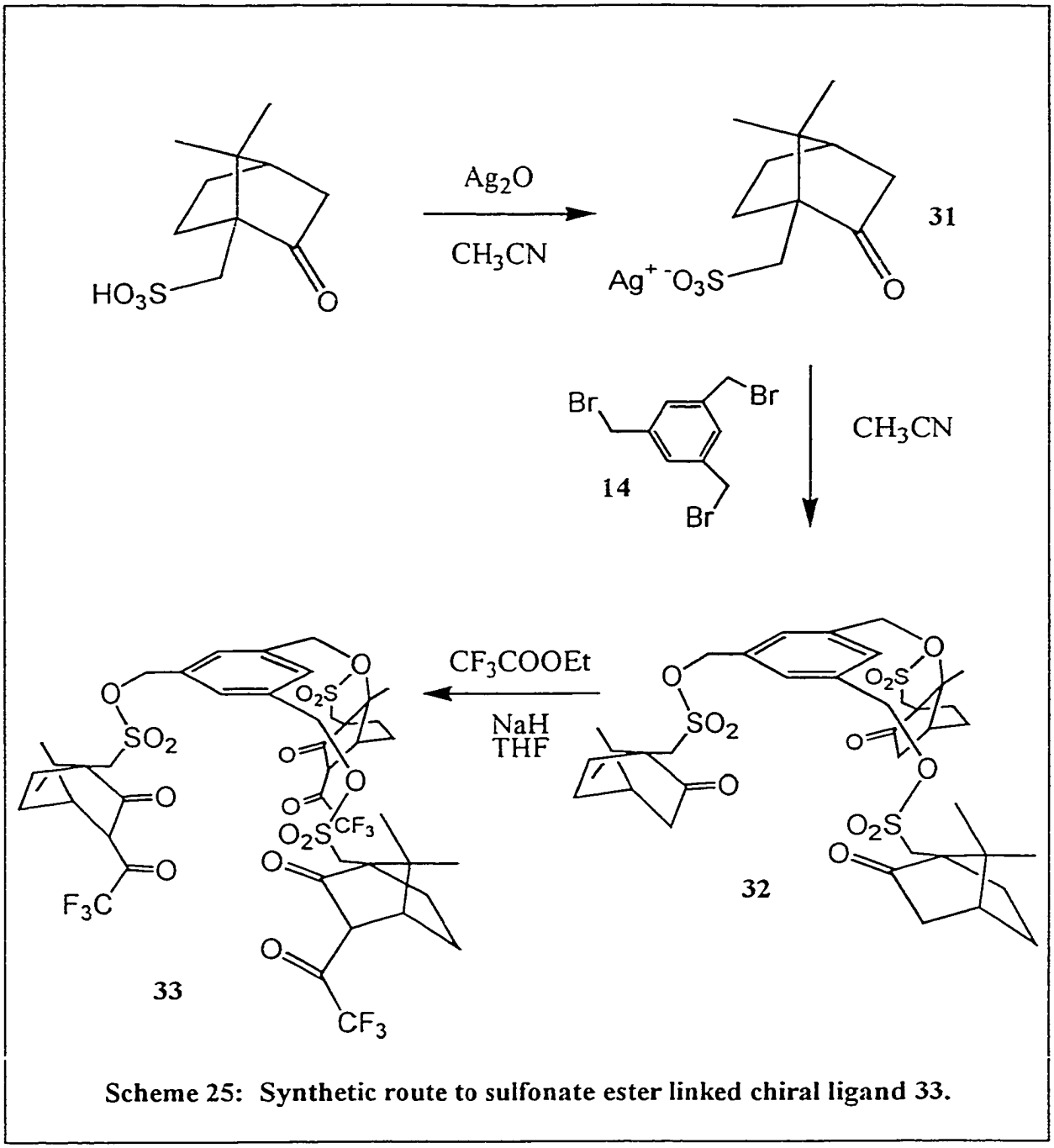
A second synthetic strategy for the preparation of a chiral ligand system was investigated. In this case a chiral ketone would be incorporated into the tripodal capping system, followed by trifluoroacetylation to build the desired fluorinated ß-diketone functionality. For this strategy to be effective it was necessary to find a chiral substituent possessing two functional groups; a ketone and a second functional group which would serve as a tether to the benzene cap. At this point the commercially available camphor sulfonic acid **30** was identified as an ideal chiral



30

ketone for our purposes. The chemistry of camphor has been investigated for many years and consequently the reactivity of this compound is well established.[185] The trifluoroacetylation of camphor has literature precedence,[186] and the resulting fluorinated ß-diketones have already been shown to bind lanthanides yielding effective Lewis acid catalysts. In this case, the sulfonic acid group is the functional group which is used to bind the chiral substituent to the tripodal benzene cap **14**. Hence the proposed synthetic route is given in Scheme 25, where the key step for formation of the chiral tripodal cap **32** relies on the large driving force of silver bromide precipitation when **31** reacts with **14**. The final step for ligand formation is the trifluoroacetylation of each of the three arms to the capping compound **32**.

On paper, the preparation of ligand **33** was straightforward, with the target ligand system being achieved in only three steps from commercially available starting materials. There were a few questions which remained about the suitability of **33** as our target ligand. First, our longterm goal in the project had been to locate the chiral substituents directly surrounding the site of crotonaldehyde coordination, yet **33** would have the chiral group at the "top" of the ligand, meaning nearest to the benzene cap. In this case the rigid bicyclic nature of the camphor moeity was anticipated to impose significant steric effects upon the ligand framework and the mode of lanthanide binding.



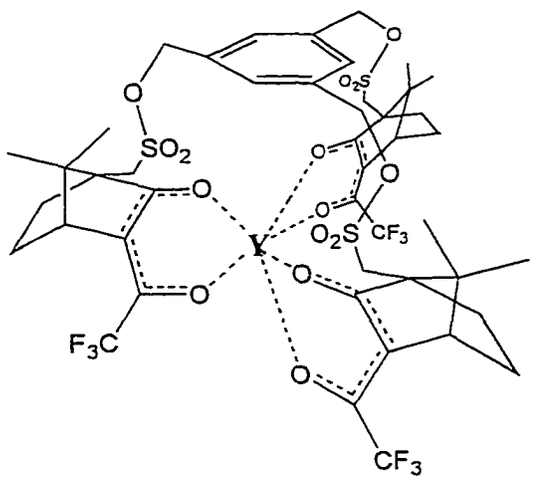
Scheme 25: Synthetic route to sulfonate ester linked chiral ligand 33.

Second, the presence of the sulfonate ester in the tether was of concern when one considers the oxophilic nature of the lanthanides. It was not clear if the oxygens of the sulfonate ester would be available to coordinate to the metal centre, thereby promoting

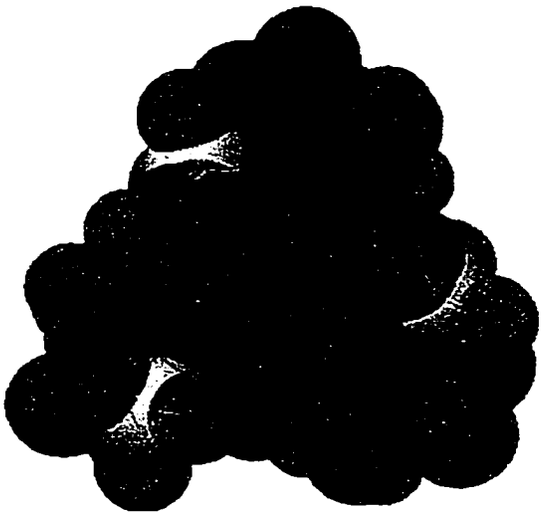
ligand decomposition. In order to better visualise these effects, computerised molecular modelling was carried out on ligand **33** and its yttrium complex.

3.5.1 Modeling Studies of Sulfonate Ester Linked Ligand **33**

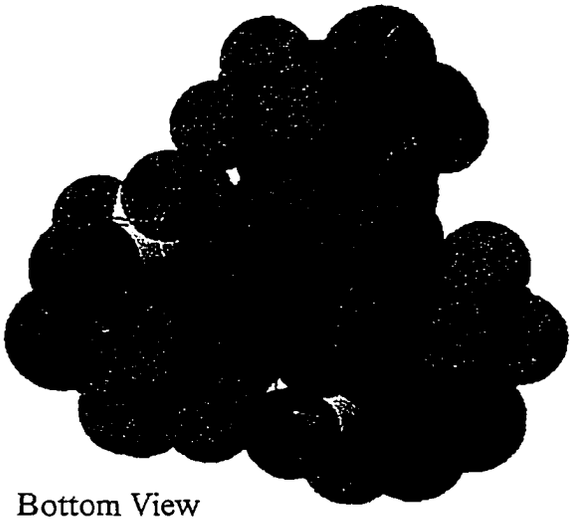
Molecular mechanics (CAChe) investigations of the yttrium complexes of ligand **33** clearly indicated the strong impact that the camphor substituent imposed on the binding mode of the ligand. Orientation about the yttrium metal centre was optimised using only steric factors (i.e. without any d-orbital induced directionality), due to its ionic bonding character. When looking at the side view (Figure 20) one can see the C_3 symmetric binding mode the ligand adopts with the benzene cap effectively blocking a potential binding site to the metal centre. Also, this optimised conformer indicated that the oxygens of the sulfonate esters would be pointed away from the metal centre. The top and bottom views clearly show the camphor groups radiating out from the metal centre in a propeller, or corkscrew like fashion, causing the ligand to bind the metal centre in a helical manner. When examining the bottom view (the only view which indicates substantial access to the metal centre), the effect of the camphor groups is noted in the canting of the chelating arms and trifluoromethyl groups. Therefore, the use of either R or S camphor sulfonic acid starting materials will lead selectively to either the Λ or the Δ metal complexes.



Side View



Top View



Bottom View

Figure 20: CAChe molecular models of the Y complex of ligand 38.

In this manner, we should be able to prepare stereochemically pure complexes which can catalyse the enantioselective synthesis of dihydropyran products from the hetero Diels-Alder reaction. The two enantiomeric lanthanide complexes should exhibit opposite facial selectivity during catalysis. Thus, this route which provides stereochemically pure lanthanide complexes, dependent upon the chosen starting material, provides selective access to both enantiomeric dihyropyran products.

Enantioselectivity of the Diels-Alder reaction relies upon the controlled *si* vs. *re* facial selectivity in the *endo* approach of the dienophile to the diene. An investigation of this selectivity was carried out by using a molecular dynamics simulation where crotonaldehyde was "bound" to the metal centre and rotated within the chiral pocket where catalysis is anticipated to occur (Figure 21).

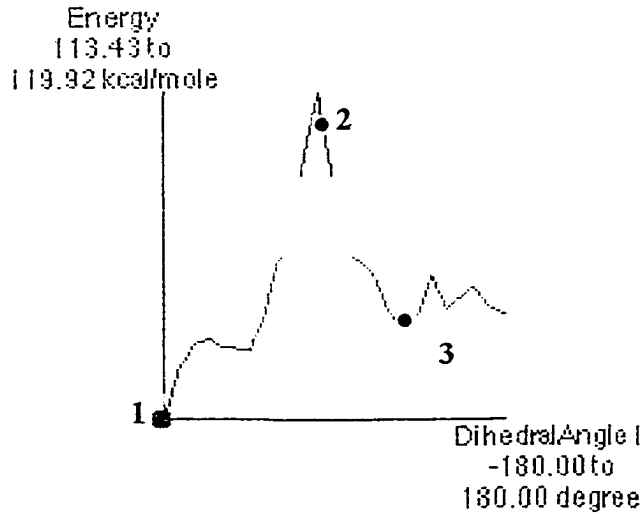


Figure 21: CAChe Dynamics generated energy profile for the rotation of crotonaldehyde in the chiral pocket of the Y complex of ligand 38, where the numbers correspond to molecular configurations shown in Figure 22.

First crotonaldehyde was added to the complex, using an expanded valency for the yttrium metal centre, and optimised using molecular mechanics. From this optimised starting position the crotonaldehyde was rotated within the chiral pocket about the yttrium-oxygen (of the aldehyde) bond in 5° increments with molecular mechanics optimisation occuring with each increment. In this manner an energetic profile of the energy of the various conformers of crotonaldehyde within the chiral pocket was generated (Figure 22).

Depictions of the molecular model along the simulation route have been included to clarify the crotonaldehyde binding mode within the catalytic site. Model 1 indicates the lowest energy conformer where clearly only one face is available for dienophile approach. Model 2 indicates the conformer where the opposite face is accessible, but as is shown in the energy profile diagram, model 2 corresponds to a very high energy conformer. Model 3 is another low energy conformer, but is not anticipated to contribute to Diels-Alder product formation as no face is available to dienophile approach because crotonaldehyde is wedged within a cleft of the ligand. It must be noted that due to the C_3 symmetric nature of the complex, all clefts are equivalent, and therefore equal contributors, in an identical fashion, to the crotonaldehyde binding mode chosen for this dynamics simulation.

As is demonstrated by the energy profile, there is a very large barrier to rotation within the chiral pocket. It is known that a 2 kcal difference in activation energy between enantiomeric transition states translates to 99% enantioselectivity. In this case the calculations suggest a significantly larger barrier of approximately 6 kcal, indicating a high degree of facial selectivity. The results of the metal complex modeling and the

crotonaldehyde binding were all very promising and indicated numerous strengths in this ligand design.

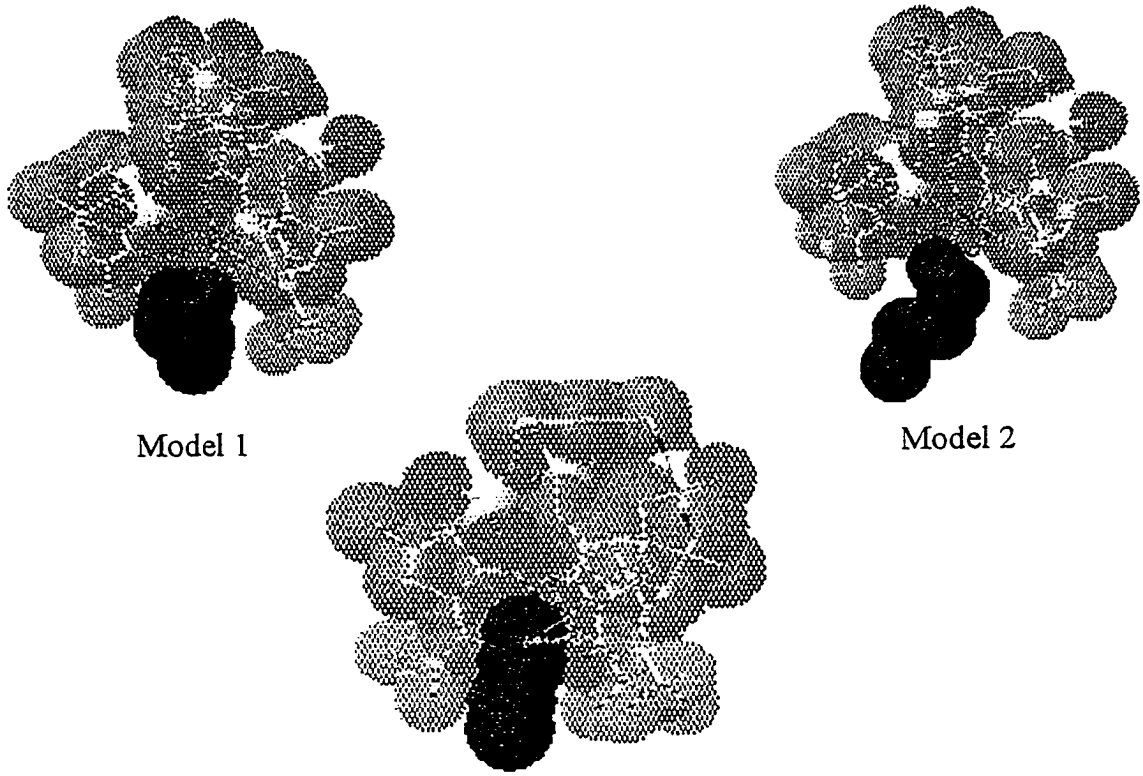
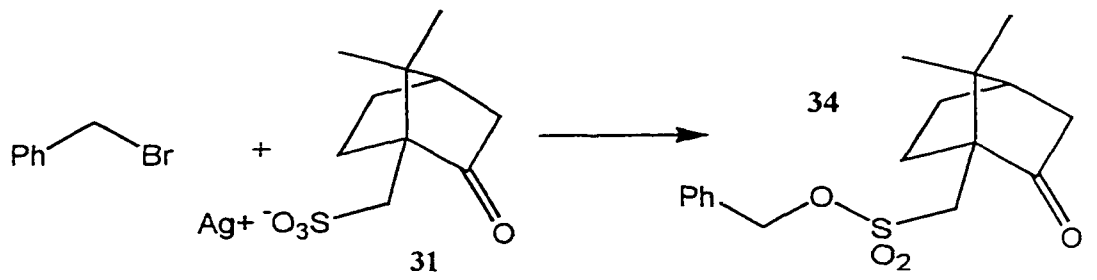


Figure 22: CAChe molecular models of dynamics simulation, showing various modes of crotonaldehyde binding in the chiral pocket of ligand 38 Y complex.

3.5.2 Ligand Synthesis and Characterisation



Scheme 26: The preparation of model compound 34.

The successful preparation of ligand **33** relied upon the facile preparation of the sulfonate ester linkage, and the ability of this linkage to survive the following basic conditions of the trifluoroacetylation (Scheme 25). The preparation of the sulfonate ester link was first demonstrated on the synthesis of the model compound **34** shown in Scheme 26.

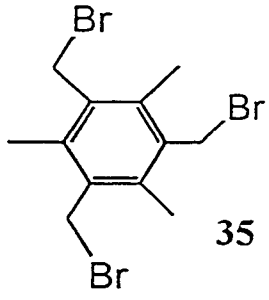
Silver salt **31** was prepared in thirty minutes, by dissolving camphor sulfonic acid **30** in dry acetonitrile and adding silver(I) oxide with vigorous stirring.[187] The resulting slurry was protected from light before being filtered and concentrated to yield a solid white material which was sparingly soluble in deuterated chloroform, but was very soluble in deuterated water. When benzyl bromide was added to an acetonitrile solution of solid **31** with stirring, the solution immediately became cloudy. The stirring at room temperature was continued for three hours before the silver bromide salts were removed

by filtration and the resulting white fluffy product **34** was isolated under reduced pressure in good yield (60%). The product was characterised by ^{1}H and ^{13}C NMR spectroscopy, where the benzyl peaks shifted from 4.5 ppm in the bromide starting material to 5.2 for the sulfonate ester linked product. Although model compound **34** was easily prepared, what remained to be determined was whether three bulky camphor substituents could be placed around one benzene ring. Therefore the reaction Scheme 25 was followed for the preparation of the chiral cap **32** and ultimately ligand **33**.

First the silver salt **31** was prepared as described above, although it was determined that due to the hygroscopic nature of the silver salt it was better to react **31** directly with the benzene cap **14** by cannula filtering the silver salt containing supernatant from the silver oxide residue into an acetonitrile solution of **14**. The reaction resulting in the formation of the sulfonate ester was carried out at room temperature for three hours and the resulting yellow-green silver bromide salts were permitted to precipitate to the bottom of the reaction vessel. All of these reactions needed to be carried out in oven dried glassware with the exclusion of atmospheric moisture. The product was once again transferred by cannula filtration into a dried round bottom flask where the solvent was removed under vacuum. The product could not be isolated with a water aspirator reduced pressure atmosphere, as that also promoted the incorporation of water into the product. The desired product **32** was isolated as a white glassy solid which was very soluble in dichloromethane. Any unreacted silver salts would appear as a cloudy white suspension in the dichloromethane product solution. This posed a serious purification challenge, with the best method being the addition of excess anhydrous $MgSO_4$ powder to the solution which would slowly aid in colloid formation and precipitation of the unwanted silver salts.

This procedure needed to be repeated several times until eventually a clear solution formed on dissolution of **32** in dichloromethane (sometimes requiring up to 4 repetitions of filtrations and precipitations). With the rigorous exclusion of water from all reactions and work-ups the product could be purified successfully in 24 hours in good yield (65%). However, even a small amount of exposure to atmospheric moisture (eg. filtration in air) would cause product **32** to be isolated as a clear oil, which contained both unreacted silver salts and water (as shown by NMR spectroscopy). Attempts to continue the synthesis of ligand **33** in the presence of even small amounts of these two contaminants resulted in the decomposition of the chiral cap in subsequent reactions and poor product yields. It was also determined over time that the source of silver oxide was very important to the success of the reaction. Newly purchased silver(I) oxide from Aldrich, when used in the preparation of the chiral cap, resulted in *poorer* reaction yields than reactions carried out with older silver(I) oxide. It was also extremely difficult to remove the unreacted silver salts from the crude product mixture when newer Ag_2O was used.

It must also be mentioned that an alternative benzene cap starting material **35** came to our attention. It was easily prepared by heating mesitylene, paraformaldehyde and KBr in acetic acid for 6 hours. The reaction mixture was then permitted to stand at room temperature overnight before work-up.[188] This methyl substituted capping system was of interest to us as the extra methyl groups were anticipated to impart increased crystallinity to both the chiral cap **32** and ligand **33**. It also provided a useful NMR handle for the identification of the C_3 symmetric products. Most importantly however was the ease of its synthesis in comparison to compound **14**.



35

Although brominated cap **14** was successfully prepared, it could not be scaled up to the 20 g scale achievable in the preparation of **35**. As a stable, frequently used starting material, compound **35** was used interchangeably with **14** in the preparation of ligand **33** (where **a** represents the compounds prepared using **14** and **b** represents the compounds prepared using **35** from this point onward). Ultimately the presence of the methyl groups on the capping systems had no remarkable effects upon the physical characteristics of either the chiral cap **32b** or the ligand **33b**.

The sulfonate ester caps **32a** and **b** were characterised by ^{1}H and ^{13}C NMR spectroscopy, where examples of compound **32b** are given in Figures 23 and 24. The integrations of the spectra, as well as their straightforward patterns were indicative of substitution three times over and the efficient preparation of the chiral, C_3 symmetric capping systems. It could be prepared on gram scale (optimised reaction conditions gave 2.1 g) but was very moisture sensitive and ideally was immediately reacted to form chiral ligands **33a** and **b**. However, **32a** and **b** could be stored for up to 4 weeks in a bench-top dessicator with minimal reduction in compound purity. Formation of **32a** was also supported by positive LSIMS where a peak at 811 is M (45%) and a signal at 579 represents M - camphor sulfonate (100%). Based on the strong NMR data and confirmatory MS, chiral cap **32a** and **b** was trifluoroacetylated to build the desired ligands **33a** and **b** respectively.

Trifluoroacetylation was carried out using sodium hydride as base and ethyl trifluoroacetate.[186] A slurry was prepared containing NaH with excess dried trifluoroacetate in THF. The chiral cap was dissolved in THF and slowly added to the slurry where enolate formation was quickly followed by nucleophilic attack of the

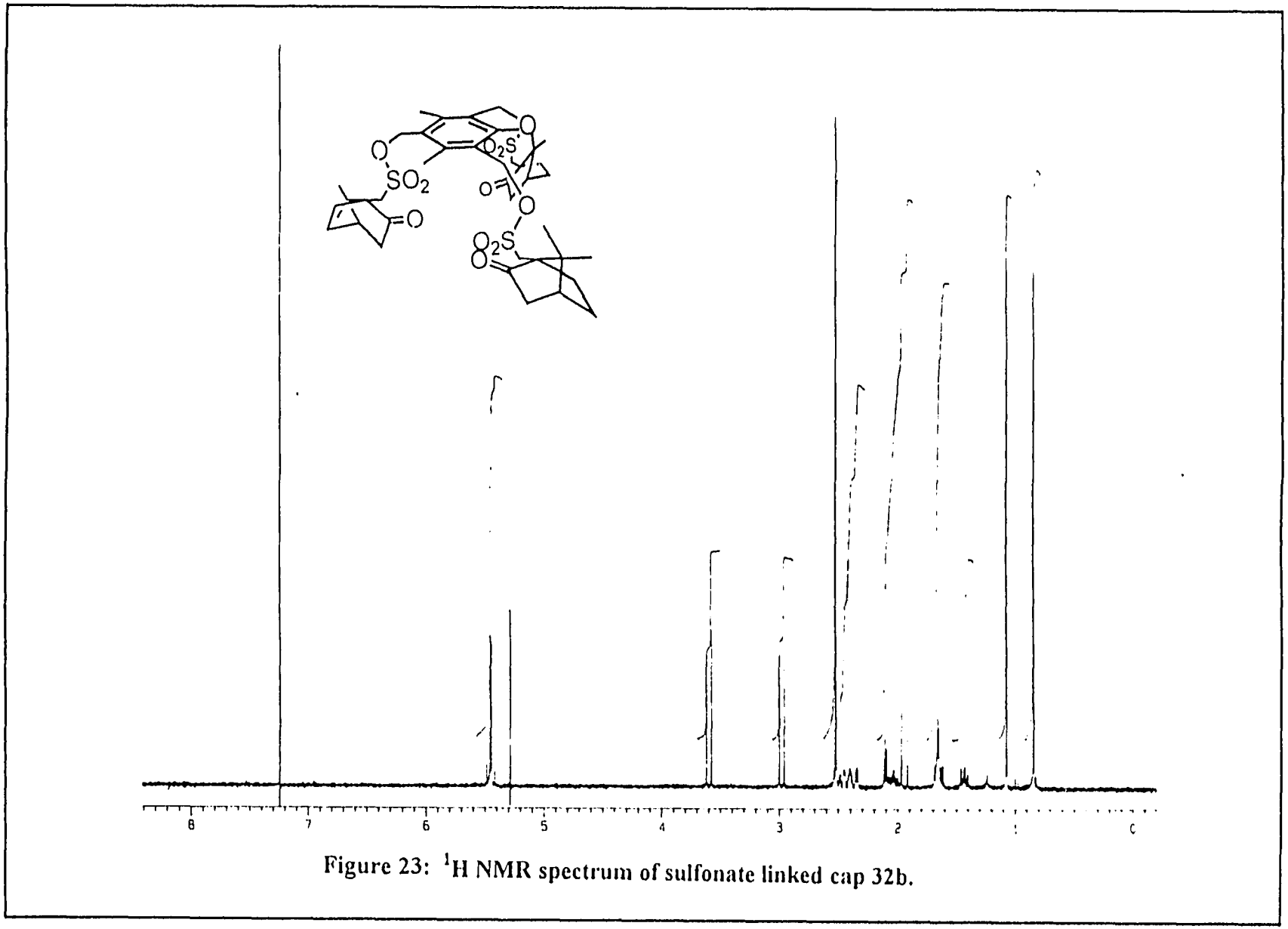


Figure 23: ^{1}H NMR spectrum of sulfonate linked cap 32b.

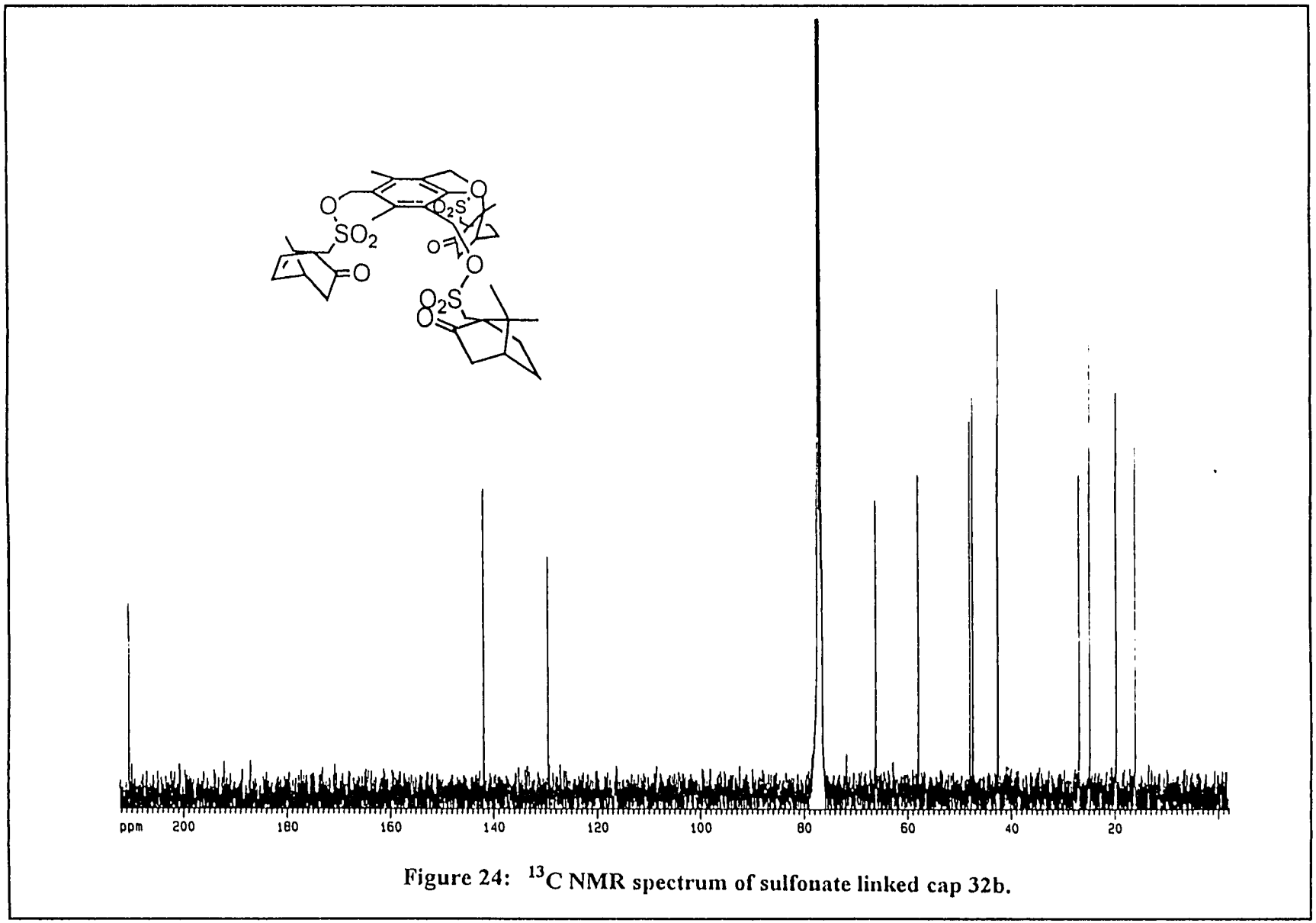


Figure 24: ^{13}C **NMR spectrum of sulfonate linked cap 32b.**

trifluoroacetate electrophile. When enolate generation followed by electrophile addition was attempted, the chiral caps **32a** and **b** were observed to decompose under the harsh reaction conditions.

The reaction could only be carried out with sodium hydride which had been stored in the glove box. Any sodium hydride which had been exposed to the atmosphere, and consequently contaminated with sodium hydroxide, was found to catalyse the decomposition of the chiral cap as well as the trifluoroacetate. Other bases, such lithium di-isopropylamide, a strong base but poor nucleophile, were also investigated. In the case of LDA, the strong electrophilic nature of the trifluoroacetate caused nucleophilic attack of the ester, rather than enolate formation. Here the side product, di-isopropyl trifluoroacetamide was isolated from the reaction mixture in excellent yield as a pale yellow oil, in which white crystals appeared over time. This solid was characterised by ^{1}H, ^{13}C and ^{19}F NMR spectroscopy as well as MS.

Therefore, after intensive investigation the optimised experimental conditions for the formation of ligands **33a** and **b** were established. The chiral cap **32**a or **b** (prepared with the exclusion of water) was dissolved in dry THF and transferred to a dropping funnel by cannula. This clear solution was added dropwise to a 0°C slurry of NaH and ethyl trifluoroacetate in dry THF. Following the addition the reaction mixture was permitted to warm to room temperature and was stirred for a further 24 hours before an acid quench and ether work-up. The crude product was isolated as an orange oil in excellent yield (2.3 g, 80%), and was shown to be largely (approximately 80%) the desired

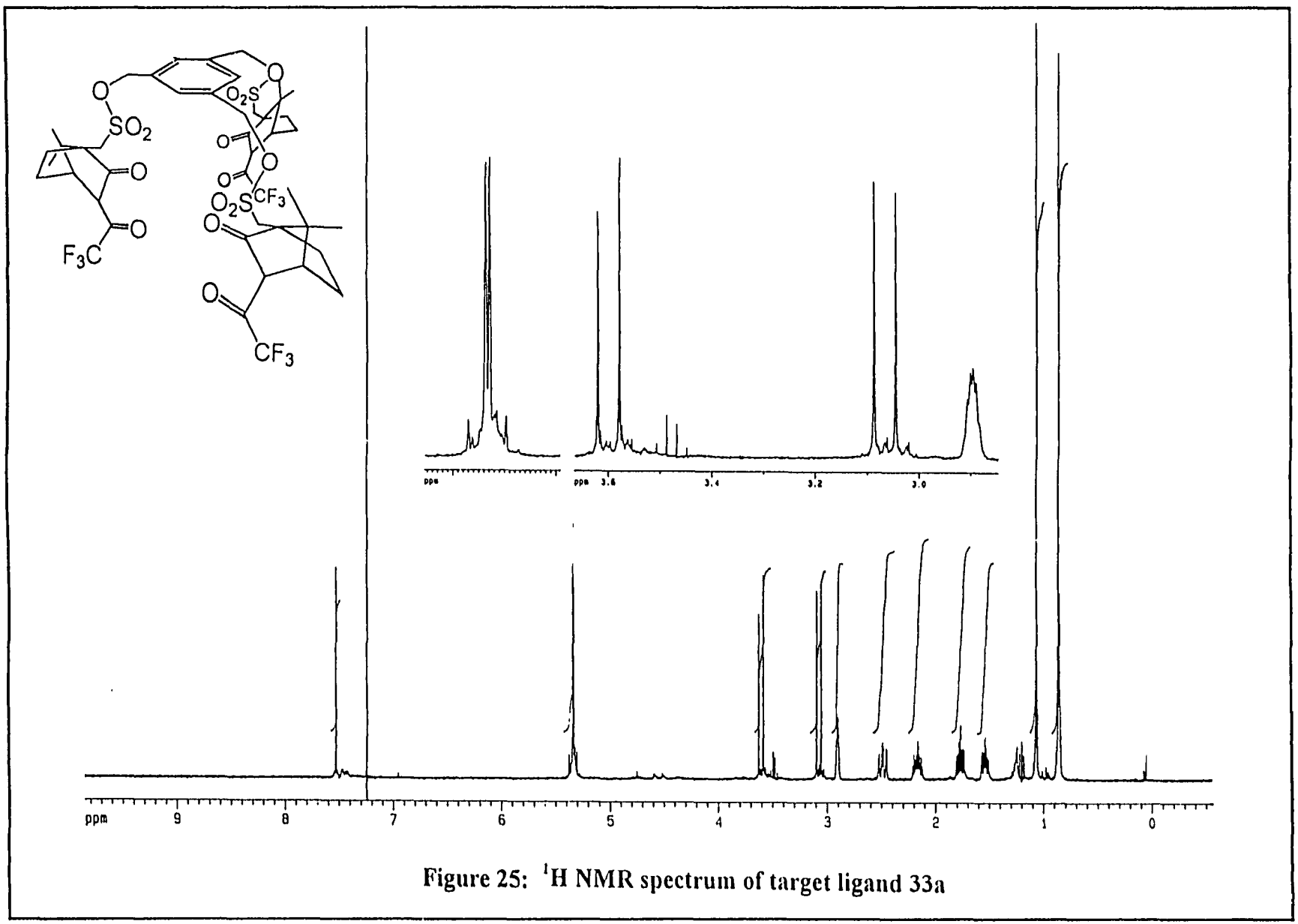


Figure 25: ^{1}H NMR spectrum of target ligand 33a

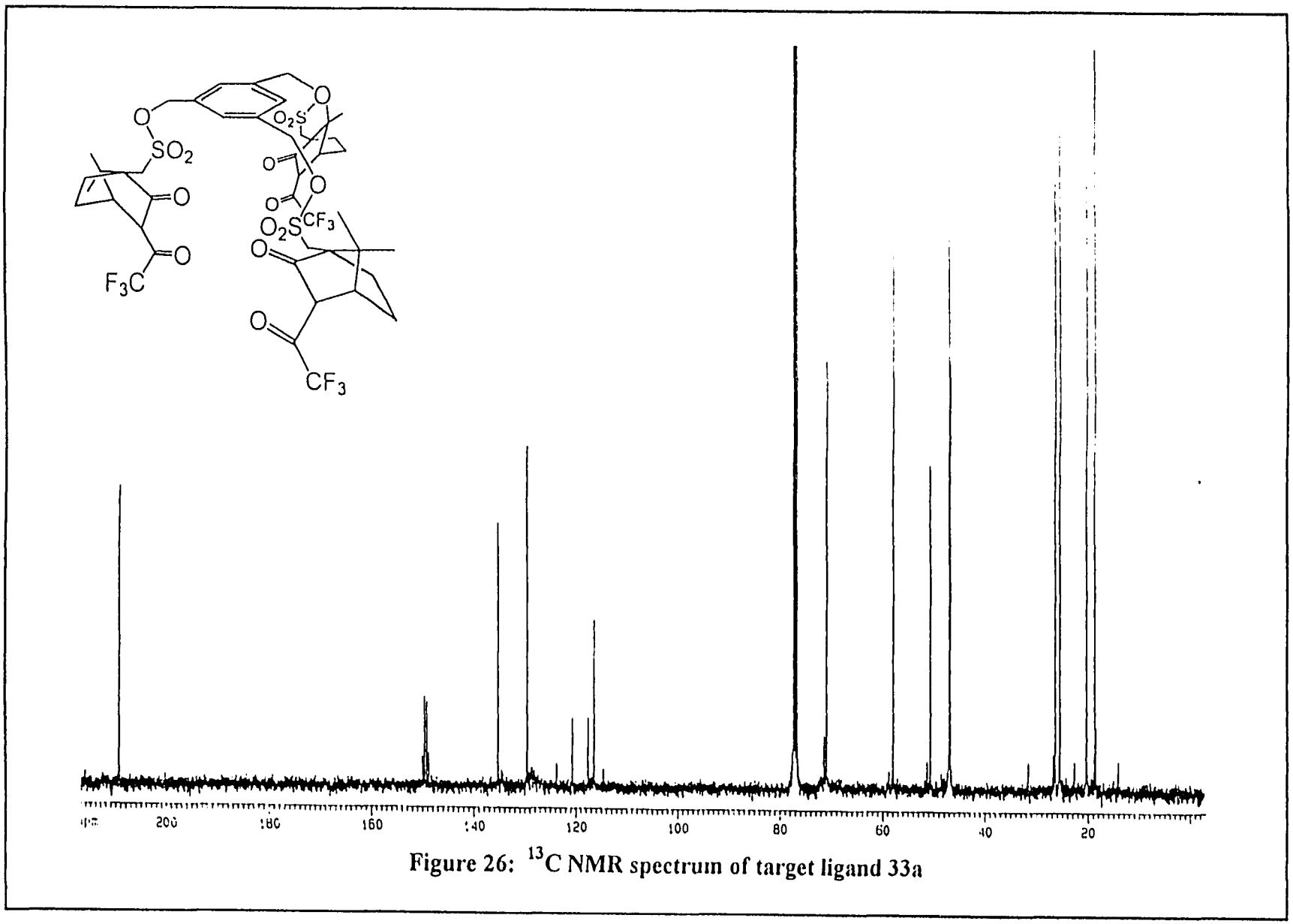


Figure 26: ^{13}C NMR spectrum of target ligand 33a

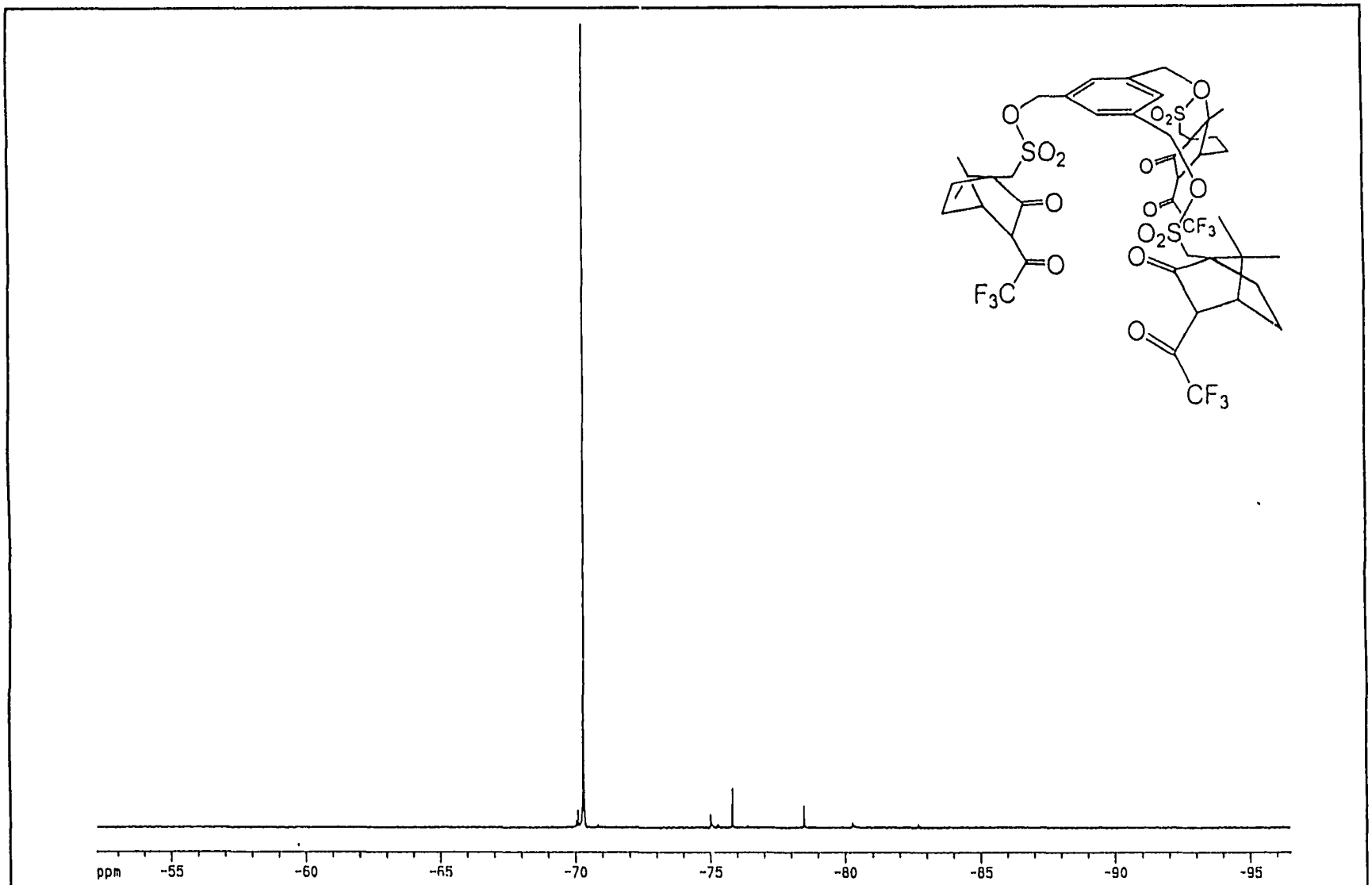


Figure 27: ^{19}F NMR spectrum of target ligand 33a

ligand by NMR. Unfortunately further purification of ligands **33a** and **b** was never optimised. The products could not be purified by silica, alumina or florisil gel chromatography, as the compounds in most cases could not be removed from the column after application, or if they could be removed, decomposition had occurred. Some crude product oils would yield crystalline, purified ligand **33** (Figures 25, 26 and 27) from mixed solvent systems at low temperatures. This product was very pure as shown in the NMR spectra. The diagnostic peaks showing the formation of the fluorinated ß-diketone structure are the new broad singlet at 2.9 ppm in the ^{1}H spectrum, the two quartets due to C-F coupling at 149 and 119 ppm in the ^{13}C spectrum and the clear singlet at -70.3 ppm in the ^{19}F spectrum.

These signals were consistent with the desired product's formation and isolation. On other occasions. no purified product could be isolated. One thing was clear, in the absence of contaminants, ligands **33a** and **b** were stable and could be stored for up to one week under nitrogen at -20°C, however in instances where purification was not achieved, the desired product in the crude oil decomposed in less than two days. The decomposition products were largely found to be the hydrolysis of the sulfonate ester linkage, leading to the formation of the sulfonate ester salt and benzyl alcohol derivative. The formation of the desired tripodal ligand **32a** was also confirmed by positive LSIMS where a peak at 1121 equals M + Na^{+} (10%). This was further supported in the fragmentation pattern where a peak at 771 represents M - 1 "arm" (where arm indicates portion which is removed after ester hydrolysis) (5%) and 443 indicates M - 2 "arms" + H (100%).

During experimentation it became clear that water was necessary for the decomposition of the sulfonate ester link. Therefore, attempts were made to isolate the

ligand under anhydrous conditions, by using a non-aqueous work up for the trifluoroacetylation reaction. In this case the isolated crude product was not as clean as the product observed immediately following the aqueous work-up conditions. Evidently the water washes removed many impurities. In the absence of an aqueous work-up it became impossible to purify ligands **33a** and **b** to any satisfactory degree. Aqueous work-up conditions consistently resulted in reasonably pure crude product (80% as mentioned above), but in this case the challenge was removing trapped water from this extensively hydrogen bonded molecule before reacting with lanthanide reagents. Standard methods, such as drying over molecular seives, or heating under vacuum could not be used, once again due to ligand decomposition.

Figure 28 shows an example of the decomposition products isolated after an attempt to dry the ligand by soxhlet extraction of water using benzene and CaH_2. In this case the sulfonate ester linkage had been hydrolysed cleanly, to yield the crystalline trifluoroacetylated camphor sulfonic acid salt. This product was isolated in the dry box and its hygroscopic behaviour was followed by NMR, where exposure to atmospheric moisture through the cap of an NMR tube caused incorporation of large amount of water into the molecule over a period of two days, as was shown by the substantial growth in the enol proton of the ß-diketone moiety. The crystals of the decomposition product lost solvent rapidly upon removal from the mother liquor, preventing X-ray crystallographic analysis.

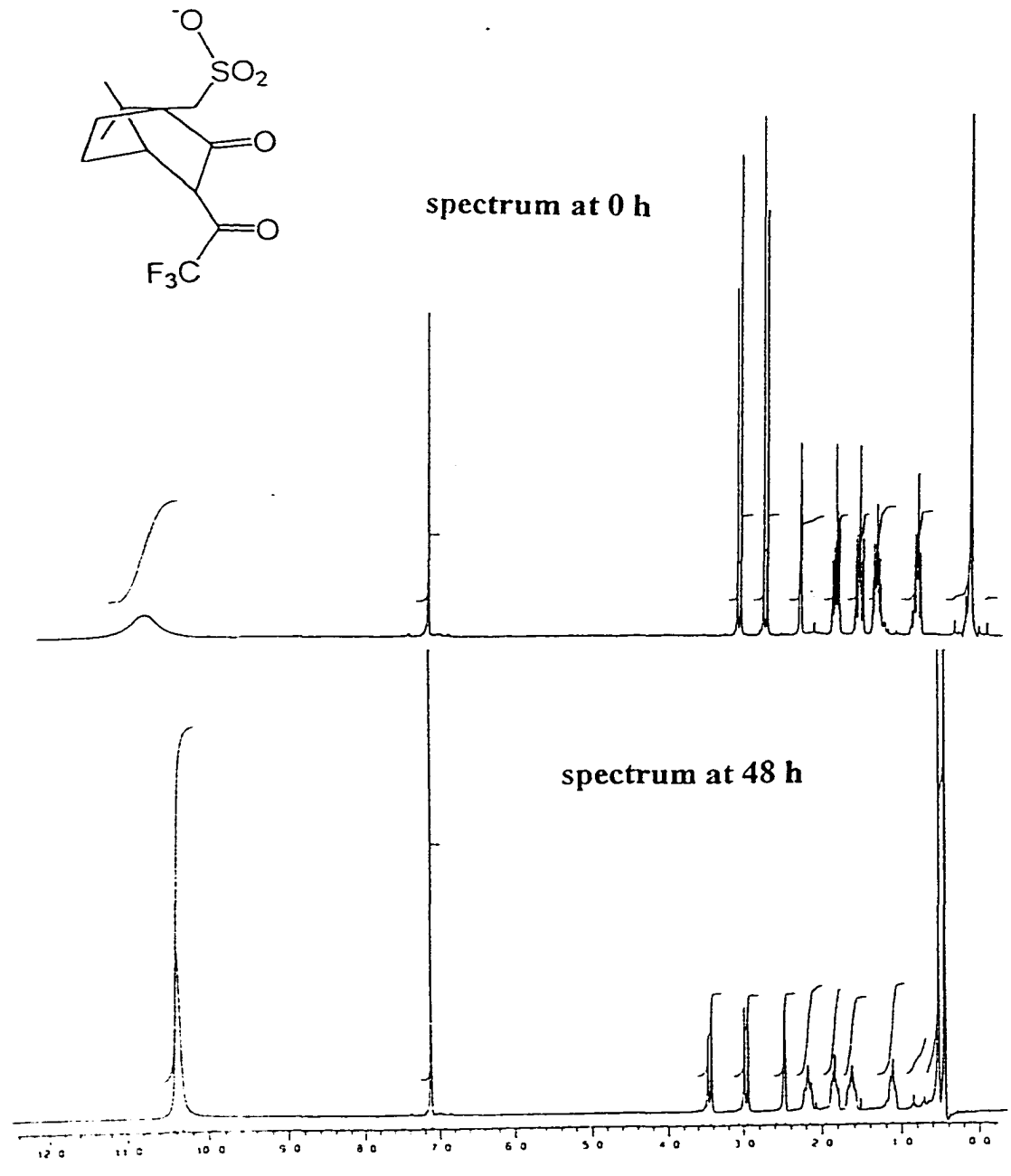


Figure 28: ^{1}H NMR spectra demonstrating hygroscopic nature of decomposition products of target ligand 33.

3.5.3 Attempted Metal Substitution of the Chiral Sulfonate Ester Linked Ligand

These challenges in ligand synthesis affected the metal chemistry attempted, as previous work preparing ß-diketonate chelates of the lanthanides had relied upon $Ln[N(SiMe_3)_2]_3$ as a starting material. However, this compound is extremely moisture sensitive. When standard complex formation reaction conditions were used, the presence of moisture in the ligand resulted in the immediate formation of lanthanide hydroxides and oxides. The number of equivalents of water trapped in the ligand was not evident, meaning that in these reactions the metal to ligand stoichiometry was not correctly balanced. In most cases the ability to prepare monomeric lanthanide ligand complexes relies on the proper stoichiometric ratios, otherwise these large metal centres have tendencies to form bridging oligomers. Therefore, for a variety of reasons, no lanthanide ligand complexes were successfully prepared or isolated by this route.

Metathesis routes into the complexes were also attempted, as shown in Equation 40.

$$LnCl_3 + M^+_3 L^{3-} \longrightarrow LnL + 3\,MCl \quad (40)$$

L = tripodal ligand

This reaction was attempted under anhydrous conditions, using THF as solvent and sodium ligand salts isolated directly from the trifluoroacetylation reaction (without further purification); and in hydrous conditions, using ethanol as solvent and potassium, sodium

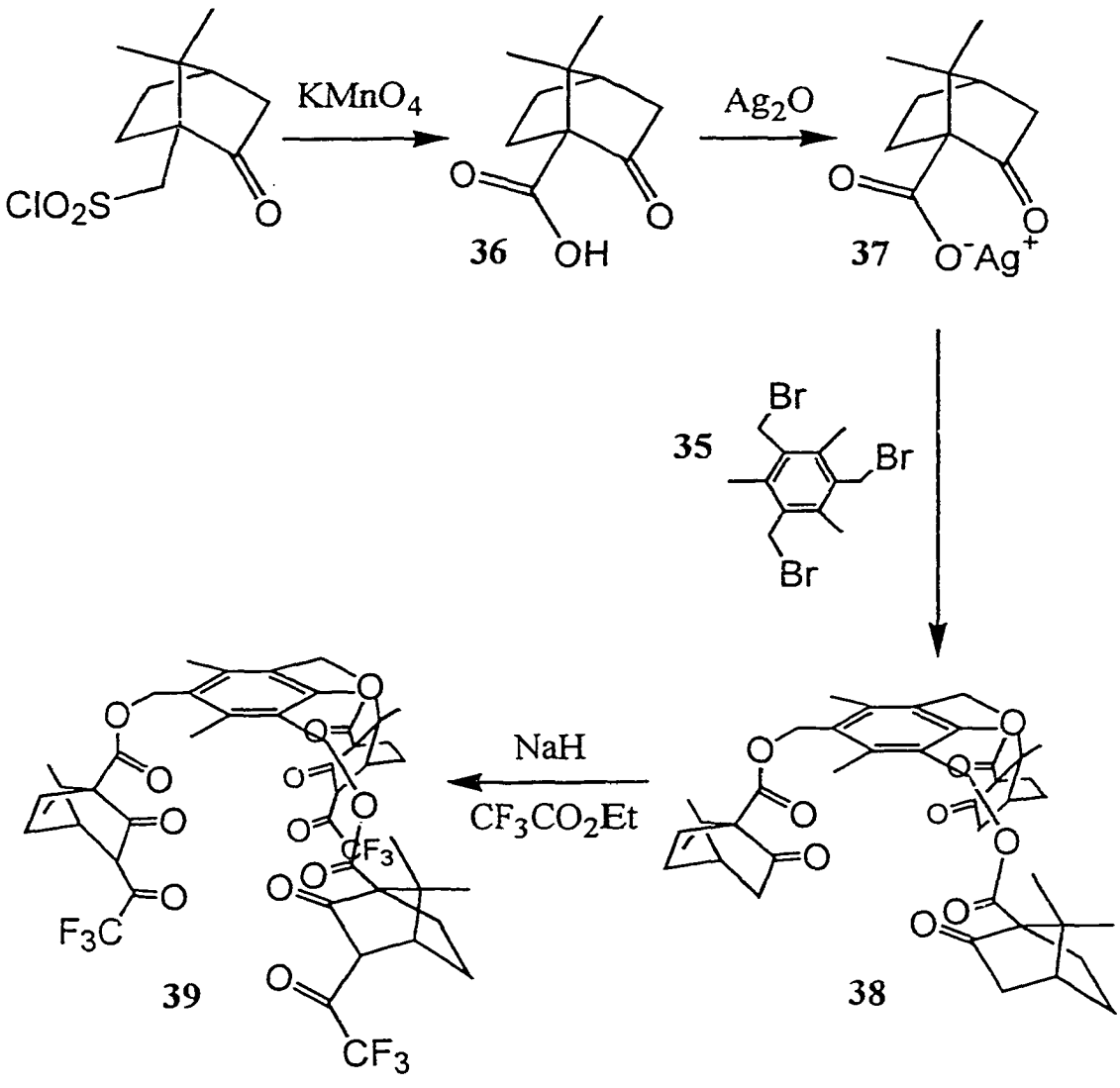
or cesium ligand salts prepared from purified ligand that was deprotonated using metal carbonates. Although metathesis is the most common method for preparing metal-ligand complexes, this route is usually worth avoiding due to the tendency of lanthanides to maintain bridging interactions with halogen leaving groups, thereby forming "ate" complexes and oligomers. However, in our case we had a large entropic factor working in our favour which was anticipated to improve our ability to isolate monomeric complexes. However, once again ligand decomposition posed many problems and chiral lanthanide complexes were never obtained.

When this ligand synthesis was undertaken it was recognised that the sulfonate ester link was a potential weakness in the design. A C_3 symmetric, chiral chelating ligand was prepared, yet it proved to be unsuitable for lanthanide complexation. Attempts to prepare crystalline material using iron as the metal centre, resulted in ruby red oils (indicating ß-diketone coordination) of limited solubility. These materials also indicated ligand decomposition over several days, as ether washes of the oils (in an attempt to remove any unwanted organic materials) when concentrated and evaluated by NMR spectroscopy showed the presence of the benzene capping system. In hind sight, the troublesome ligand isolation was indicative of the sensitivity of the sulfonate ester link and hinted at the potential difficulties encountered when trying to substitute this ligand on the Lewis acidic lanthanide metal centre.

3.6 Carboxylate Ester Route

In an effort to improve the robustness of the capping system/chiral substituent tether we turned toward a carboxylate ester link. This could be prepared using very similar methodology, using the commercially available camphor sulfonyl chloride as starting material, as shown in Scheme 27. Camphor carboxylic acid (ketopinic acid) **36** was easily prepared using a $KMnO_4$ oxidation of camphor sulfonyl chloride.[189] As in the sulfonic acid case, the silver salt of camphor carboxylate was prepared quantitatively using silver(I) oxide and reacted directly with brominated benzene cap **35** to yield the tripodal, chiral cap **38**. This capping system was then trifluoroacetylated using the same methodology developed in the preparation of **33** to give the desired chiral, C_3 symmetric ligand **39**. Ligand **39** was different from **33** in two fundamental ways. First, the sulfonate ester link had been changed to a carboxylate ester link, where the carboxylate ester link was anticipated to exhibit enhanced stability over the sulfonate case. Second, the tether between the benzene cap and the chiral substituent was shortened significantly by removing the CH_2SO_2 group and replacing it with a C=O of the carboxylic acid group.

The effect of the shortened tether was examined by molecular modeling as shown in Figure 29. Qualitatively this change did not seem to affect the chelation of the metal centre, with the low energy conformation still binding the metal centre in a helical type



Scheme 27: Synthesis of Carboxylate Ester Linked Tripodal Ligand.

fashion. As had been seen before, the metal centre was accessible at only one site and the effectiveness of the chiral pocket was anticipated to be similar to that demonstrated in the molecular modelling of chiral ligand **33**.

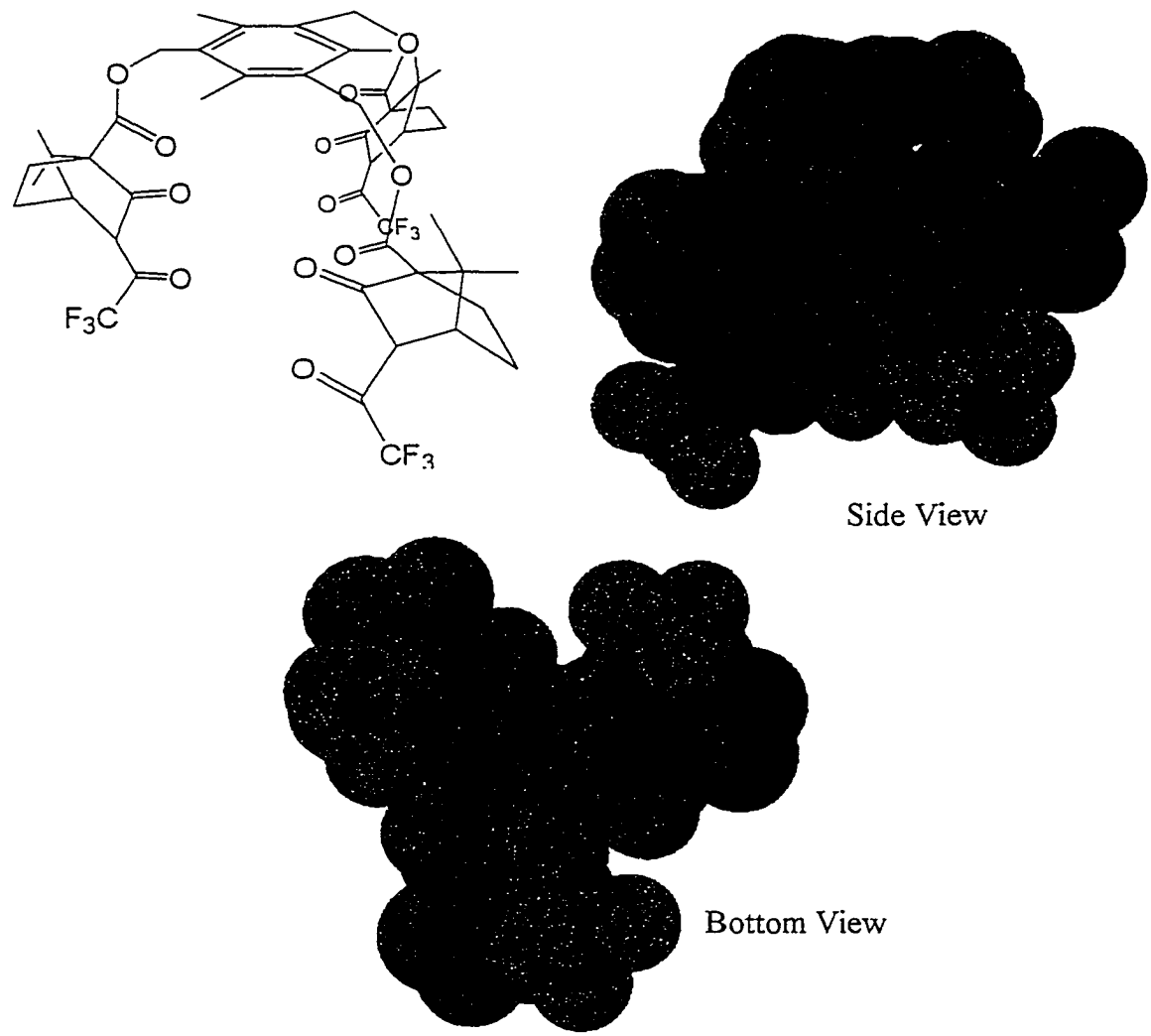


Figure 29: CAChe molecular models of ligand 39.

However, one similarity persisted in the behaviour of ligand **39** in comparison with ligand **33**; it was also susceptible to ester hydrolysis.

The ligand precursor was successfully prepared in good yield (65%) with the ^{1}H NMR data for the tripodal cap **38** shown in Figure 30.

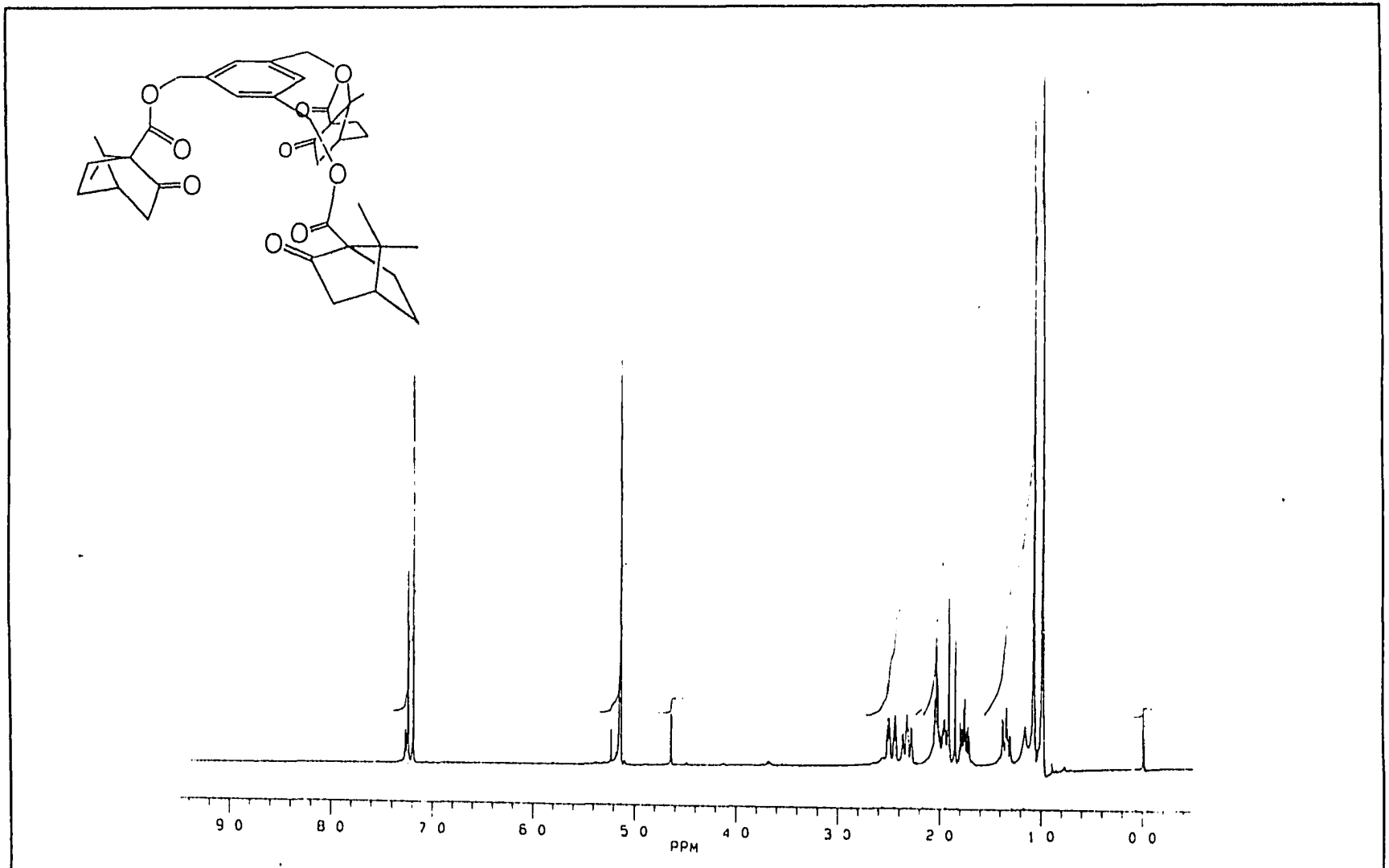


Figure 30: ^{1}H NMR spectrum of carboxylate linked cap 38a.

The trifluoroacetylation reaction was successful with the following diagnostic peaks being visible in the crude product ^{1}H NMR spectrum (Figure 31): enol proton, a broad signal centred at 10.4 ppm, and a broad singlet at 2.8 ppm for the bridgehead proton. It is also evident from this spectrum that there are a number of contaminants, including unreacted ethyl trifluoroacetate, as well as ethanol and THF. Furthermore, the product is not entirely substituted three times over as is clearly indicated by the benzyl (5.3 ppm) and methyl (2.4 ppm) signals for the unsymmetrical capping system. Although this crude product NMR spectrum indicates successful reactivity, the desired ligand was never successfully purified. In attempts to purify various crude reaction mixtures by using mixed solvent recrystallisations, the slow hydrolysis of the ester link was observed. Therefore, the anticipated improved robustness of the ligand tether was not achieved and this ligand system was not investigated any further.

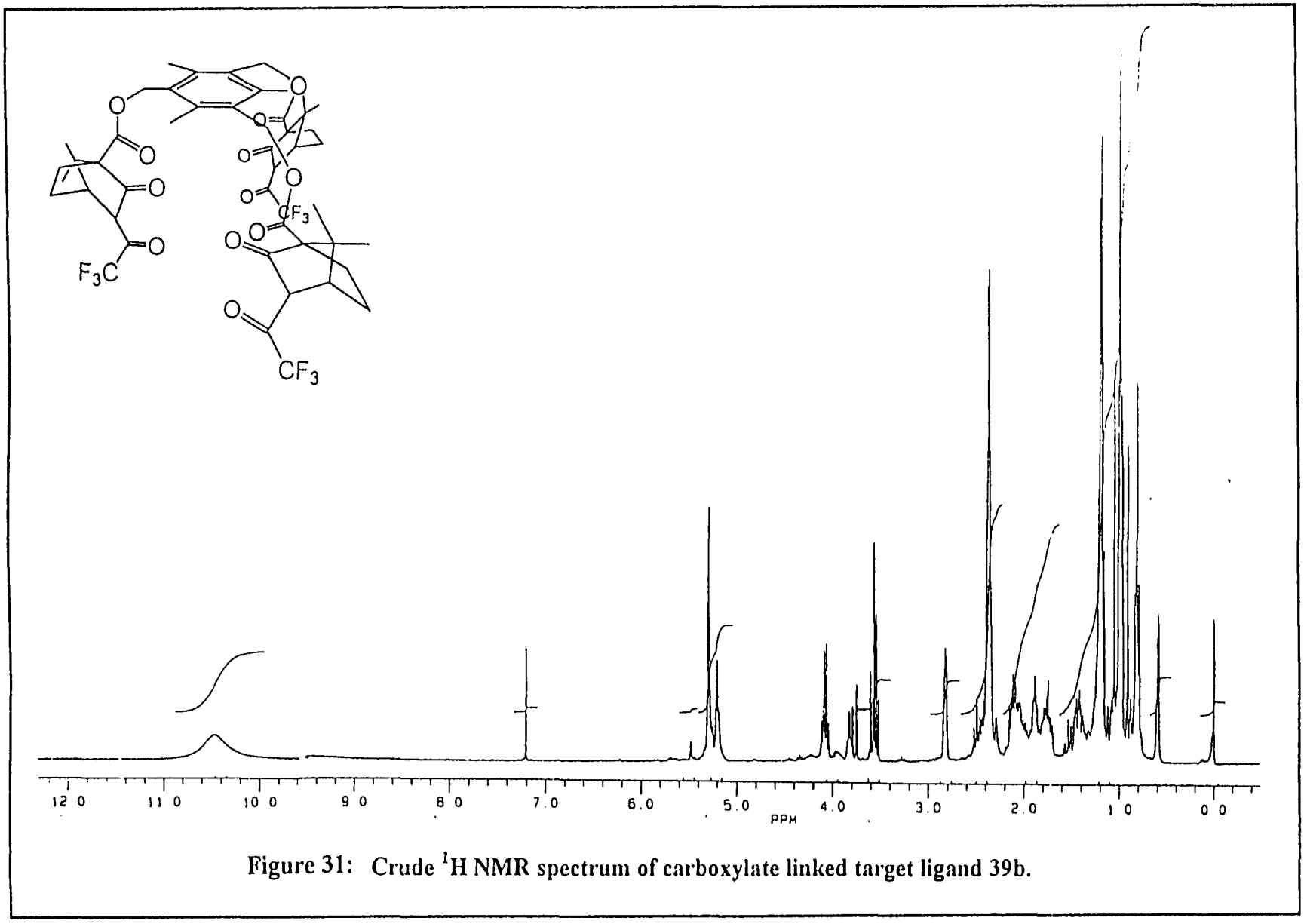


Figure 31: Crude ^{1}H NMR spectrum of carboxylate linked target ligand 39b.

3.7 Conclusions

The preparation of chiral ß-diketone ligand systems was pursued through a variety of synthetic strategies. General routes into the desired class of ligand systems were shown to not be synthetically achievable due to either the challenges of working with fluorinated synthons and/or direct fluorination agents. The synthetic experience gained while investigating a variety of synthetic protocols discussed early in the chapter helped to define the synthetic targets pursued in the following C_3 symmetric systems. Above all it became clear that reliable, "simple" chemistry needed to be the cornerstone of the synthetic pathways, as reactivity at three centres on the same molecule consistently proved difficult.

The use of camphor as a chiral substituent in the synthesis of tripodal, ß-diketone ligand systems is of extreme interest. The rigid bicyclic nature of camphor imposes very attractive features to the ligand binding mode, as estimated in molecular modelling studies. However, easy synthetic routes into these desired compounds do not yield ligand systems which are sufficiently robust to effectively bind Lewis acidic lanthanide metals. Therefore, the synthesis of target ligand **33** did not result in the preparation of a lanthanide Lewis acid catalyst. We have clearly demonstrated the route of decomposition to be hydrolysis of the ester tether. Thus, other more robust tethers, such as ethers or amines would be of intense interest. The possibility of forming these alternative linkers in a tripodal array was briefly investigated and the results are presented in the following chapter.

CHAPTER 4: Chiral Alcohol Ligand Syntheses

4.1 Introduction

Tripodal ligand systems which incorporate camphor into the ligand backbone have been identified as desirable targets. However, the easily prepared camphor sulfonate ester and carboxylate ester linkers have been shown to be insufficiently robust for the Lewis acidic environment of the lanthanide metal centres. Therefore, various other synthetic targets available by using derivatives of camphor sulfonic acid were evaluated for their potential as new sources for more robust linkers. Figure 32 shows various camphor compounds that are easily accessed.

These four compounds provide access to a host of potential linking systems, such as thio-ethers, ethers and secondary amines. Intermediates along the synthetic route toward chiral ß-diketones, were chiral, tripodal alcohols (*vide infra*), which are themselves well suited for substitution on lanthanide metals. Although the resulting complexes are unlikely to yield Lewis acids sufficiently active to catalyse the inverse demand hetero Diels-Alder reaction (as was shown in investigations of alcohol ligands described in Chapter 2), they could be useful for various lanthanide alkoxide promoted transformations, such as reactions 40 through 43:[2]

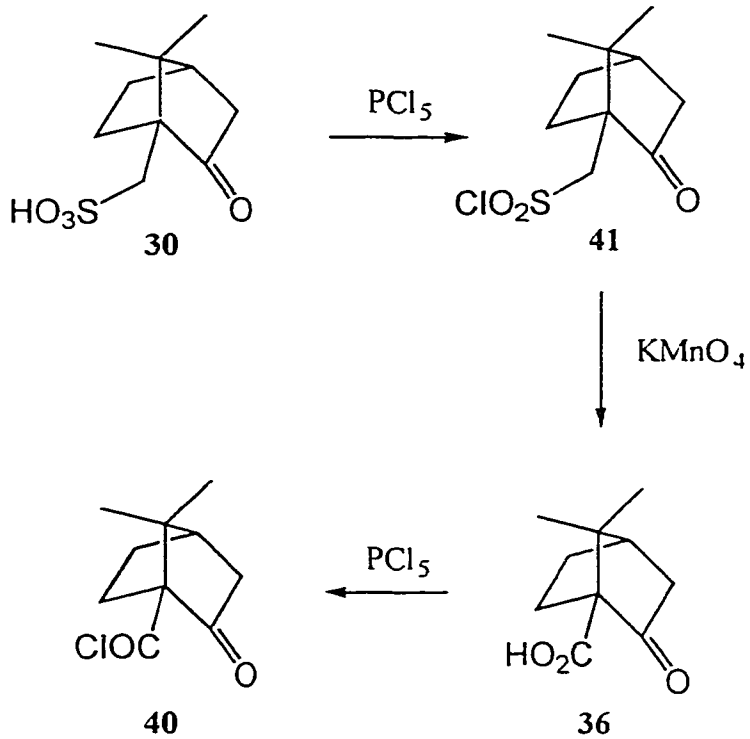
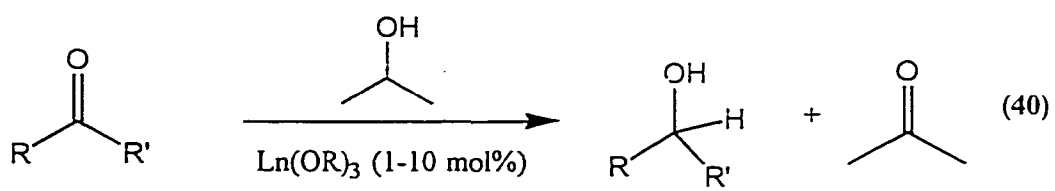


Figure 32: Accessible camphor derivatives.

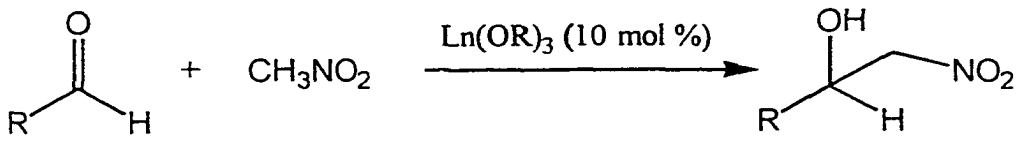
Meerwein-Ponndorf-Verley Reductions



(40)

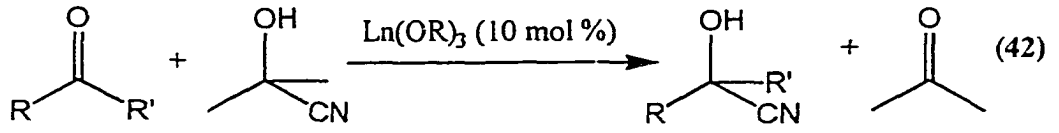
R' = H or alkyl group

Aldol Reactions between Adehydes and Nitroalkanes



(41)

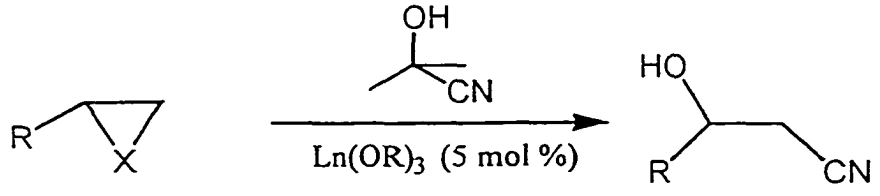
Hydrocyanation of Carbonyl Compounds



(42)

R' = H or alkyl group

Ring Opening Reactions



(43)

X = O, or NTs

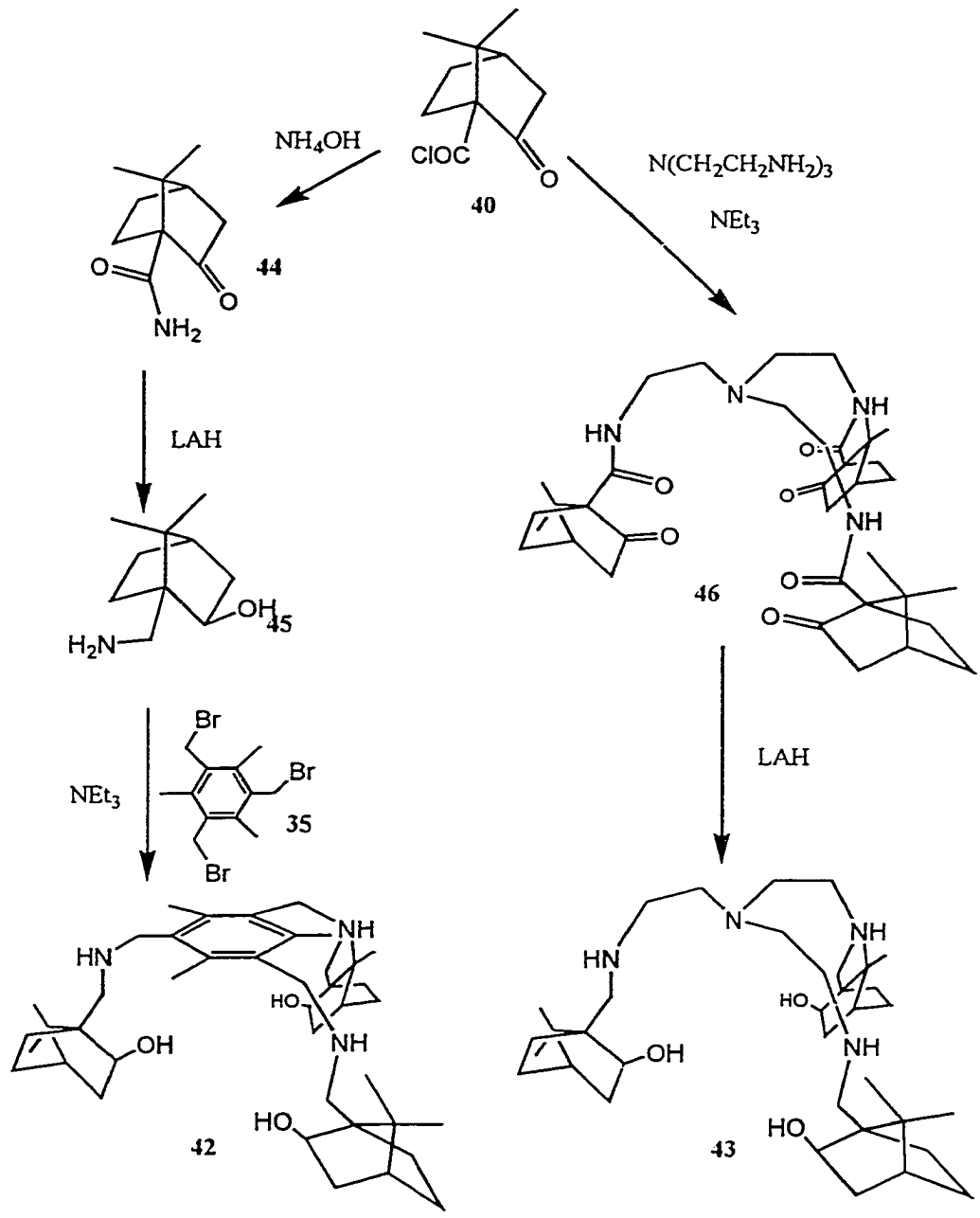
The use of chiral lanthanide alkoxides for enantioselective versions of Equations 40 - 43 are currently being investigated by other groups.[24] However, most research has focused on the *in situ* generation of unidentified catalytic species with commercially available chiral ligands such as BINOL.[44, 59] Additionally, there have been no reports of

chiral, tripodal lanthanide alkoxides as catalysts for any of these reactions. For all of these reasons, the intermediate chiral, tripodal ligands themselves were determined to be desirable target systems.

4.2 Ligand Design and Synthetic Progress

The challenges of previous efforts to prepare C_3 symmetric ligands clarified the importance of targeting reliable synthetic protocols for the preparation of tripodal ligand systems. With this in mind an investigation was undertaken to determine the possibility of using various derivatives of camphor (shown in Figure 32) as starting materials for the preparation of new robust linkers leading to a series of new chiral alcohol ligands. A variety of synthetic routes were available, all of them leading to the goal of a camphor containing C_3 symmetric, multidentate ligand. It should be noted that this work began in the spring of 1998 and represents just the beginning of an interesting area of work for future group members.

Camphor acid chloride **40**[190, 191] was easily prepared from carboxylic acid **36** in a reaction with PCl_5. Camphor carboxylic acid was dried with gentle heating under vacuum before adding the solid PCl_5 (with stirring) until both solids melted. The $O{=}PCl_3$ by-product was removed using vacuum (bp. 106°C) and after one hour a pale yellow



Scheme 28: Preparation of N linked alcohol ligands.

crystalline solid was available for immediate reaction. This product was used without any further purification or characterisation.

The highly electrophilic carbonyl of **40** is ideally suited for nucleophilic attack by amines resulting in the formation of amides. Subsequent reduction of the amide functionality provides a route into amine linkers, which are anticipated to exhibit improved stability in comparison with the earlier ester links. There are two possible amine linked ligand systems which could be accessed in this general manner (Scheme 28), a benzene capped system (**42**), or a return to the tren capping group (**43**).

In order to prepare ligand **42**, first the amide **44** was easily prepared by cooling the acid chloride **40** before adding aqueous ammonium hydroxide with stirring. The solution became clear upon formation of the desired product, which was isolated by extraction with ether. The white solid product (**44**) was isolated in quantitative yield and was shown to be the desired compound by the ^{1}H (Figure 33) and ^{13}C NMR spectroscopy. Note the two inequivalent amide protons at 7.5 ppm and 5.6 ppm, which indicate the two different chemical environments of the amide protons in compound **44**. These amide signals are diagnostic in determining the success of the subsequent reduction step to form amine **45**. Compound **44** was added dropwise to a slurry of lithium aluminum hydride in THF and heated to reflux for 16 hours. The desired amine product was formed as indicated by the disappearance of the amide peaks and an appearance of two doublets at 3.0 and 2.8 ppm, for the two newly formed diastereotopic hydrogens (Figure 34). From comparison with literature compounds[192, 193] it was established that the *exo* isomer was the major product.

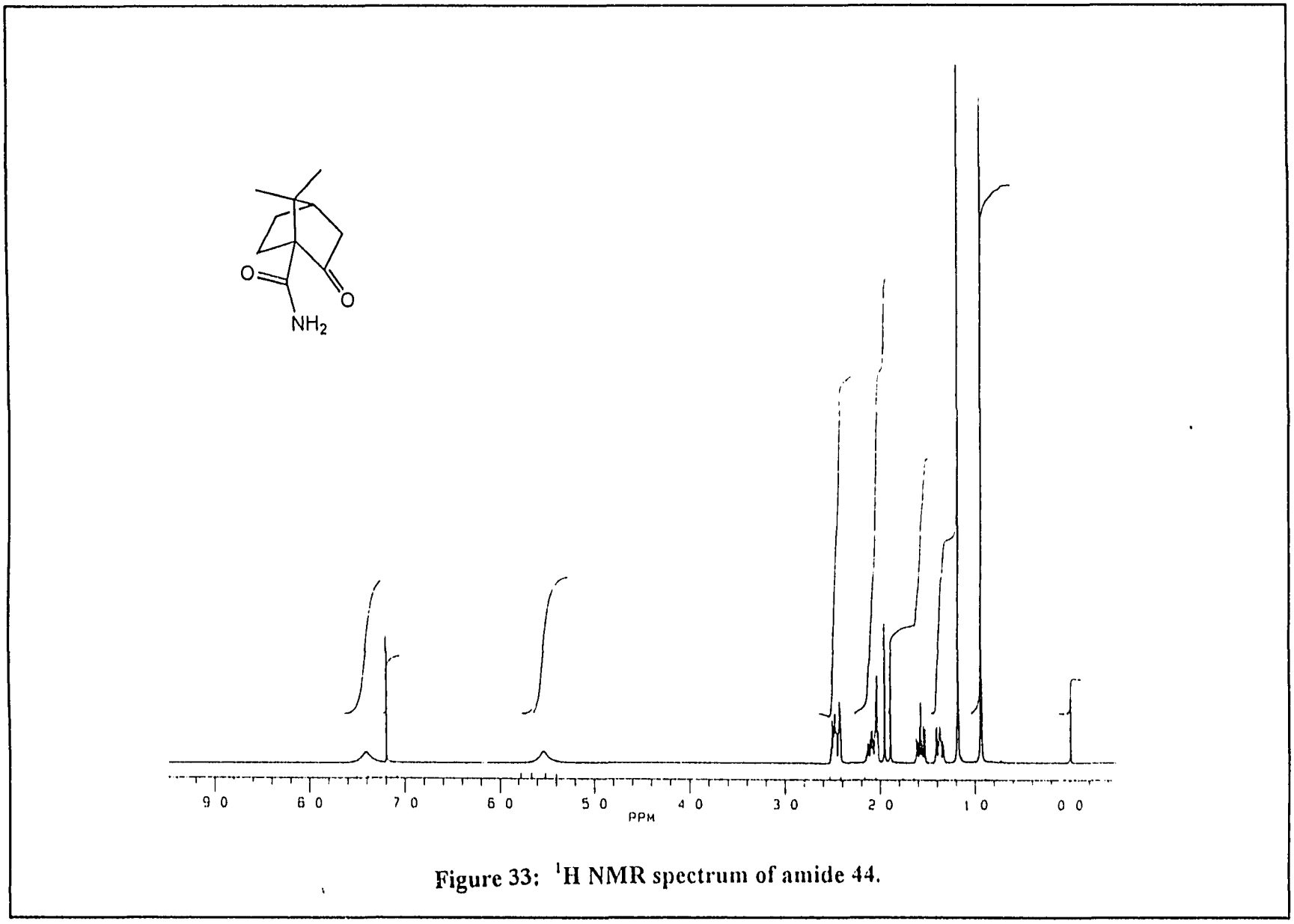


Figure 33: ^{1}H NMR spectrum of amide 44.

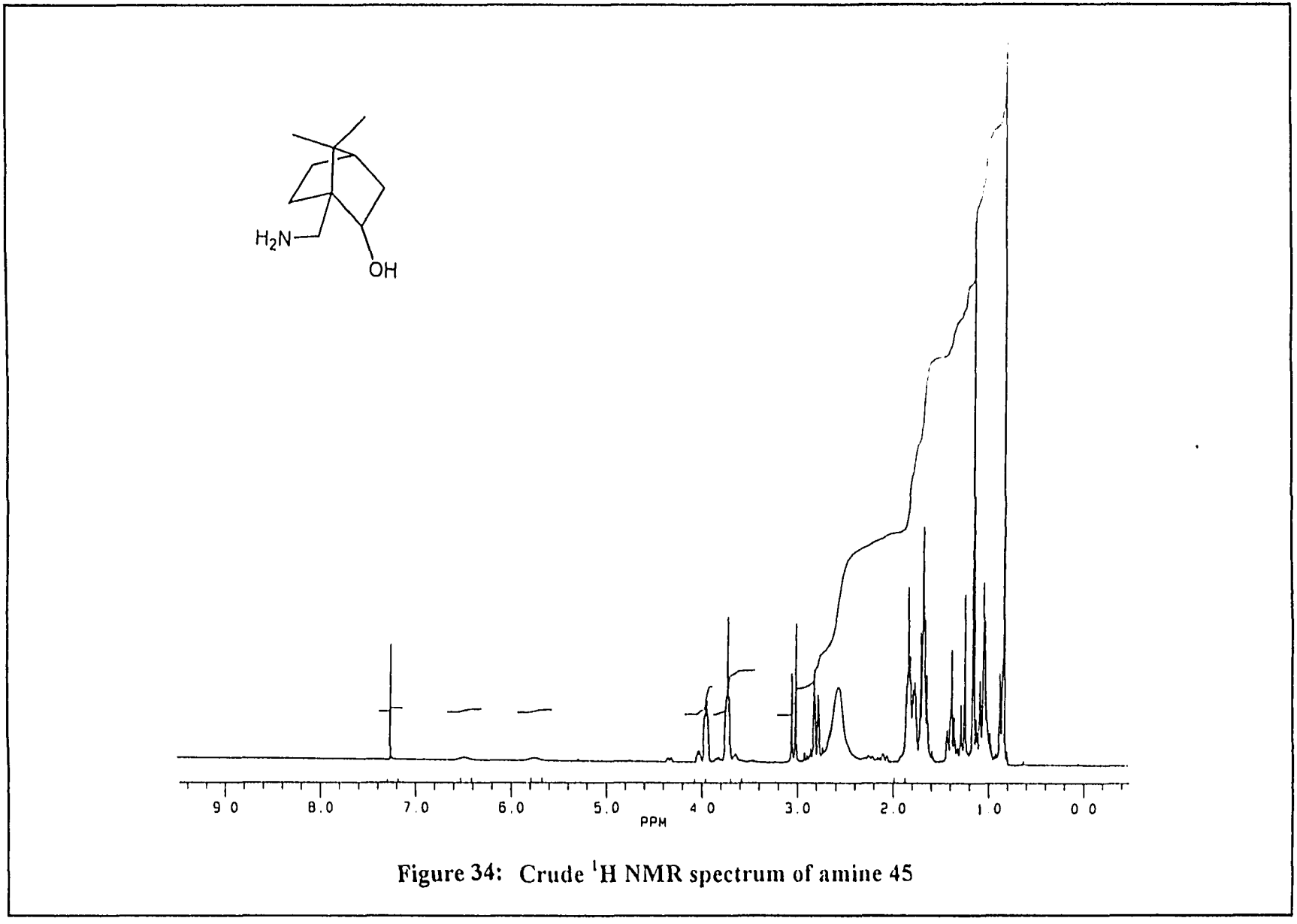


Figure 34: Crude ^{1}H NMR spectrum of amine 45

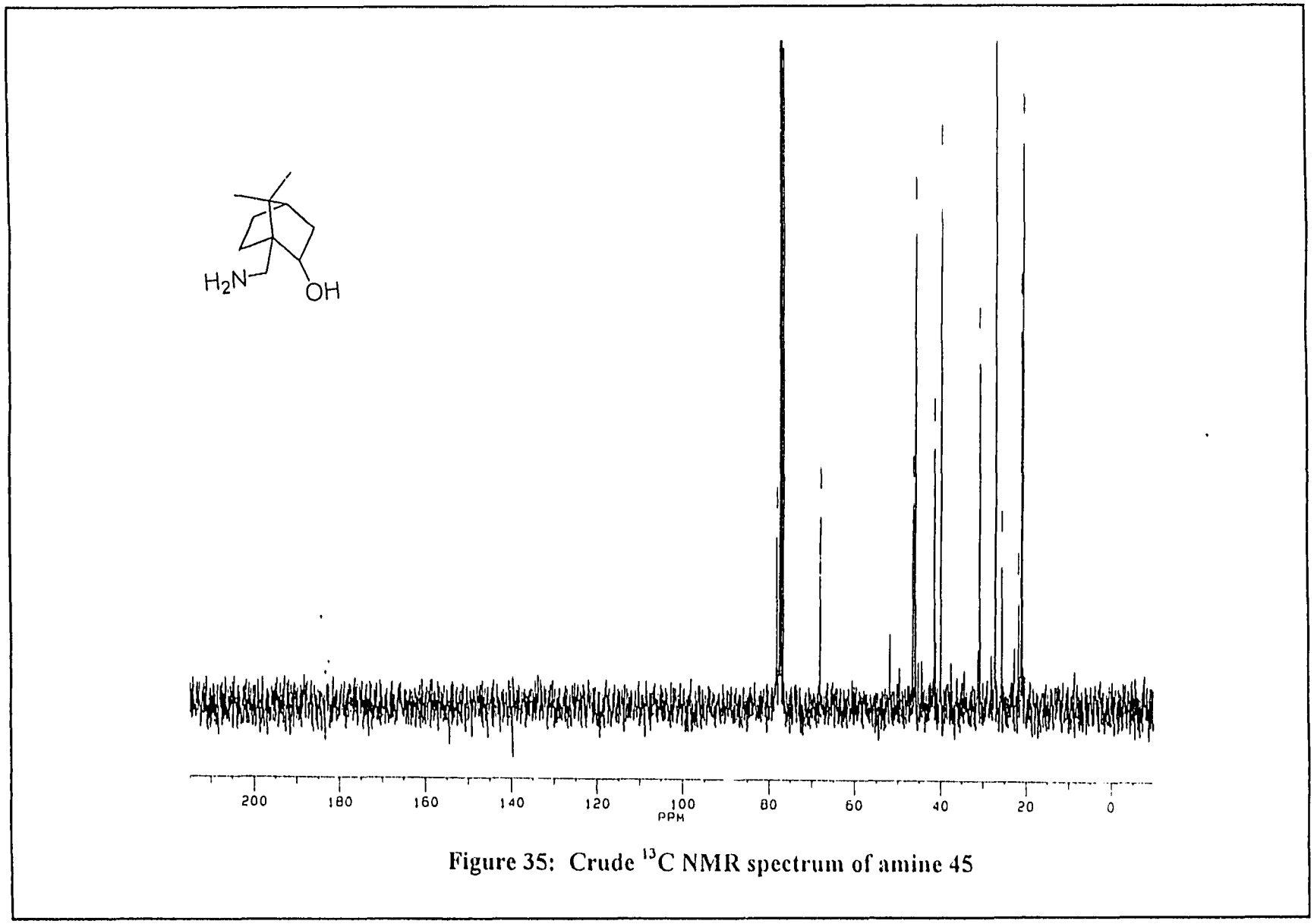


Figure 35: Crude ^{13}C NMR spectrum of amine 45

The diastereoselectivity of the reduction using LAH was significant as indicated by ^{1}H NMR data and more clearly evident in the ^{13}C NMR spectrum (Figure 35), where the opposite diastereomer was only apparent in small quantities (approx. 10%). The success of the reduction was also supported by mass spectroscopy (HRMS (EI) calc.=169.1467, found = 169.1469).

Attempts to prepare amine **45** using diborane were less successful, due to the difficulty in removing the desired product from the borane salts. Standard work-up procedures require an acid reflux to hydrolyse the B-N bond,[139] however the bicyclic frame of camphor and its derivatives are extremely susceptible to decomposition and rearrangement under acidic conditions. Also, the low product quantities which were successfully isolated indicated no diastereoselectivity when using borane as the reducing agent. Although the reduction proceeded through to completion more quickly using diborane (as indicated by the disappearance of the broad downfield singlets) the isolation of the desired amine product proved to be more difficult than for LAH reduction conditions.

Initial attempts to prepare the benzene capped ligand **42** by reacting the crude product **45** with benzyl bromide cap **35** gave complex product mixtures as shown by NMR spectroscopy. This reaction would be drastically improved by further purifying amine **45** before attempting to attach it to the tripodal capping unit. Initial attempts at purification of **45** by crystallisation (of both the protonated and unprotonated form) were unsuccessful, although further improvements could be made here. However, the success of another alcohol ligand synthesis precluded the further development of methodology toward the benzene capped, amine linked alcohol ligand. With only one step yet to be established in

this synthetic route into target ligand **42**, this work is clearly worthy of further experimentation.

The second amine linked target ligand, **43**, indicates a return to the initial design concept of using tren as a useful C_3 symmetric capping substituent. The camphor backbone is quickly incorporated into the ligand by reacting tren with the acid chloride **40** using a standard amine protection protocol using triethylamine as a base in CH_2Cl_2.[140] The acid chloride was dissolved in a 50/50 mixture of dichloromethane and triethylamine to which tren was added and stirred for 2 hours. The product was diluted with ether and washed extensively with a 1M acid solution to yield the desired product cleanly as shown by both ^1H and ^{13}C NMR spectroscopy (Figures 36 and 37). The clear amide proton at 7.7 ppm and its integration of 1:2 with respect to the methylene protons of the tren tether (3.3 ppm) were clear indicators of the formation of the desired tripodal amide **46**. This conclusion was further supported by mass spectroscopy data (*m/z* M+1 = 639) and elemental analysis (Anal. Calcd C, 67.68%; H, 8.52%; N, 8.77%; Found: C, 67.23%; H, 8.55%, N 8.51%).

Once again, the reduction of the amide linker to the desired amine **43** proved to be troublesome. When diborane was used, a disappearance of the amide proton signal at 7.7 ppm was observed, but the other diagnostic signals disappeared as well! All that was observed by NMR spectroscopy was a forest of peaks from approximately 4.2 ppm to 0.6 ppm, indicating the continued presence of borane and/or the decomposition of the compound upon acidic work-up conditions. Alternative work-ups, such as acidic methanol reflux[141,142] did not result in improved product isolation. Alternative borane

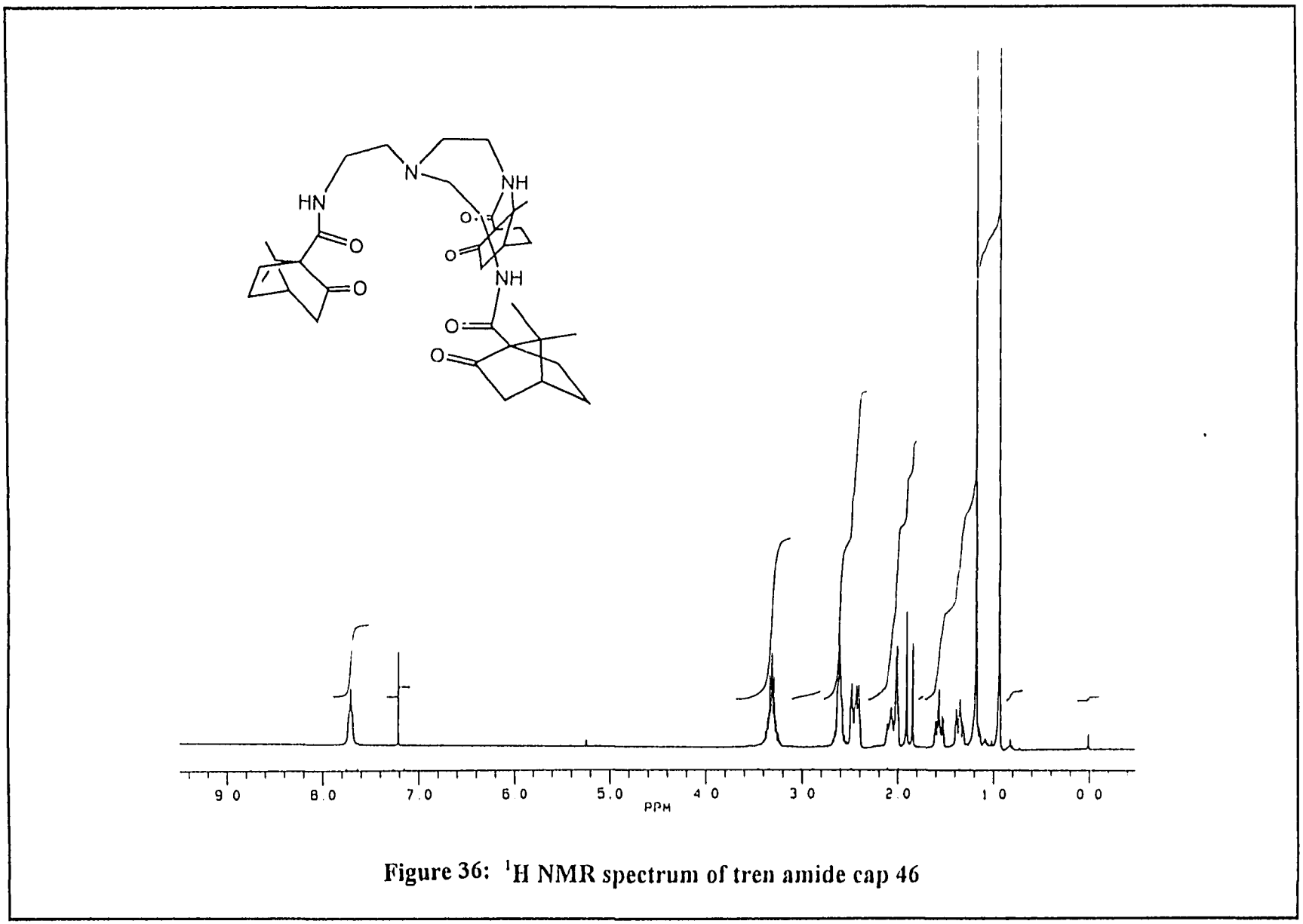


Figure 36: ^{1}H NMR spectrum of tren amide cap 46

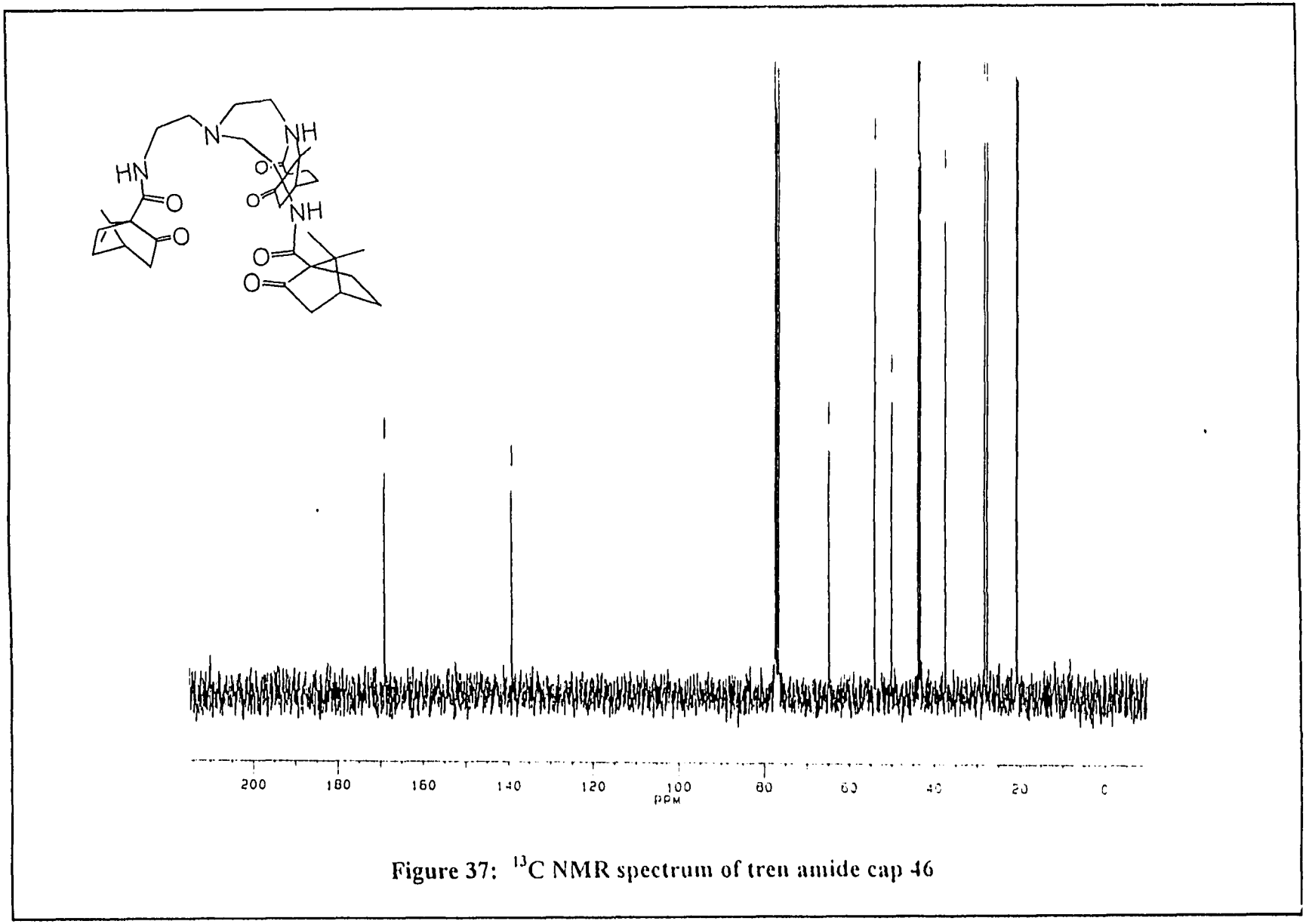
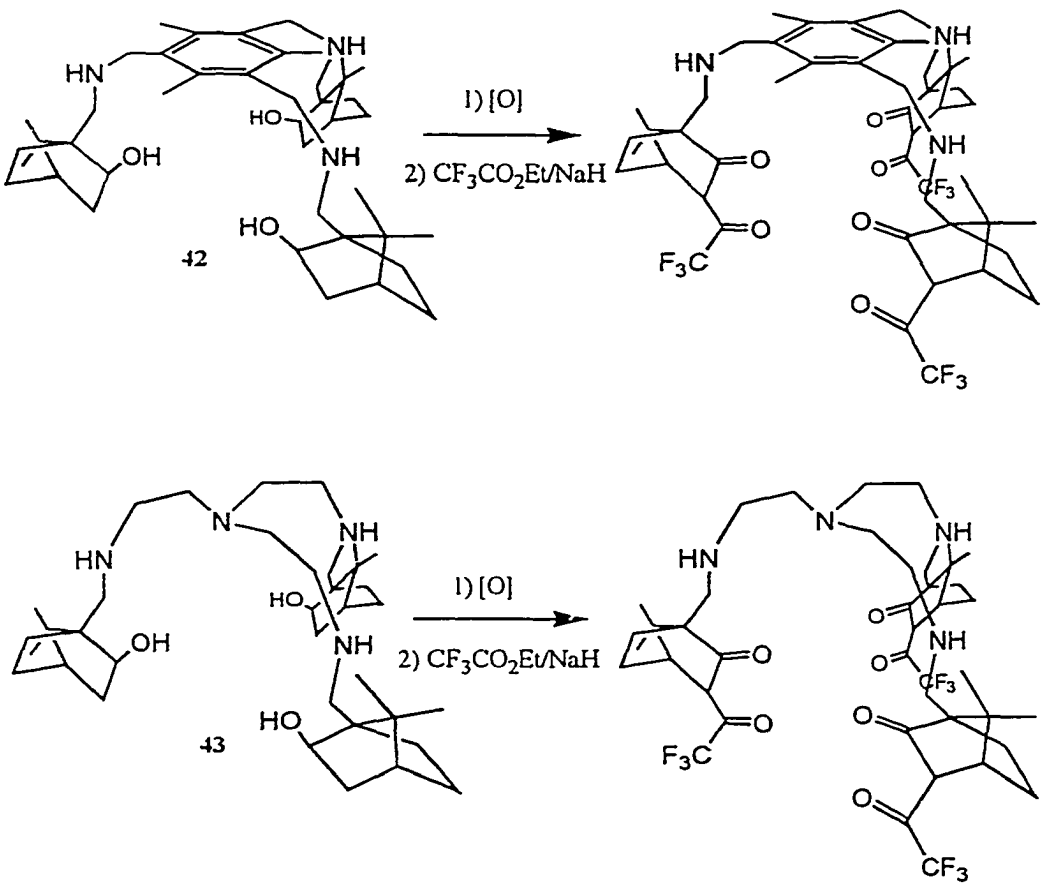


Figure 37: ^{13}C NMR spectrum of tren amide cap 46

reducing agents, such as borane-dimethyl sulfide complex[143,144] did not provide any notable improvement. Lithium aluminum hyrdride was noted to effect the desired reduction, although sluggishly (requiring 2 days at reflux) but the product yield was very poor with most product remaining inseparable from the aluminum salts. Further reduction strategies were not attempted due to time constraints, however, alternative work-up procedures using additives which chelate boron or aluminum, such as triethanolamine, would be worth pursuing.[145]



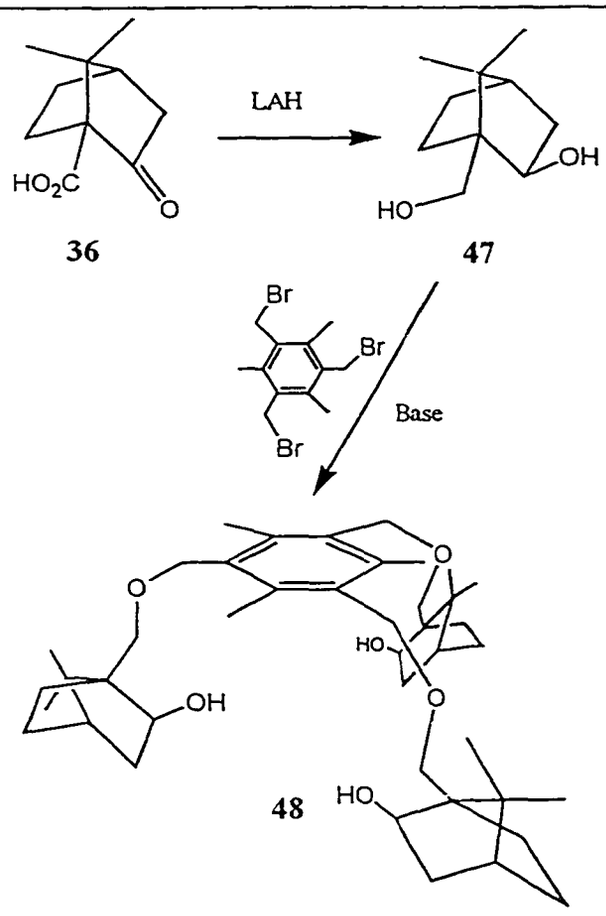
Scheme 29: Preparation of ß-diketone ligands from 42 and 43.

Both target ligands **42** and **43** are interesting systems for a variety of reasons. The first is the inclusion of the rigid bicyclic component in the ligand framework, which is anticipated to promote significant steric constraints upon the ligand binding mode (as do all the target alcohol ligand systems). Secondly, the amine linkers, and in the case of the tren system, the apical nitrogen, may also function as donors to the metal centre, which would enhance the likelihood of preparing characterisable, monomeric complexes. Most importantly though, in addition to their potential to form complexes displaying interesting applications in the organic reactions catalyzed by lanthanide alkoxides, they are precursors to chiral, tripodal ß-diketone ligands as shown in Scheme 29.

Oxidation using Dess-Martin Periodinane would regenerate the carbonyl without affecting the nitrogen linker, as it is a selective oxidizing agent that is known to not affect secondary nitrogens.[146] Subsequent trifluoroacetylation would be achieved as in previous ligand syntheses. Therefore, these ligand syntheses represent a very desirable area of future research. The four ligands shown in Scheme 29 would allow extensive investigations regarding lanthanide Lewis acid catalysis of a wide range of reactions. Also, the contrasting steric and electronic demands of the benzene and tren capping systems would provide valuable information regarding effective ligand design.

While this work was being pursued, several other synthetic strategies were also being investigated. Camphor carboxylic acid **36** provided a route into an ether linked system as shown in Scheme 30. The preparation of diol **47** was achieved using a lithium aluminum hydride reduction, where the crude product was prepared with 90% diastereoselectivity (*exo* isomer) and overall quantitative yield.

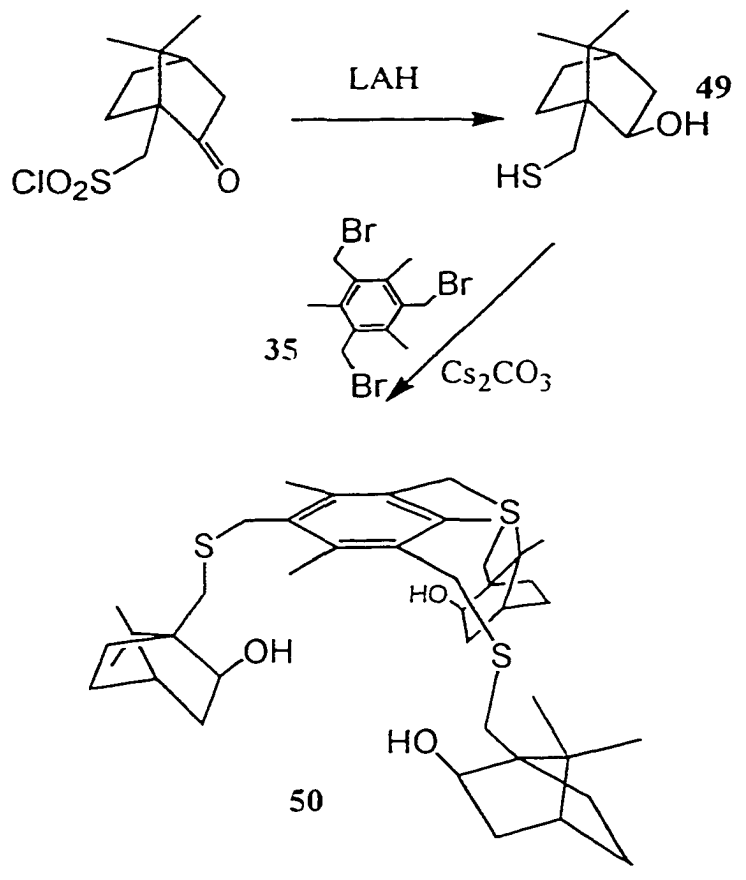
The difficulty in the following step, which would yield ligand **48**, is trying to get primary vs. secondary alcohol addition, on all three arms. It has been demonstrated in this group that diol **47** can be selectively protected at the primary alcohol site[147] using benzene sulfonyl chloride. Benzyl bromide can also be used as an alcohol protecting group, but efforts to effect the desired transformation to **48** were not successful. Literature precedence showed that selectivity had been demonstrated using NaH as base at low temperatures,[148] however in our case the isolated material showed a mixture of products.



Scheme 30: Preparation of ether linked ligand.

There is also the possibility that one diol could react with two different benzyl bromide sites on the same capping system. If the primary alcohol reacts successfully, then the secondary alcohol is in very close proximity to another benzyl site, thereby increasing the likelihood of this kind of bidentate attack. The obvious solution to this problem is a protection of the ketone in compound **36**, followed by deprotection once

the tripodal array was assembled. This route was never pursued, but would be of interest as ligand **48**, in addition to being suitable for metal complexation itself, is also a precursor to an ether linked chiral ß-diketone ligand.



Scheme 31: Synthetic route toward S linked alcohol ligand

Finally, camphor sulfonyl chloride **41** was used as a starting material for the preparation of a thio ether linked system (Scheme 31). The reduction of commercially available camphor sulfonyl chloride with lithium aluminum hydride resulted in a highly diastereoselective reduction (95% of the exo isomer) to give thiol **49** in excellent yield

(90%). The ^1H spectrum (Figure 38) showed a change in chemical shift to 2.7 and 2.5 ppm for the diastereotopic hydrogens adjacent to the thiol group from δ 3.5 and 2.9 ppm in the sulfonate ester case. These peaks also exhibited complicated coupling patterns in product **49**, due to coupling with each other as well as coupling to the thiol hydrogen. Also, the appearance of a new peak at δ 3.9 ppm, with its complicated coupling pattern, indicated the reduction of the carbonyl group to the *exo* alcohol,[192] while the much smaller peak at 4.3 ppm was assigned as the equivalent signal for the opposite diastereomer. The formation of **49** was further supported by ^{13}C NMR data as well as mass spectroscopy results (*m/z* M+1 $-H_2O$ = 169).

This product, a colourless sticky solid, was stirred with the brominated benzene cap **35** in 95% ethanol using Cs_2CO_3 as base for 2 hours at room temperature to yield the desired ligand **50** as a white crystalline solid in excellent yield (95%). The ^1H NMR spectra (Figures 39 and 40) clearly indicate the C_3 symmetric substitution with the benzyl peaks at 3.6 ppm (in 40), which correctly integrate 2:1 with respect to one of the diastereotopic proton signals. (Note the coupling constant of 12 Hz for the two chemically different benzylic protons.) The ^{13}C NMR spectrum was also indicative of desired compound formation, while the mass spectral data, using negative LSIMS, revealed a strong molecular ion (*m/z* M-1 = 713). The *exo* stereochemistry of the alcohol group was verified by NOESY spectroscopy (Figure 41), where three through space interactions with the C*H*OH signal centred at δ 3.80 ppm indicated its positioning on the "bottom" face of the ring.

This solid had a melting point of 128°C and was dried by melting with gentle

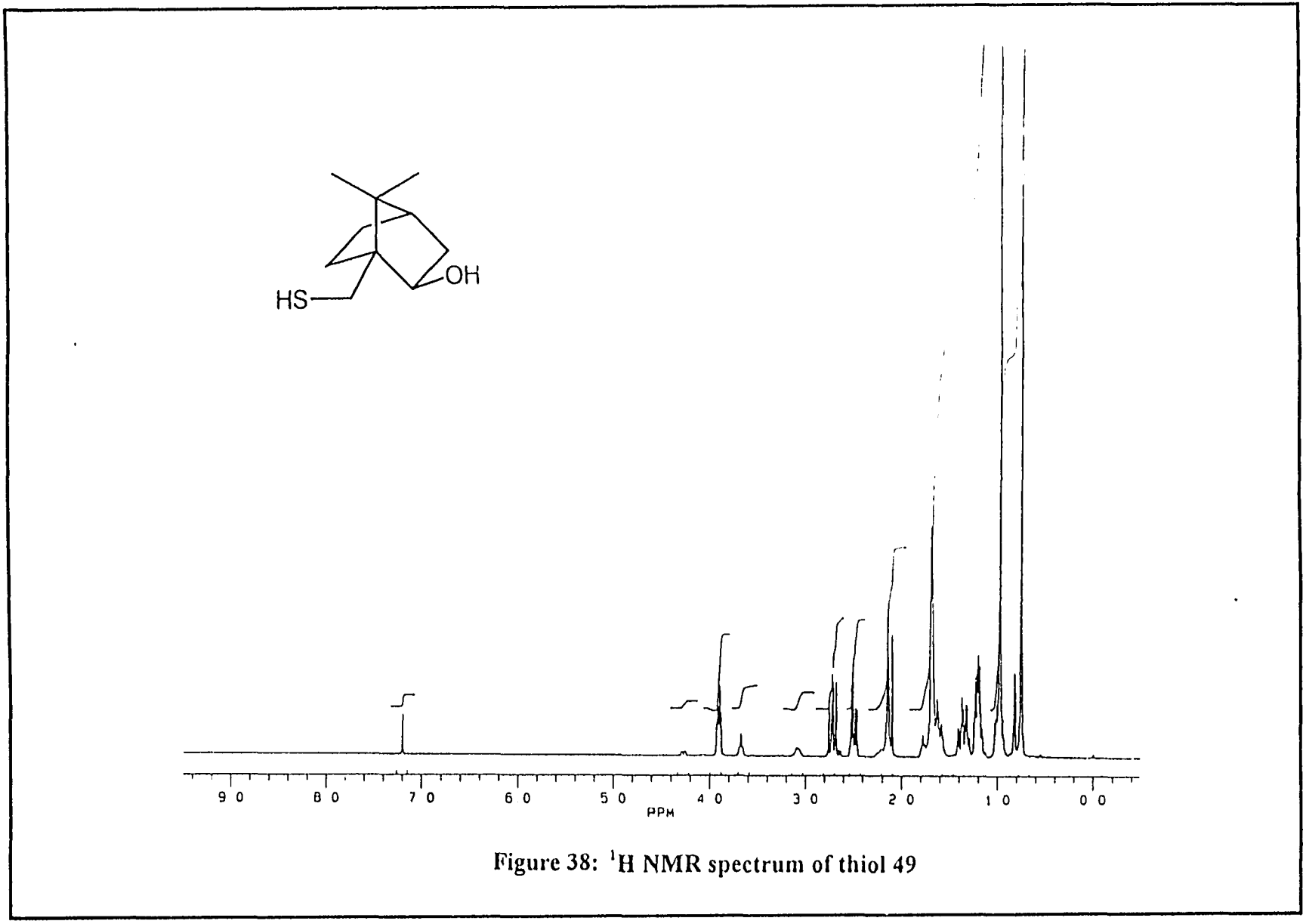


Figure 38: ^{1}H NMR spectrum of thiol 49

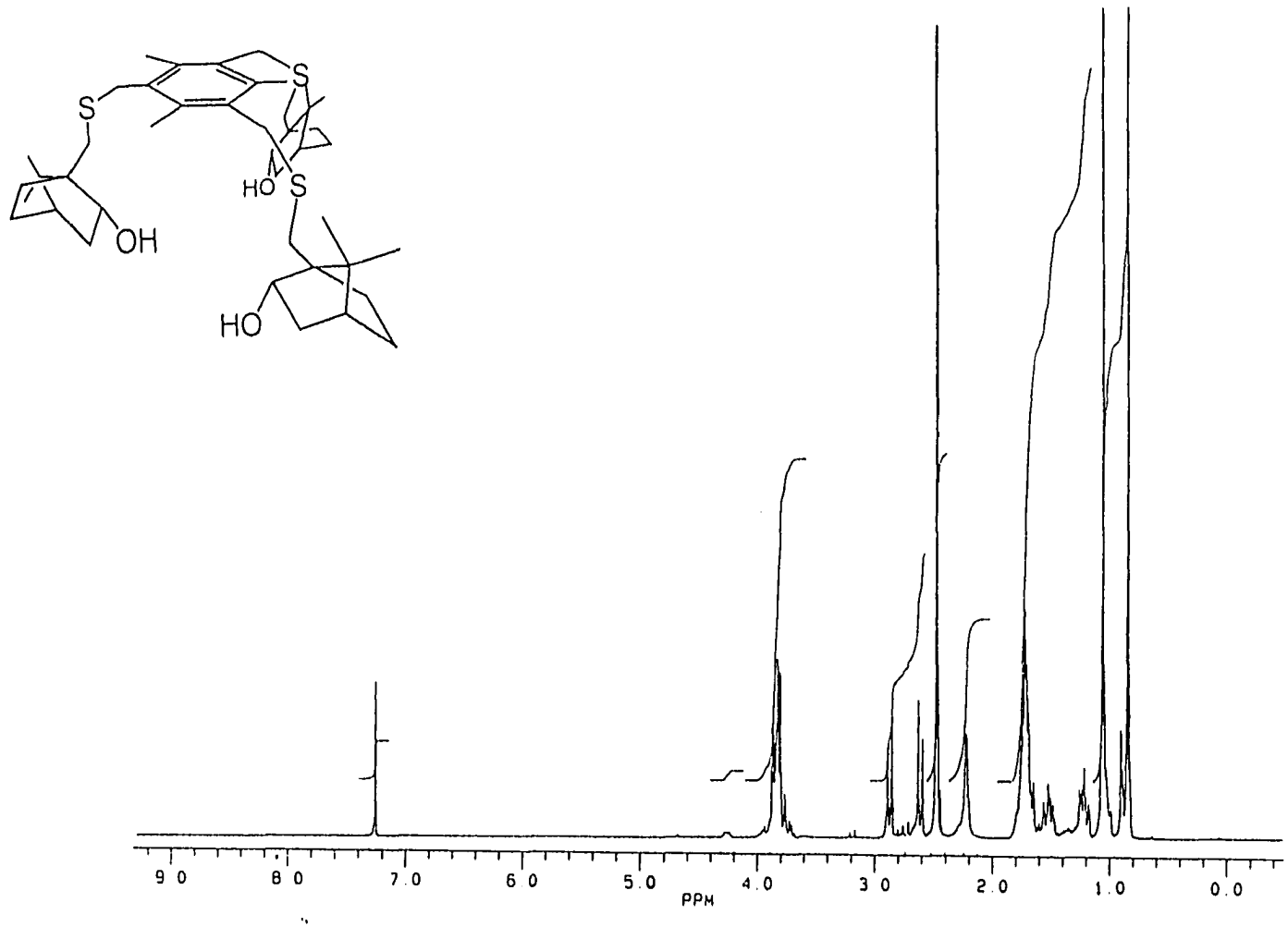


Figure 39: ^{1}H NMR spectrum of sulfur linked ligand 50 in $CDCl_3$

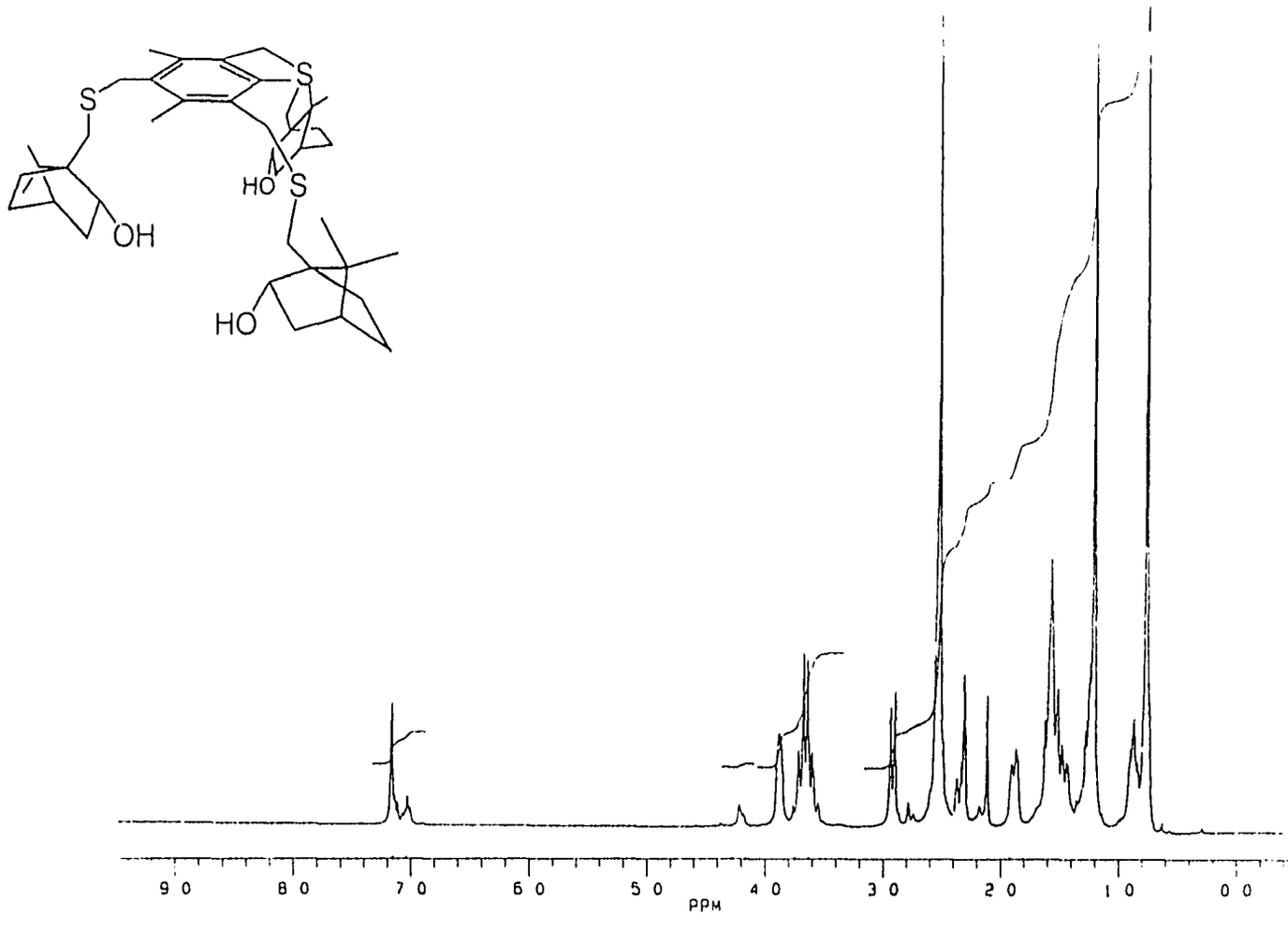


Figure 40: ^{1}H NMR spectrum of sulfur linked ligand 50 in C_6D_6

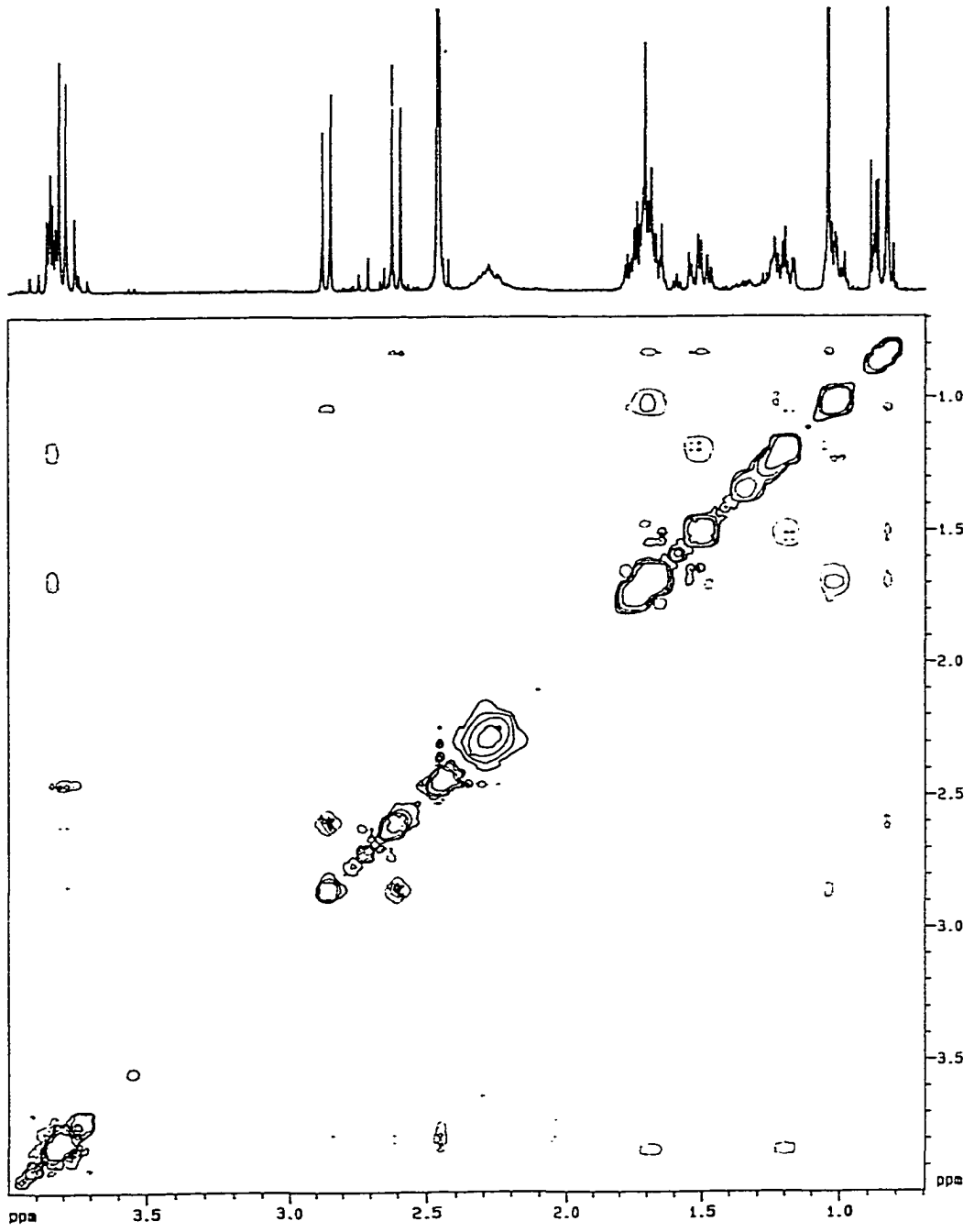


Figure 41: ^{1}H NOESY spectrum of sulfur linked ligand 50 in $CDCl_3$

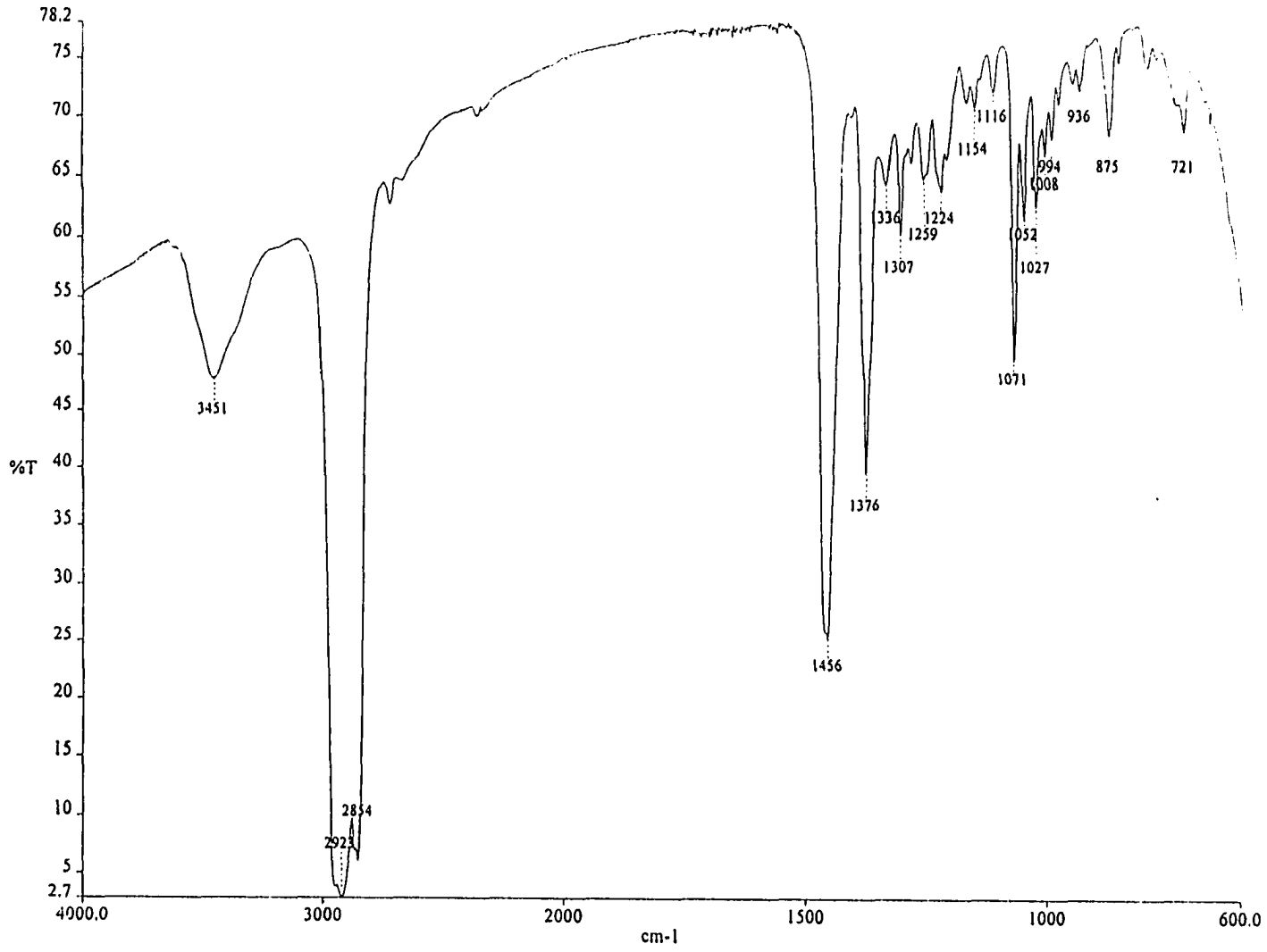


Figure 42: IR spectrum of sulfur linked ligand 50 in nujol, air reference

These very similar values indicate that heating under vacuum, as described above, was sufficient for removing any substantial quantities of water.

The IR spectrum of ligand **50** is presented in Figure 42. Here the diagnostic signals were assigned in the following manner: OH stretch at 3451 cm^{-1}, secondary alcohol C-O stretch at 1071 cm^{-1}, symmetrically substituted aromatic C-H bend at 875 cm^{-1} and the thio-ether C-S stretch at 721 cm^{-1}.

Both thiol **49** and S linked alcohol ligand **50** were susceptible to oxidation (as seen in changes of the ^1H NMR spectrum) when stored in air. Also, the final product was found to be hygroscopic. The spectrum of the ligand was significantly different when using d_6-benzene as solvent (Figure 40) versus $CDCl_3$. Such changes are often encountered in compounds capable of strong molecule-molecule and molecule-solvent ($CDCl_3$) hydrogen bonding interactions.

In summary, this route, in 24 hours, and two high yielding steps, gave chiral alcohol ligand **50** in multigram quantities. The product, a white powder could be dried by heating under vacuum, which prepared the ligand for reactivity with moisture sensitive metals. As a starting point for the investigation of chiral alcohol ligands, compound **50** became the focus of remaining work. It was because of the success of this ligand preparation that the afore-mentioned synthetic routes were abandoned before completion.

It should be noted that although ligand **50** is easily prepared, this ligand is not easily amenable to further elaboration toward ß-diketone ligands. The attempted oxidation of the alcohol using PCC, PDC and $ZnClCrO_3$-9 H_2O[149, 150] also resulted in the oxidation (and sometimes decomposition) of the sulfur linkage, as observed by changes in the ^1H NMR spectrum. Even if the oxidation of both the alcohol and sulfide linker could

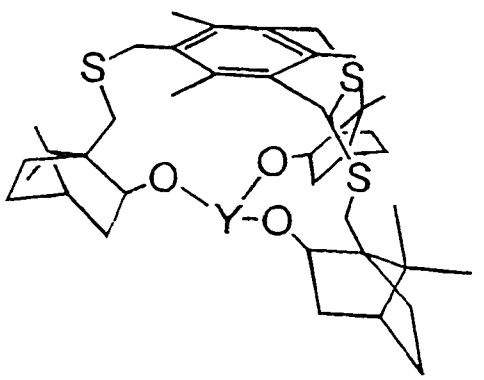
be carried out cleanly, the subsequent trifluoroacetylation reaction, in the presence of both the new carbonyl and sulfonyl groups may present some regioselectivity problems. Therefore ligand **50**, while well-suited to a formation of a lanthanide complex itself, is probably not suitable as a precursor for subsequent ß-diketone ligand formation.

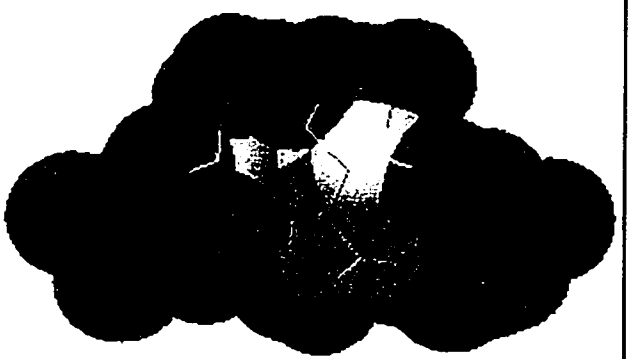
4.3 Metal Complexation with Chiral S Linked Alcohol Ligand

4.3.1 Molecular Modelling

All previous modelling had been done using the chelating ß-diketone ligand systems, yielding a hexadentate binding site. In the present case, there would be only three available binding sites, which may affect the steric implications of the ligand significantly as it no longer possesses a very rigid chelating binding mode. Also, we were interested in noting how alkoxide bonding would vary from a chelating interaction with respect to the orientation of the ligand arms about the metal centre.

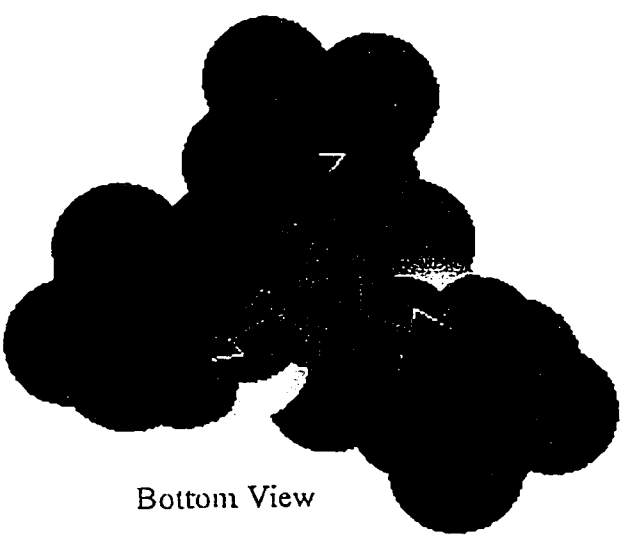
Figure 43 depicts the lowest energy conformation of the monomeric, yttrium complex of ligand **50**. The side view shows that the ligand remains sterically demanding about the metal centre, where access to the metal centre is restricted to the coordination site defined by the "chiral pocket". As is clear from the top and bottom views, the binding mode of the ligand is C_3 symmetric. In this case, like the other modelled systems, the camphor groups impose the desired propeller type twist within the complex, leading to the selective formation of the Λ and Δ complexes using either the R or the S enantiomers of





Side View

Top View



Bottom View

Figure 43: CAChe molecular models of the Y complex of ligand 50

the camphor starting materials. The bottom view shows the accessible metal centre and the chiral pocket created, ideal for enantioselective catalysis. Therefore, the modelling studies indicated that the complex of ligand **50** would display the features we wanted in our ligand design. What remained to be determined was whether the sulfide linker would be sufficiently robust to endure the Lewis acidic environment of the lanthanide metal centre.

4.3.1 Synthetic Routes and Results

The chiral S linked alcohol ligand **50** offers a number of preparative advantages over other previously prepared ligands. As mentioned earlier, it can be easily prepared in multigram quantities from commercially available starting materials, in two high yielding steps. Secondly, the ligand can be rigorously dried and stored in the glove box to prevent any ligand oxidative decomposition. Also, the ligand itself is soluble in hexanes and toluene, two solvents available in the glove box. Therefore complexes could be prepared in toluene in the glove box and any unreacted ligand could be washed away with hexanes, upon completion of the reaction.

$$Ln(N(SiMe_3)_2)_3 + H_3L \longrightarrow LnL + 3\ HN(SiMe_3)_2 \quad (44)$$

Initial attempts at preparing lanthanide complexes in toluene in the box using the reaction shown in Equation 44 resulted in immediate formation of a cloudy solution with slow deposition of precipitate. Usually the formation of precipitate in such a fashion is indicative of oligomer formation. One possible configuration leading to oligomerisation is shown in Figure 44 where the three arms radiating from the benzene ring do not all extend in the same direction to form a monomer, but rather bind in a bridging fashion.

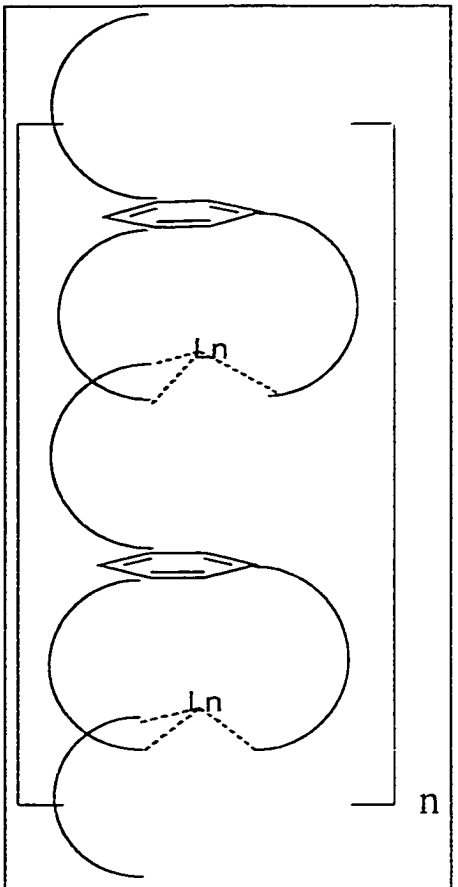


Figure 44: One possible bridging interaction of ligand 50

The materials isolated from reactions carried out in non-coordinating solvents were insoluble and remained insoluble in coordinating solvents such as pyridine and THF. Although NMR spectrocopic evalutions of the metal complexes of ligand **50** could not be carried out, elemental analyses of the materials confirmed a stoichiometric formulation of one to one ligand to metal complexes (eg. Y complex anal. calcd: C, 62.974%; H, 7.927%; found: C, 62.99%; H, 8.01%). Decomposition of this oligomeric material by hydrolysis yielded free ligand, which remained intact and showed no evidence of decomposition of the sulfide linker. The IR spectra of these complexes (Figure 45) showed a disappearance of the OH stretch and a shift of the secondary alcohol signal from 1072 to 1081 cm^{-1}. The IR spectra of various

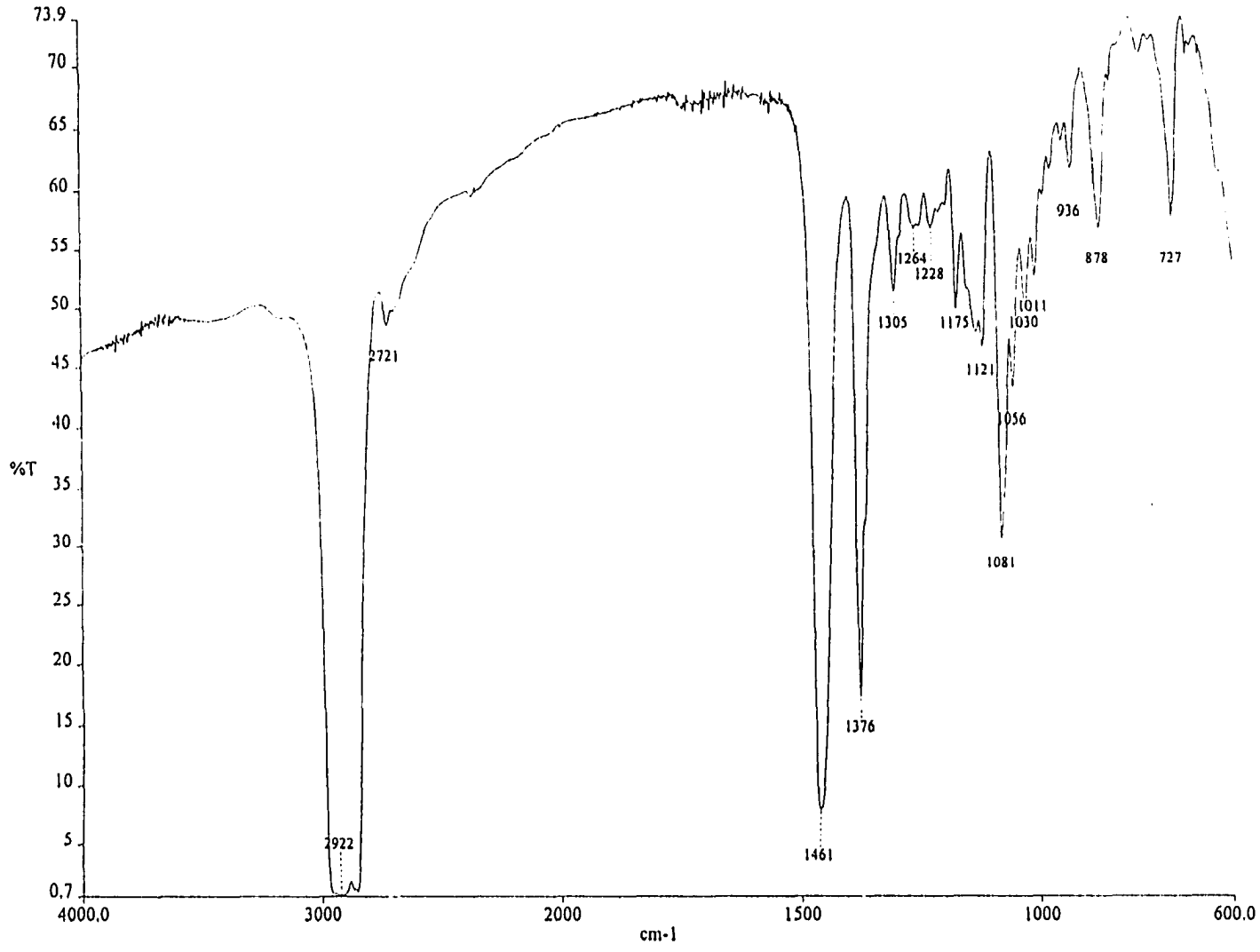


Figure 45: IR spectrum of Y complex of ligand 50 in nujol, air reference

lanthanide complexes including Ce and Nd show similar patterns, indicating that the ligand behaviour does not vary significantly when metal centres of different ionic radii are used.

Unfortunately, lanthanide complexes prepared in coordinating solvents, such as THF and ether did not yield monomeric complexes. Instead, cloudy solutions formed slowly resulting in insoluble precipitates. Due to the lack of solubility it has been impossible to obtain information about the metal centre.

Unfortunately due to time constraints, complexes of ligand **50** were not evaluated for catalytic behaviour. Although little is known about the structure of these complexes, they may still exhibit enantioselective catalysis. Unfortunately, our goal of preparing C_3 symmetric, well characterised, monomeric, crystalline materials for catalytic studies was not obtained with these complexes.

As has been demonstrated in this section, ligand **50** has a propensity toward forming oligomeric species, even in the presence of coordinating solvents. Regardless, the isolated free flowing powders were established as 1:1 ligand to metal complexes by elemental analysis. The isolation of intact ligand upon complex hydrolysis is a testament to the robustness of the sulfide linker and its ability to resist deomposition in a Lewis acidic environment. Future work with this ligand will investigate early transition metal complexes in an effort to prepare soluble, crystalline materials. Also, these complexes will be evaluated for their catalytic behaviour in the Meerwein-Ponndorf-Verley reduction reaction.

4.4 Conclusions

The various camphor derivatives shown in Figure 32 have demonstrated their usefulness in providing access to camphor containing tripodal ligand systems with robust linkers. There has been synthetic progress demonstrated for both benzene and tren capped amine linked systems (ligands **42** and **43** respectively), where these systems indicate substantial applications in both lanthanide alkoxide, as well as lanthanide ß-diketonate mediated catalysis. Another possibility which has been probed is the use of an ether tether as a route into interesting alcohol and ß-diketone ligands.

Most importantly we have established a facile synthesis of a chiral, C_3 symmetric multidentate alcohol ligand (**50**) by using a sulfide linker. This linker has been shown to be resistant to decomposition in the Lewis acidic environments of the lanthanides. We have begun to establish the reaction chemistry of this ligand with a variety of lanthanides. This ligand system represents only the beginning of a wide range of investigations resulting in the formation of multidentate alkoxide complexes. These complexes are foreseen to have interesting applications as enantioselective catalysts for a host of lanthanide alkoxide mediated reactions, as well as early transition metal organometallic chemistry and Lewis acid catalysis. The results from the sulfide linked system will provide valuable information regarding the scope of future work using amine and ether linked ligand systems.

CHAPTER 5: Conclusions and Future Directions

The preparation of chiral lanthanide complexes which are suitable for enantioselective Lewis acid catalysis of the inverse demand hetero Diels-Alder reaction has proven to be a formidable task. The initial focus on the ligand structure, catalyst function relationship revealed the required ligand attributes for preparing successful lanthanide Lewis acid catalysts. These features include the presence of a ß-diketone ligand of sufficiently low pKa to ensure a suitably Lewis acidic metal centre. Our investigations demonstrated the necessity of carefully enhancing the Lewis acidic nature of the metal centre; if the metal is not Lewis acidic enough, the ligand complex does not promote catalysis; on the other hand, if the metal centre is too strong a Lewis acid (as in the case of the lanthanide triflates) the metal centre promotes polymerization of the starting materials crotonaldehyde and ethyl vinyl ether.

The results from the ligand structure catalyst function investigations were incorporated into the design of a new C_3 symmetric, multi-dentate, ß-diketone ligand system (**13**). The yttrium and ytterbium complexes of this new ligand system were demonstrated to be efficient catalysts for the test Diels-Alder reaction of choice. In addition to the fact that these complexes were of competitive reactivity with the commerically available $Yb(fod)_3$, they were considerabley less air-sensitive than other known catalysts. In fact, our lanthanide complexes were shown to be air and moisture stable with the reactivity rate slowing somewhat upon exposure to air. Most importantly, these complexes continued to display notable catalytic function even after bench-top

storage in an open vial for up to 3 months. This enhanced stability was attributed to the multidentate nature of the ligand system. Consequently, the success of the achiral ligand complexes of ligand **13** were excellent models for second generation chiral, multidentate ß-diketone ligands.

The preparation of a chiral, multidentate, fluorinated ß-diketonate ligand was very challenging and was pursued with several different strategies. First, chiral elaboration of the starting materials for the preparation of ligand **13** was attempted, but was shown not to be a viable route into the desired systems. Next, our attempts to use a modular approach were demonstrated to not be synthetically feasible. However, two chiral synthons, which could be elaborated using established methodology to yield the desired ß-diketone structure caught our attention: nopol and camphor. The ligand preparation using nopol was pursued with limited success, but abandoned due to the success of synthetic efforts using camphor.

Camphor provided access to the first C_3 symmetric, chiral ß-diketone ligand system (**33**) designed for lanthanide substitution. Molecular modeling of this ligand system on a yttrium metal centre revealed promising behaviour with respect to facial selectivity in the dienophile approach for the Diels-Alder reaction. Thus, this ligand was prepared using well established methodology to generate a sulfonate ester link via silver salt precipitation. Next the fluorinated ß-diketone functionality was generated by trifluoroacetylation of the camphor group using NaH as base. This ligand could be prepared in multi-gram quantities and was characterised by NMR spectroscopy. Unfortunately, during ligand preparation and purification the sulfonate ester linkers were shown to be susceptible to decomposition by hydrolysis. This fact was an indication of the

lack of stability of these same sulfonate linkers in the presence of the lanthanides. Unfortunately, all attempts to substitute this chiral, tripodal ligand onto a lanthanide metal centre were unsuccessful. Therefore, we began to screen other possible linkers and capping groups in the search for a more robust linker while retaining the camphor substituent. These linkers included carboxylate esters, amine, ether and sulfide groups.

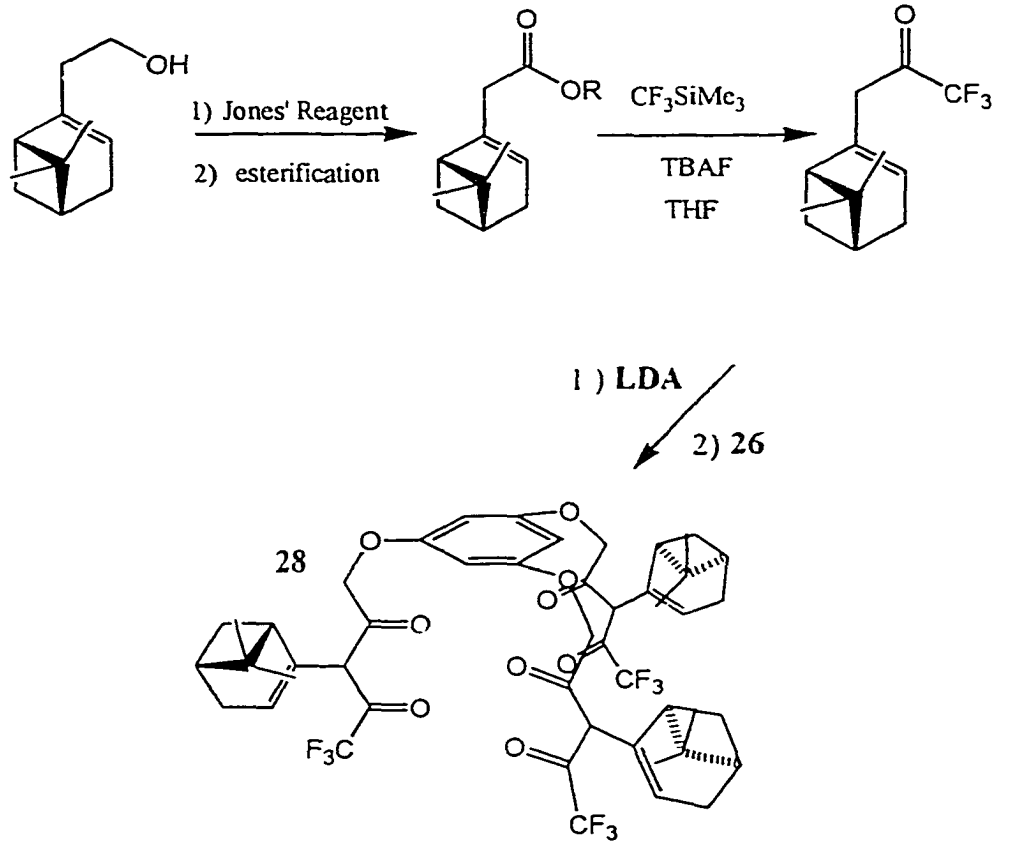
While working toward new C_3 symmetric ß-diketone ligands, we proposed to generate C_3 symmetric chiral alcohol ligands. These were quickly identified as desirable targets themselves as lanthanide alkoxides are known to carry out a number of desirable synthetic transformations as described in section 4.1. This work was investigated briefly and some synthetic protocols were established. In particular, the methodology for a 2 step preparation of a sulfide linked chiral, tripodal alcohol ligand (**50**) in multi-gram quantitities was developed. This ligand was then substituted onto several lanthanide metals, yielding insoluble, oligomeric complexes. It is possible that these complexes will display desirable catalytic behaviour in a number of synthetic protocols, such as Merwein-Pondorf Verley reductions.

This brief work on alternative linking systems also saw significant contributions toward future project goals. Many of these possibilities for future work are outlined in Chapter 4. However, in particular a class of ligands described in Scheme 28 that focus on amine linked systems, represent an interesting series of ligands worthy of future investigation.

Some other work which was begun in the project and is of interest for future experimentation is the preparation of the nopol target ligand proposed in section 3.4. A modification of Scheme 23 is given in Scheme 32, where the target ligand **28** should be

readily accessible due to recent advances reported in the literature.[184] This improved route avoids the troublesome partial oxidation of the allylic alcohol. Ligand **28** represents an interesting target because the chiral substituent is far removed from the metal centre. Well-characterised complexes of the proposed ligand **28** would provide important information about steric effects the ligand must impose in order to achieve enantioselective Lewis acid catalysis.

With a ligand design suitable for the formation of monomeric lanthanide complexes, much future work revolves around investigating the scope of both the metal coordination and catalysis chemistry. It would be very interesting to prepare a variety of lanthanide complexes of a given ligand. Another important aspect of the thorough investigation of a ligand is the screening of a number of Lewis acid catalysed reactions. In this work we focused on the inverse demand hetero Diels-Alder reaction. However, there are a wide range of lanthanide promoted reactions as discussed in section 1.2. It would be of extreme interest to probe a range of lanthanide Lewis acid promoted reactions. Thus with one successful ligand design a variety of lanthanide complexes can be prepared and their respective usefulness for a range of Lewis acid promoted reactions can be investigated.



Scheme 32: Alternative route into Nopol target ligand 28.

In conclusion, we have determined that fluorinated ß-diketone ligands of sufficiently low pKa effectively catalyse the Diels-Alder reaction between crotonaldehyde and ethyl vinyl ether (eq 34).[79] These functionalities can be incorporated into a multi-dentate C_3 symmetric ligand system which yields air-stable lanthanide complexes displaying the desired catalytic function.[111] We have shown that these same functionalities can be incorporated into the preparation of tripodal, chiral ligand systems. Through molecular modeling studies we anticipate effective facial selectivity for the enantioselective

Diels-Alder reactions. We have established the need for robust functionalities to be incorporated into future ligand design and have briefly investigated several new routes into amine and sulfide linked ligands. The effect of these higher symmetry ligand systems upon Lewis acid catalysis remains to be established and promises to be an important contribution to this area.

CHAPTER 6: Experimental

6.1 Apparatus

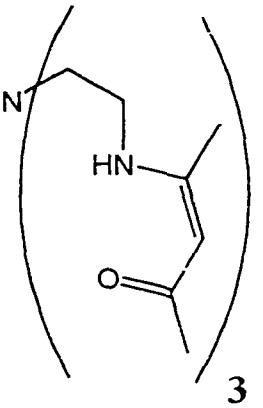
Nuclear magnetic resonance spectra of ^{1}H, ^{13}C, and ^{19}F were recorded on a Bruker WM 250 MHz, Bruker AC-300 MHz or Bruker AMX-360 MHz spectrometer. Spectra were recorded in C_6D_6, or d_8-THF solvent, previously distilled from sodium under argon, or in $CDCl_3$ dried and stored over 4Å molecular sieves. ^{1}H and ^{13}C NMR spectra were referenced to residual solvent resonances, ^{19}F was referenced to C_6F_6. ^{13}C spectra were assigned with the aid of 135 DEPT spectra, as indicated with + and - signs. Mass spectra were recorded on a Finnigan 3300 or a Kratos Concept H spectrometer using chemical ionisation, electron impact (70 eV) or FAB sources. Liquid secondary ion mass spectra (LSIMS) were recorded on the Kratos Concept double focusing magnetic instrument using either glycerol or meta-nitrobenzyl alcohol as the matrix. Gas chromatography was performed on a Fisons E980 GC equipped with a DB-1 capillary column and FID detector. Infrared spectra were recorded on a Perkin Elmer Spectrum 1000 FT-IR instrument as nujol mulls on KBr plates. X-ray crystallographic details are given in the experimental section. Melting points were recorded using a Gallenkamp melting point apparatus. Thin layer chromatography was performed using KODAK Chromogram Silica Sheets with fluorescent indicator. Flash column chromatography was done using Merck 60 silica gel. Elemental analyses were performed by Canadian Microanalytical Services, Delta, BC, Canada.

6.2 Procedures

All reactions using lanthanide metals were performed under an atmosphere of argon, with rigorous exclusion of oxygen and water, using standard glovebox (Braun MB150-GH) and Schlenk techniques, except as noted in text. Tetrahydrofuran, diethyl ether, hexane and toluene and benzene were dried by distillation from sodium benzophenone ketyl under inert atmosphere (nitrogen or argon) immediately prior to use. Acetonitrile was dried by distillation from calcium hydride under nitrogen immediately prior to use. Di-isopropylamine and triethylamine were distilled from sodium hydride under nitrogen immediately prior to use. Anhydrous yttrium, cerium and ytterbium trichlorides were prepared from the hydrated salts by prolonged reflux in neat $SOCl_2$ followed by vacuum distillation of excess $SOCl_2$ and drying at 150°C (10^{-2} Torr) for 16 to 20 hours. Hexamethyldisilazane was purchased from Aldrich and dried by distillation from sodium metal. Lanthanide silylamides, $Ln[N(SiMe_3)_2]_3$ (Ln = Ce, Y and Yb).[91] were prepared as reported in the literature. Yttrium tris(2,6-*t*-butylphenoxide) (complex of 7) was prepared using the procedure in Inorganic Syntheses.[117] Yttrium amino siloxide (complex of **8**) was prepared as reported in the literature.[118] 2,4-Pentanedione (**4a**), 1,1,1,-trifluoro-2,4-pentanedione (**4b**) and 1,1,1,5,5,5-hexafluoro-2,4-pentanedione (**4c**) were purchased from Aldrich and purified by distillation before using. Salicylaldehyde (**6a**) and 2-hydroxyacetophenone (**6b**) were purchased from Aldrich and purified by vacuum distillation. 2,4,6-Trimethylbenzoic acid (**10**) was purchased from Aldrich and purified by sublimation before using. Lanthanide reagents $Yb(fod)_3$, $Yb(tfc)_3$, $Yb(hexanoate)_3$ and $Yb(OTf)_3$ (complexes of **4d**, **5**, **11** and **12** respectively) were all

purchased from Aldrich, handled under a flow of argon and used without further purification. All other chemicals were of reagent grade, unless otherwise specified.

Tris(3-aza-4-methyl-6-oxo-hept-4-en-1-yl)amine, H_3trac (1)[93]



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In a 500 mL round bottom flask equipped with a stirbar and Dean Stark trap, tris(aminoethyl)amine (tren) (25.0 mL, 24.4 g, 167 mmol) was dissolved in 200 mL of dry benzene. To this solution acetylacetone (acac) (51.5 mL, 50.2g, 501 mmol) was added via syringe and the reaction mixture was refluxed for 2 hours. The resulting solution was concentrated under reduced pressure to obtain an oily solid which could be purified by silica gel column chromatography using chloroform:methanol (1:1) as eluent. The product was isolated as an orange oil (58.4 g, 95%) and stored in the freezer over activated molecular sieves.[93] ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.74 (br, 3H, N*H*), 4.89 (s, 3H, C*H*=CMe), 3.33-3.24 (m, 6H, N-CH_2-CH_2), 2.72-2.66 (m, 6H, CH_2-NH), 1.93 (s, 9H, CH_3), 1.86 (s, 9H, CH_3). ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.5 (*C*=O), 162.7 (*C*-NH), 95.2 (+, *C*H=CMe), 54.6 (-, N-*C*H_2-CH_2), 41.5 (-, *C*H_2-NH), 28.5 (+, *C*H_3), 18.7 (+, *C*H_3).

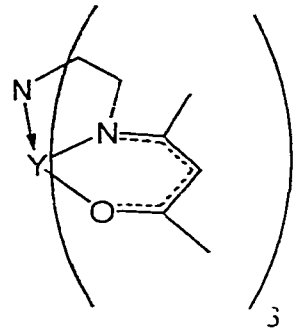
General procedure for the preparation of Ln complexes of all ligands

In a Schlenk tube equipped with a stirbar, under an inert atmosphere, the ligand was dissolved in dry THF. In a separate oven dried Schlenk tube equipped with a stirbar, under an inert atmosphere, $Y(N(SiMe_3)_2)_3$ was dissolved in dry THF and transferred via cannula into the ligand solution while stirring. Stirring was continued for 20 min. before

removing the solvent and resulting $HN(SiMe_3)_2)_3$ under reduced pressure, thereby isolating the desired product as a powder. The insoluble solids were repeatedly washed with toluene and hexanes to give free flowing powders. The same procedure was used with $Yb(N(SiMe_3)_2)_3$ and $La(N(SiMe_3)_2)_3$ for their respective metal complexes.

Y trac Complex (Y Complex of 1)[93]

Prepared using the general procedure on page 166. The reaction of H_3trac ligand (1.93 g, 4.92 mmol) with $Y(N(SiMe_3)_2)_3$ (2.80 g, 4.92 mmol) in THF yielded the yttrium complex as a white powder. The product could be purified by vacuum sublimation at 200°C at 10^{-2} Torr yielding 1.0 g (46%) of cream coloured crystalline material.[93] ^{1}H NMR (250 MHz, d_8-THF) δ 4.82 (s, 3H, C*H*=CMe), 3.48 (t, J = 6 Hz, 6H, CH_2-N-Y), 2.80 (t, J = 6 Hz, 6H, N-CH_2-CH_2), 1.82 (s, 9H, CH_3), 1.67 (s, 9H, CH_3). ^{13}C NMR (63 MHz, d_8-THF) δ 178.6 (*C*-O-Y), 170.1 (*C*-N-Y), 100.1 (+, *C*H=CMe), 55.3 (-, N-*C*H_2-CH_2), 47.3 (-, *C*H_2-NH), 26.8 (+, *C*H_3), 21.9 (+, *C*H_3).



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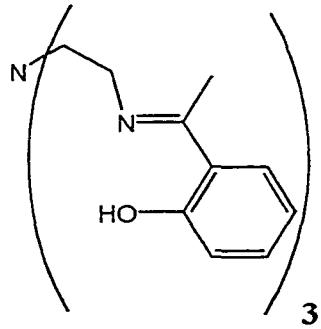
H_3Hatren Ligand, 2[93]

In a 100 mL round bottom flask equipped with stirbar and 4 Å molecular sieves, 2-hydroxyacetophenone (3.9 g, 3.4 mL, 28 mmol) was added to tren (1.4 g, 1.4 mL, 9.0 mmol) in 50 mL of ethanol. The mixture was refluxed for one hour. The sieves were removed by filtration and the resultant solution was stored for 16 hours at 5°C. The product was collected as a yellow flaky



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precipitate which was dried in vacuo (10^{-2} Torr) at room temperature for 6 hours.[93] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24-7.26 (m, 3H, Aryl*H*), 7.23-7.20 (m, 3H, Aryl*H*), 6.85-6.84 (m, 3H, Aryl*H*), 6.62-5.99 (m, 3H, Aryl*H*), 3.69-3.60 (m, 6H, NCH_2CH_2), 3.06-2.99 (m, 6H,CH_2N=C), 2.23 (s, 9H, CH_3).

Ytterbium Hatren Complex, (Yb Complex of 2)[93]

Prepared using the general procedure on page 166. The reaction of $Yb(N(SiMe_3)_2)_3$ (1.4 g, 2.1 mmol) with H_3Hatren **2** (1.1 g, 2.1 mmol) yielded 1.1 g (80 %) of yellow powder. Mp >200°C dec. (lit.[93] mp > 200°C dec.).

Catalytic Testing Protocol

GC Calibration

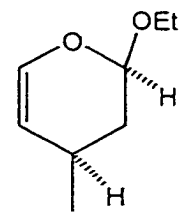
GC detector response was tested by preparing a standard curve. Diethyl ether solutions of known concentrations of crotonaldehyde and catalytic product (prepared using $Yb(fod)_3$)[77] were plotted versus integration values for the GC output.

Catalyst Testing

In an oven dried Schlenk tube equipped with stirbar, catalytic metal complex (30.5 g, 2 mol %) was loaded. Freshly distilled ethyl vinyl ether (5.0 mL) was added via syringe and the vessel tightly capped. The reaction mixture was stirred as 0.2 mL distilled *trans*-crotonaldehyde was added via syringe. Every 4 hrs an aliquot of solution was removed by syringe, diluted to 0.5 mL with diethyl ether and injected (0.5 μL) into a Fisons E980 Gas Chromotagraph to detect product formation. A 100 μL (1.2 mmol) dioxane standard can be used in the reaction mixture to better quantify results. Upon reaction completion the

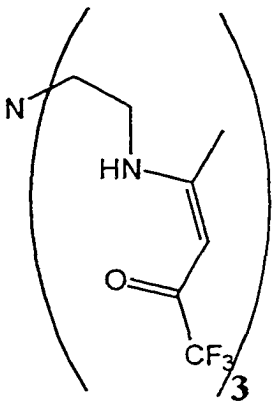
mixture was quenched with 1 N aqueous HCl and stirred for 30 minutes. Extraction with ether of the organic layer and removal of the solvent from the combined organic fractions under reduced pressure gave a crude product that can be further purified[77] by column chromatography using a 4:1 pentanes:ether eluant or by distillation (if crotonaldehyde is no longer present in the crude product).

Catalytic Product: *cis*-2-ethoxy-4-methyl-3,4-dihydro-2-pyran[77]



^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 6, 2 Hz, 1H, C*H*CHMe), 4.87 (dd, *J* = 9, 2 Hz, 1H, OC*H*O), 4.53-4.52 (m, 1H, C*H*O), 3.88 (dq, *J* = 10, 7 Hz, 1H, C*H*HCH$_3$), 3.55 (dq, *J* = 10, 7 Hz, 1H, CHC*H*O), 2.44-2.31 (m, 1H, C*H*CH$_3$), 2.02-1.95 (m, 1H, ring C*H*H), 1.45 (d of br.t, *J* = 14, 9 Hz, 1H, ring CH*H*), 1.20 (t, *J* = 7 Hz, 3H, C*H*$_3$CH$_2$), 1.99 (d, *J* = 7 Hz, 3H, CHC*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3 (+, *C*HO), 107.4 (+, *C*HCHMe), 99.4 (+, O*C*HO), 64.2 (-, O*C*H$_2$), 37.0 (-, ring *C*H$_2$), 26.1 (+, *C*HCH$_3$), 21.3 (+, CH*C*H$_3$), 15.2 (+, CH$_2$*C*H$_3$).

Tris(3-aza-4-methyl-6-oxo-7,7,7-trifluorohept-4-en-1-yl)amine, H_3F_3trac (3)



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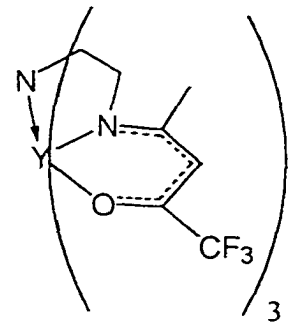
In a 25 mL round bottom flask equipped with a stirbar and Dean Stark trap, tris(aminoethyl)amine (0.10g, 0.68 mmol) was dissolved in 10 mL of dry benzene. 1,1,1-Trifluoroacetylacetone (4.0 mL, 5.1 g, 33 mmol) was added via syringe and the reaction mixture was refluxed for 16 hrs. The resulting solution was concentrated under reduced pressure to obtain a sticky, golden powder. Purification by repeated triturations with ether gave an isolated yield of 0.38 g (85%) of the desired tripodal ligand. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.11(br s, 3H, *H*NCH$_2$), 5.24(s, 3H, C*H*=C), 3.48 (q, J = 7 Hz, 6H, NC*H*$_2$CH$_2$), 2.84 (t, J = 7 Hz, 6H, NHC*H*$_2$CH$_2$), 2.06 (s, 9H, C*H*$_3$). ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.45 (q, $^2J_{CF}$ = 31 Hz, *C*=OCF$_3$), 170.02 (*C*NHCH$_3$), 117.63 (q, $^1J_{CF}$ = 281 Hz, *C*F$_3$), 89.73 (+, *C*H=C), 54.36 (-, *C*H$_2$NH), 42.41 (-, *C*H$_2$N), 19.38 (+, *C*H$_3$). ^{19}F NMR (338 MHz, $CDCl_3$) δ -76.84 (s). HRMS (EI) *m/z* calcd for $C_{21}H_{27}F_9N_4O_3$: 152.1201; found: 152.1205.

Yttrium tris(3-aza-4-methyl-6-oxo-7,7,7-trifluorohepten-1-yl)amine (Y complex of 3)



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Prepared following the general procedure given on page 166. The reaction of $Y(N(SiMe_3)_2)_3$ (0.20 g, 0.35 mmol) with ligand **3** (0.19 g, 0.35 mmol) in 20 mL of dry THF, afforded a quantitative yield (0.22 g) of creamy white powder. It could be recrystallized from warm toluene upon standing, yielding colourless brick-like crystals in modest quantities. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46 (s, 3H, C*H*=C), 3.63-3.57 (m, 6H, NCH_2CH$_2$), 2.99-2.86 (m, 6H, NHCH_2CH$_2$), 1.29 (s, 9H, CH_3). ^{13}C NMR (90 MHz, C_6D_6) δ 173.5 (CNHCH$_3$), 161.9 (q, $^2J_{CF}$ = 29 Hz, *C*=OCF$_3$), 120.9 (q, $^1J_{CF}$ = 269 Hz, *C*F$_3$), 98.8 (+, *C*H=C), 52.7 (-, *C*H$_2$NH), 46.7 (-, *C*H$_2$N), 22.0 (+, *C*H$_3$). ^{19}F NMR (338 MHz, C_6D_6) δ -74.76.

X-ray Crystallographic Data: The crystal structure was solved by M. Marc Drouin of the Université de Sherbrooke. The crystallographic data was obtained from a clear crystal on a Enfraf-Nonius CAD4 diffractometer at 193 K, equipped with a graphite filtered Cu $K\alpha_{av}$ radiation. The structure was solved using the program SOLVER from NRCVAX[194] using direct methods and refined using the program LSTSQ from NRCVAX. Hydrogens were placed geometrically and not refined. There are 3 independant molecules per unit cell.

Summary of the crystallographic data, and lists of selected bond distances and angles are given in the following tables.

Table 3: Summary of Crystallographic data for $Y(F_3trac)$

empirical formula	$3(C_{21}H_{24}F_9O_3N_4Y)$
fw	383.46
crystal system	monoclinic
space group	P $2_1/a$
a (Å)	18.344(2)
b (Å)	15.161(2)
c (Å)	28.104(2)
β (deg)	96.28(1)
V (Å^3)	7769.2(9)
Z	12
ρ (calcd) (g cm^{-3})	1.642
μ (cm^{-1})	9
radiation, λ (Å)	1.54184
temperature	193
$2\theta_{max}$ (deg)	143.6
no. of observed reflections	15407
no. of unique reflections	15272
no. of parameters	1028
R [a]	0.045
R_w [b]	0.060

[a] $R = \Sigma (F_O-F_C)/\Sigma(F_O)$

[b] $R_w = [\Sigma (w(F_O-F_C)^2/\Sigma(wF_O)^2]^{1/2}$

Table 4: Selected Bond distances (Å) and angles (deg) for Y(F_3trac)

atoms	distance	atoms	distance
Y1-N1	2.447(3)	F6-C14	1.322(6)
Y1-N2	2.479(3)	F7-C21	1.303(7)
Y1-N3	2.493(3)	F8-C21	1.336(7)
Y1-N4	2.474(3)	F9-C21	1.327(7)
Y1-O1	2.206(3)	O1-C5	1.279(5)
Y1-O2	2.212(3)	O2-C12	1.279(5)
Y1-O3	2.217(3)	O3-C19	1.280(5)
N1-C1	1.491(5)	C1-C2	1.514(6)
N1-C8	1.477(5)	C3-C4	1.437(6)
N1-C15	1.477(5)	C3-C6	1.509(6)
N2-C2	1.472(5)	C4-C5	1.367(6)
N2-C3	1.303(5)	C5-C7	1.520(6)
N3-C9	1.481(5)	C8-C9	1.525(6)
N3-C10	1.306(5)	C10-C11	1.436(6)
N4-C16	1.481(6)	C10-C13	1.515(6)
N4-C17	1.302(6)	C11-C12	1.355(6)
F1-C7	1.326(6)	C12-C14	1.528(6)
F2-C7	1.313(6)	C15-C16	1.497(7)
F3-C7	1.318(6)	C17-C18	1.436(8)
F4-C14	1.330(6)	C17-C20	1.508(7)
F5-C14	1.333(6)	C18-C19	1.360(8)
		C19-C21	1.530(7)

atoms	angle	atoms	angle
N1-Y1-N2	68.51(11)	N2-C3-C6	122.0(4)
N1-Y1-N3	68.87(11)	C4-C3-C6	115.3(4)
N1-Y1-N4	68.54(11)	C3-C4-C5	124.1(4)
N1-Y1-O1	125.97(11)	O1-C5-C4	128.4(4)
N1-Y1-O2	126.68(11)	O1-C5-C7	112.7(4)
N1-Y1-O3	128.73(11)	C4-C5-C7	118.9(4)
N2-Y1-N3	105.42(11)	F1-C7-F2	104.7(5)
N2-Y1-N4	108.90(12)	F1-C7-F3	105.5(4)
N2-Y1-O1	74.86(11)	F1-C7-C5	111.2(4)
N2-Y1-O2	85.13(11)	F2-C7-F3	107.9(4)
N2-Y1-O3	160.37(11)	F2-C7-C5	112.0(4)
N3-Y1-N4	108.62(11)	F3-C7-C5	114.9(4)
N3-Y1-O1	161.98(11)	N1-C8-C9	112.6(3)
N3-Y1-O2	75.01(10)	N3-C9-C8	110.8(3)
N3-Y1-O3	90.72(11)	N3-C10-C11	122.4(4)
N4-Y1-O1	87.83(11)	N3-C10-C13	121.7(4)
N4-Y1-O2	163.26(12)	C11-C10-C13	115.8(4)
N4-Y1-O3	75.30(13)	C10-C11-C12	125.5(4)
O1-Y1-O2	87.14(10)	O2-C12-C11	128.5(4)
O1-Y1-O3	86.33(11)	O2-C12-C14	112.5(4)
O2-Y1-O3	89.44(12)	C11-C12-C14	119.0(4)
Y1-N1-C1	108.06(22)	F4-C14-F5	106.0(4)
Y1-N1-C8	107.45(23)	F4-C14-F6	107.3(4)
Y1-N1-C15	107.61(23)	F4-C14-C12	110.8(4)
C1-N1-C8	111.2(3)	F5-C14-F6	106.9(4)
C1-N1-C15	110.7(3)	F5-C14-C12	114.0(4)
C8-N1-C15	111.6(3)	F6-C14-C12	111.5(4)
Y1-N2-C2	117.14(25)	N1-C15-C16	111.2(4)
Y1-N2-C3	125.5(3)	N4-C16-C15	110.6(3)
C2-N2-C3	117.3(3)	N4-C17-C18	122.2(5)
Y1-N3-C9	115.67(24)	N4-C17-C20	121.6(5)
Y1-N3-C10	127.8(3)	C18-C17-C20	116.2(4)
C9-N3-C10	116.5(3)	C17-C18-C19	125.8(4)
Y1-N4-C16	115.98(25)	O3-C19-C18	127.2(4)
Y1-N4-C17	127.0(3)	O3-C19-C21	113.6(5)
C16-N4-C17	117.0(4)	C18-C19-C21	119.2(4)
Y1-O1-C5	125.6(3)	F7-C21-F8	105.2(4)
Y1-O2-C12	130.5(3)	F7-C21-F9	106.5(6)
Y1-O3-C19	126.9(3)	F7-C21-C19	111.7(4)
N1-C1-C2	112.5(3)	F8-C21-F9	107.7(5)
N2-C2-C1	110.0(3)	F8-C21-C19	113.0(6)
N2-C3-C4	122.7(4)	F9-C21-C19	112.3(4)

Ytterbium Tris(acac) (Yb Complexes of 4a)

Prepared using the general procedure on page 166. The reaction of $Yb(N(SiMe_3)_2)_3$ (1.38 g, 2.1 mmol) with dry acetylacetone (0.65 mL, 6.3 mmol) yielded 0.51 g (52%) of the desired material. IR (Nujol) cm^{-1} 1583(s), 1521(s), 1269(m), 1247(m), 1018(m), 923(m). MS (EI) *m/z* of Yb Analogue: calcd for $C_{15}H_{21}O_6Yb$ = 471; found 468 (30%), 469 (60%), 470 (55%), 471 (100%), 472 (20%), 473 (40%); with the expected isotopic pattern for the ytterbium complex being 468 (44%), 469 (68%), 470 (50%), 471 (100%), 472 (16%), 473 (40%). $Y(acac)_3$ was prepared in analogous fashion.[115] ^1H NMR (250 MHz, C_6D_6) 5.29 (s, 3H, C*H*CO), 1.86 (s, 18H, COCH_3).

Ytterbium Tris(F_3acac), (Yb Complex of 4b)

Prepared using the general procedure on page 166. The reaction of $Yb(N(SiMe_3)_2)_3$ (1.4 g, 2.1 mmol) with dry trifluoroacetylacetone (0.77 mL, 6.3 mmol) yielded 0.65 g (50%) of the desired material, purified by sublimation at 90 °C at 10^{-4} mmHg. IR (Nujol) cm^{-1} 1627(s), 1538(s), 1302(s), 1191(s), 1141(s). MS (EI) *m/z* of Yb analogue: calcd for $C_{15}H_{12}F_9O_6Yb$ = 633; found: 630 (45%), 631 (70%), 632 (60%), 633 (100%), 634 (20%), 635 (40%); with the expected isotopic pattern for the ytterbium complex being 630 (44%), 631 (68%), 632 (50%), 633 (100%), 634 (16%), 635 (40%). $Y(F_3acac)_3$ was prepared in analogous fashion. ^1H NMR (250 MHz, C_6D_6) δ 5.87 (s, 3H, C*H*CO), 1.75 (s, 9H, COCH_3).

Ytterbium Tris(1,1,1,5,5,5-hexafluoroacetylacetone), (Yb Complex of 4c)

Prepared using the general procedure on page 166. The reaction of $Yb(N(SiMe_3)_2)_3$ (1.4 g, 2.1 mmol) with hexafluoroacetylacetone (0.90 mL, 6.3 mmol) yielded 0.83 g (50%) of the desired material, purified by sublimation at 120°C at 10^{-2} mmHg. MS (EI) *m/z* of Yb analogue: calcd for $C_{15}H_3F_{18}O_6Yb$ = 795; found: 792 (45%), 793 (65%), 794 (60%), 795 (100%), 796 (15%), 797 (35%); with the expected isotopic pattern for the ytterbium complex being 792 (44%), 793 (68%), 794 (50%). 795 (100%), 796 (16%), 797 (40%). $Y(F_6acac)_3$ was prepared in analogous fashion. EI MS *m/z* 710 (M^+, 5%), 641 (M-CF_3, 20%), 139 (ligand-CF_3, 100%).

1,1,1-Trichloro-2,4-pentanedione, Cl_3acac (4e)[116]

In an oven dried 250 mL round bottom flask, di-isopropylamine (5.9 mL, 4.2 g, 42 mmol) was added to 50 mL of dry THF and cooled to -78°C. LDA was prepared with the addition of n-BuLi in hexanes solution (26 mL of 1.6 M). This mixture was stirred for 5 minutes at low temperature. To the mixture, dry acetone (3.1 mL, 2.4 g, 42 mmol) was added and the solution stirred for a further 5 minutes. Next, methyl trichloroacetate (5.0 mL, 7.4 g, 42 mmmol) was added by syringe and the resulting solution was stirred for 20 minutes at -78°C. The cooling bath was removed and the reaction was quenched with 1 M HCl until the aqueous layer was strongly acidic. The desired product was extracted into CH_2Cl_2 (3 x 50 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure to give a yellow viscous oil. This crude product was purified by silica gel column chromatography using 5% MeOH in $CHCl_3$ as eluent. The

desired product **4e** was isolated in good yield (5.1 g, 60%).[116] ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.62 (br s, 1H, O*H*), 6.15 (s, 1H, C=OC*H*=C), 2.18 (s, 3H, CH_3).

Yttrium Tris(1,1,1-trichloroacetylacetone), Y(Cl_3acac)$_3$, (Y Complex of 4e)

Prepared using the general procedure from page 166. The reaction of Y(N($SiMe_3$)$_2$)$_3$ (0.71 g, 1.3 mmol) with dry trichloroacetylacetone (0.76 g, 3.9 mmol) yielded 0.42 g (49%) of orange powder.

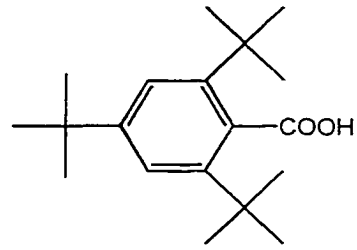
Ytterbium Tris(salicylaldehyde), (Yb Complex of 6a)

Prepared using the general procedure on page 166. The reaction of Yb(N($SiMe_3$)$_2$)$_3$ (1.4 g, 2.1 mmol) with dry salicylaldehyde (0.76 g, 6.3 mmol) yielded 0.58 g (51%) of pale yellow powder. Mp 152°C (dec.) IR (Nujol) cm^{-1} 1629(s), 1527(m), 1146(m), 901(s). Anal. calcd for $C_{21}H_{15}O_6Yb$: C, 47.02%; H, 2.82%; found: C, 45.87%; H, 2.94%.

Ytterbium Tris(hydroxyacetophenone), (Yb Complex of 6b)

Prepared using the general procedure on page 166. The reaction of Yb(N($SiMe_3$)$_2$)$_3$ (1.4 g, 2.1 mmol) with dry 2-hydroxyacetophenone (0.75 mL, 6.3 mmol) yielded 0.58 g (48%). Mp 196°C (dec.) Anal. calcd for $C_{24}H_{21}O_6Yb$: C, 49.83%; H, 3.66%; found: C, 49.44%; H, 3.76%.

2,4,6-Tri-*t*-butylbenzoic acid (9)



An oven dried Schlenk tube was charged with 2-bromo-1,3,5-tri-t-butylbenzene[127] (1.4 g, 6.3 mmol) in 125 mL of dry hexanes. Then n-BuLi, 1.6 M in hexanes (3.9 mL,6.3 mmol) was added and the resulting mixture was left to stir at -78 °C for 1 hr. Carbon dioxide (dry ice vapour passed through Drierite drying tube) was bubbled through the solution for 4 hrs. The mixture was quenched with 3M aqueous HCl until the water layer was approximately pH 1. The two phases were separated and the aqueous phase was extracted with ether. The combined organic portions were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Washing the product with hexanes repeatedly yielded 0.4 g (35%) of the desired product.[128] ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.40 (s, 2H, Aryl*H*), 1.57 (s, 18H, *ortho*-*t*butyl*H*), 1.34 (s, 9H, *para*-*t*butyl*H*). ^{13}C NMR (63 MHz, $CDCl_3$) δ 179.24 (*C*=OOH), 150.69 (Aryl*C*-C=OOH), 146.39 (Aryl*C*), 127.46 (Aryl*C*), 122.16 (+, Aryl*C*), 35.06 ($C(CH_3)_3$), 32.22 ($C(CH_3)_3$), 31.56 (+, CH_3), 31.26 (+, CH_3).

Yttrium Tris(2,4,6-tri-*t*-butylbenzoate) (Y complex of 9):

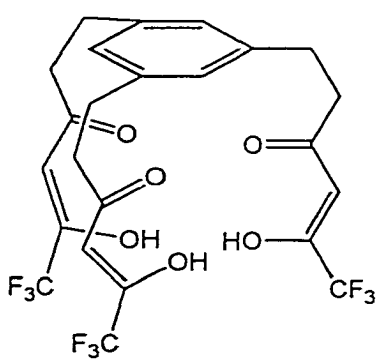
Prepared as described in the general procedure on page 166. The reaction of $Y(N(SiMe_3)_2)_3$ (0.39 g, 0.69 mmol) with ligand **9** (0.60 g, 2.1 mmol) gave a white powder in 75% yield after repeated washing with hexanes. ^{1}H NMR (360 MHz, C_6D_6) δ 7.42 (s, 2H, Aryl*H*), 1.46 (s, 18H, *ortho*-CH_3), 1.31 (s, 9H, *para*-CH_3). ^{13}C NMR (90 MHz, C_6D_6) δ 179.94 (*C*=OO), 150.68 (Aryl*C*COO), 146.33 (Aryl*C*), 127.53 (+, Aryl*C*), 122.16

(ArylC), 37.63 ($C(CH_3)_3$), 35.05 ($C(CH_3)_3$), 32.22 (+, CH_3), 31.26 (+, CH_3). Yb tris(2,4,6-tri-*t*-butylbenzoate) was prepared in analogous fashion yielding a paramagnetic powder. ^{1}H NMR (250 MHz, C_6D_6) 7.42 (br. s, 2H, Aryl H), 1.50 (br.s, 18 H, *ortho*-CH_3), 1.25 (br. s, 9H, *para*-CH_3).

Yttrium Tris(2,4,6-trimethylbenzoate) (Y complex of 10):

Prepared as described in the general procedure on page 166. The reaction of $Y(N(SiMe_3)_2)_3$ (0.38 g, 0.67 mmol) with 2,4,6-trimethyl benzoicacid **10** (0.33 g, 2.0 mmol) gave the desired product in 54% yield after repeated washing with hexanes. ^{1}H NMR (360 MHz, C_6D_6) δ 7.23 (s, 2H, ArylH), 2.43 (s, *ortho*-CH_3), 2.24 (s, *para*-CH_3). ^{13}C NMR (90 MHz, C_6D_6) δ 177.74 (C=OO), 149.32 (ArylCCOOH), 144.42 (ArylC). 126.92 (+, ArylC). 121.20 (ArylC), 35.55 (+, CH_3), 33.43 (+, CH_3).

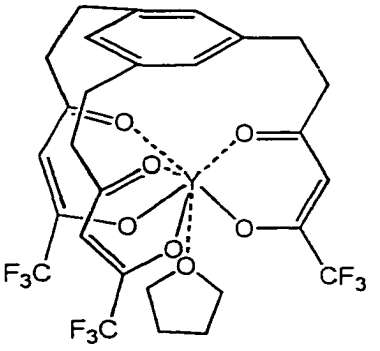
1,3,5-Tris(3,5-dioxo-6,6,6-trifluorohexan-1-yl)benzene (13)



A solution of 1,1,1-trifluoroacetylacetone (2.0 mL, 2.6 g, 17 mmol) in 20 mL of dry THF was prepared in an oven dried Schlenk tube equipped with a stirbar and was cooled to -78 °C. In a separate oven dried Schlenk tube was prepared an LDA solution in 10 mL of dry THF using dry di-isopropylamine (2.6 mL, 2.0 g, 20 mmol) and 1.6 M n-butyllithium in hexanes (13 mL, 20 mmol). After cooling to -78 °C the trifluoroacetylacetone solution was transferred by cannula to the LDA solution while maintaining the temperature at -78 °C. In a third oven dried Schlenk tube was prepared a

second LDA solution in 20 mL of dry THF using dry di-isopropylamine (2.0 mL, 1.5 g, 15 mmol) and 1.6 M n-butyllithium in hexanes (9.5mL, 15 mmol). After cooling to -78 °C this LDA solution was transferred into the previous one, maintaining the temperature at -78 °C. The mixture was stirred for 20 min and a solution of 1,3,5-tribromomesitylene (1.0 g, 2.8 mmol) in 20 mL of dry THF was added via a cannula into the dianion solution at -78 °C. The reaction was stirred for 4 hrs while slowly warming to room temperature. The reaction was quenched with a 3 M HCl solution, ensuring that the water layer was acidic, and extracted with ether exhaustively. The combined organic fractions were dried over magnesium sulfate, filtered and concentrated under reduced pressure. Crystallisation of the resulting golden oil using a dry THF/hexane mixed solvent system gave pale yellow crystals that were further purified by sublimation at 140 °C/10^{-2} mmHg yielding 0.63 g (40%) of the desired benzene capped tripodal ligand **13**. ^{1}H NMR (250 MHz, C_6D_6) δ 6.86 (s, 3H, Aryl*H*), 5.85 (s, 3H, *CH*=CO), 3.45 (t, J = 7 Hz, 6H, CH_2C=O), 2.87 (t, J = 7 Hz, 6H, CH_2Aryl). ^{13}C NMR (63 MHz, C_6D_6) δ 196.2 (*C*=OCH_2), 174.7 (q, $^{2}J_{CF}$ = 36 Hz, *C*-OHCF_3), 140.6 (Aryl*C*), 126.5 (+, Aryl*C*H), 117.0 (q, $^{1}J_{CF}$ = 282 Hz, *C*F_3), 96.2 (d, *C*H=CO), 40.2 (-, *C*H_2CO), 31.0 (-, *C*H_2Aryl). ^{19}F NMR (338 MHz, C_6D_6 in δ): -76.76 (s). HRMS (EI) *m/z* calcd for $C_{24}H_{21}F_9O_6$: 576.1194; found: 576.1194. Anal. calcd: C, 50.01%; H, 3.67%; found: 50.02%; H 3.64%.

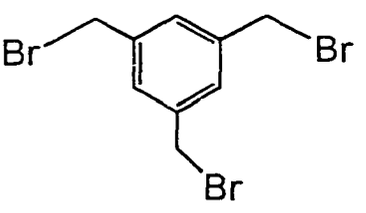
Yttrium 1,3,5-tris(3,5-dioxo-6,6,6-trifluorohexan-1-yl)benzene (Y complex of 13)



Prepared as described in the general procedure on page 166. The reaction of ligand **13** (0.76 g, 1.3 mmol) dissolved in 5 mL of dry THF and $Y[N(SiMe_3)_2]_3$ (0.74 g, 1.3 mmol) dissolved in 5 mL of dry THF afforded a pale yellow powder in quantitative yield (0.85 g). In spite of many efforts, we were unable to grow X-ray quality crystals. Various mixed solvent systems and temperatures were attempted. ^{1}H NMR (360 MHz, C_6D_6) δ 6.41 (s, 3H, Aryl*H*), 5.83 (s, 3H, *CH*=CO), 3.78-3.72 (m, 4H, THF), 2.43 (t, J = 7 Hz, 6H, C*H*$_2$C=O), 2.06 (t, J = 7 Hz, 6H, C*H*$_2$Aryl), 1.31-1.23 (m, 4H, THF). ^{13}C NMR (90 MHz, C_6D_6) δ 201.1 (*C*=OCH$_2$), 169.9 (q, $^2J_{CF}$ = 32 Hz, *C*=OCF$_3$), 138.5 (Aryl*C*), 128.0 (q, obscured by solvent peak, *C*F$_3$), 127.9 (+, Aryl*C*H), 97.3 (*C*H=CO), 69.2 (-, THF), 42.2 (-, *C*H$_2$CO), 33.2 (-, *C*H$_2$Aryl), 25.4 (-, THF). ^{19}F NMR (338 MHz, C_6D_6 in δ): -75.66 (s). HRMS (EI) *m/z* calcd for $C_{24}H_{18}F_9O_6Y$: 662.0018; found: 662.0000. A satisfactory elemental analysis was not obtained for this compound.

1,3,5-Tris(bromomethyl)benzene, 14

Method 1: *via* NBS Bromination of Mesitylene[138]



In a 250 mL round bottom flask equipped with a stirbar, powdered N-bromosuccinimide (NBS) (15 g, 83 mmol) was dissolved in 50 mL ethyl formate. By syringe, mesitylene (3.5 mL, 3.0 g, 25 mmol) was added to the mixture, followed by a small spatula of AIBN radical initiator. The flask was equipped with a reflux condenser and a flood lamp (300 W) was positioned near the vessel. After heating to reflux for 12 hours under the flood lamp, the resultant red solution was washed with water, and then saturated aqueous sodium carbonate solution. The organic layer was separated and dried *in vacuo* to yield a crude solid that was subsequently recrystallized from hot cyclohexanes. NMR spectroscopy showed a mixture of mono, bis and tris brominated products. The desired tri-brominated product could be isolated by repeated recrystallizations from hot cyclohexane, although the yield of **14** in this manner was poor (15%).

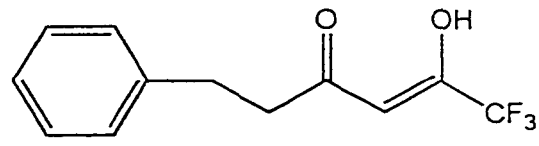
Method 2: *via* 1,3,5-benzenetricarboxylic acid reduction

In an oven dried 1L round bottom flask equipped with a stirbar, lithium aluminum hydride (2.0 g, 74 mmol) was added to 200 mL of dry THF. 1,3,5-Benzenetricarboxylic acid (5.0 g, 23.8 mmol) dissolved in 200 mL of dry THF was added dropwise into the stirring slurry over 2 hrs under an atmosphere of N_2 while cooling with an ice bath. The resulting slurry was heated to reflux for 16 hrs using a condenser equipped with a drying

tube. Enough water was then added to destroy any excess LAH, the solvent was removed under reduced pressure and the resulting salts were dried under vacuum. To this vessel was added 150 mL of 48% HBr solution and 250 mL of benzene. The mixture was heated to reflux for 16 hrs. The organic layer was separated and the aqueous portion was extracted with Et_2O, the organic layers combined, dried over $MgSO_4$ and the solvent removed under reduced pressure. Recrystallisation of the crude solid from hot cyclohexane yielded 6.9 g (80%) of the desired white crystalline solid. Mp 94°C, (lit.[138, 137] mp 94°C) ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33 (s, 3H, Aryl*H*), 4.43 (s, 6H, C*H*$_2$Br). ^{13}C NMR (90 MHz, $CDCl_3$) δ 139.0 (Aryl*C*CH$_2$), 129.6 (+, Aryl*C*H), 32.2 (-, *C*H$_2$Br).

Trial conditions for the reaction of benzyl bromides with trifluoroacac

*The goal of this experiment was to test whether benzyl bromide reacted to indicate formation of compound **15**.*

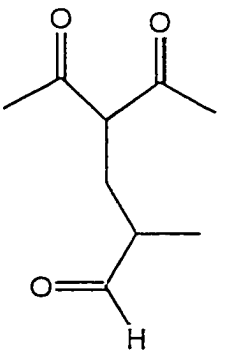


In an oven dried Schlenk tube equipped with stirbar trifluoroacac (1.0 mL, 8.2 mmol) was dissolved in 20 mL dry THF and cooled to -78°C. In a second Schlenk tube an LDA solution was prepared using di-isopropylamine (1.1 mL, 0.83 g, 8.3 mmol) and 1.6 M n-BuLi in hexanes (5.2 mL) in 10 mL dry THF at -78°C. The LDA solution was stirred for 10 minutes before transferring to the acac solution by cannula. The reaction mixture was permitted to stir for 20 minutes at low temperature before the addition of a further 5.2 mL of 1.6 M *n*-BuLi solution. The reaction was maintained at -78°C for 10 minutes before the dropwise addition of distilled benzylbromide (1.0 mL, 6.7 mmol). The mixture was stirred for a further 10 minutes before slowly warming to room temperature

over 3 hours. The reaction was quenched with the addition of 1 M HCl until the aqueous layer was acidic. The desired product was extracted into CH_2Cl_2 (3 x 50 mL). The combined organic fractions were then washed with sat. aq. Na_2CO_3 and water (2 x 50 mL). The aqueous fractions were combined, acidified with 1 M HCl and re-extracted with CH_2Cl_2 (3 x 50 mL) and dried over $MgSO_4$. Concentration of the organic fractions gave a pale yellow oil in good yield (1.0 g, 62%). ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34-7.20 (m, 5 H, Aryl*H*'s), 5.87 (s, 1H, C=OC*H*=C), 2.96 (t, J = 7Hz, 2H, CH_2C=O), 2.74 (t, J = 7 Hz, PhCH_2). The diagnostic pair of triplets indicated these conditions were viable for preparation of the tripodal version, compound **13**.

Trial of Michael addition catalysed by sodium proline salt[154]

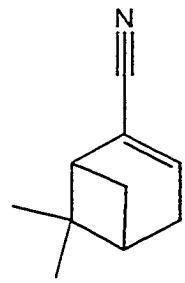
The goal of this experiment was to test whether proline salt catalysed the addition of acac and methacrolein, to indicate formation of compound 16.



A solution of 2,4-pentanedione (0.25 ml, 0.24 g, 2.4 mmol) and methacrolein (0.14 mL, 0.11 g, 1.6 mmol) in 9 mL of methanol was prepared in a 25 mL round bottom flask equipped with stirbar. To this mixture sodium proline salt[154] (22 mg, 0.16 mmol) was added before refluxing 20 hours. The resulting yellow solution was quenched with 1M HCl and the products were extracted into CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated yielding a yellow oil. The product was purified using silica gel chromatography with 1:1 ethyl acetate: hexanes as eluent, and was obtained as a pale yellow oil in 20% yield (50 mg). NOTE: The NMR spectrum of this oil indicated a

solution equilibrium between the keto and enol tautomers (1:1). ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.69 (d, J = 2Hz, 1H, C=O*H*), 9.53 (d, J = 2 Hz, 1H, C=O*H*), 3.74 (t, M of MABX, J = 7 Hz, 1 H, C=OC*H*C=O), 3.48-3.27 (m, AB of ABX, J_{AB} = 12 Hz, 2H, MeCHC*HH*), 2.75-2.66 (m, AB of MABX, J_{AB} = 12 Hz, 2H, MeCHC*HH*), 2.59-2.35 (m, X of MABX, 1H, C*H*CH_3), 2.32-2.10 (m, X of ABX, 1H, C*H*CH_3), 2.22 (s, 3H, CH_3C=O), 2.19 (s, 3H, CH_3COH), 2.12 (s, 6H, CH_3C=O), 1.12 (d, J = 7 Hz, 6H, CHC*H*$_3$). The diagnostic disappearance of the alkene protons of methacrolein, shift of the aldehyde signals and appearance of the ABX and MABX patterns indicated that these conditions were viable for the attempted addition of myrtenal to trifluoroacetylacetone.

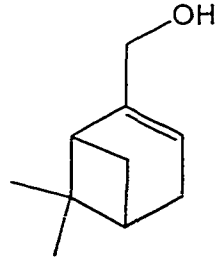
Myrtenitrile (17)



The reaction was carried out in an oven dried 100 mL round bottom flask equipped with stirbar and purged with nitrogen. A solution of myrtenal (1.0 mL, 1.0 g, 6.7 mmol), O,N-(trifluoroacetyl)hydroxylamine[156] (3.0 g, 13 mmol) and pyridine (1.0 mL, 1.1 g, 13 mmol) was prepared in 50 mL dry benzene. The solution was heated to reflux for 2 hours, cooled and acidified with 1 M HCl. Ether was added and the organic layer was washed 3 x 30 mL with water. The organic layer was concentrated to a yellow oil which was approximately 70% desired product as determined by NMR spectroscopy. The resulting nitrile product was inseparable from the aldehyde starting material by column chromatography. Therefore the crude product mixture was subject to $NaBH_4$ reduction. In a 25 mL round bottom flask $NaBH_4$ (300 mg, 8 mmol), $CeCl_3 \cdot 7H_2O$ (1.5 g, 4.0 mmol) and the crude product were dissolved in 10 mL of MeOH. The solution

was stirred for 3 hours before quenching with 1 M HCl. The organic products were extracted into CH_2Cl_2 (3 x 20 mL), dried over $MgSO_4$ and concentrated. The reduction products could be purified by silica gel column chromatography using 3:1 hexanes:ethyl acetate as eluent. Myrtenitrile was isolated as a pale yellow oil in modest yield (270 mg, 27%).[195] ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.56-6.51 (m, 1H, *H*C=C), 2.51-2.38 (m, 4H, C*H*H-*H*C-C=CH-C*H*$_2$), 2.18-2.09 (m, 1H, CH_2-C*H*-(C(Me$_3$)$_2$)-CH_2), 1.29 (s, 3H, C*H*$_3$), 1.22 (d, $J_{gem\ H\text{-}H}$ 9 Hz, 1H, CH-C*H*H-CH), 0.85 (s, 3H, C*H*$_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 142.0 (+, H*C*=C), 120.7 (*C*≡N), 118.3 (*C*=CH), 44.3 (+, CH_2-*C*H-C=C), 39.6 (+,CH_2-*C*H-CH_2), 38.1 (*C*-(CH_3)$_2$), 32.4 (-, *C*H_2-CH=C), 31.1 (+, CH-*C*H_2-CH), 25.5 (+, *C*H_3), 20.8 (+, *C*H_3). Myrtenol **18** was isolated as a side product.

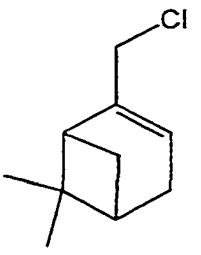
Myrtenol (18)



In a 25 mL round bottom flask myrtenal (0.3 mL, 0.3 g, 2 mmol), $CeCl_3$•7 H_2O (0.8 g, 2 mmol) and $NaBH_4$ (0.2 g, 4 mmol) were dissolved in 7 mL of MeOH. The mixture was stirred for 2 hours and the progress of the reaction was monitored by tlc using 3:1 hexanes: ethyl acetate as eluent. The reaction was quenched with 1 M HCl and the organic products were extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated to yield a golden oil which could be further purified using silica gel column chromatography with the eluent described above. The desired product was obtained as a pale yellow oil in excellent yield (0.29 g, 95% yield).[196] ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.46-5.43 (m, 1H, *H*C=C), 3.95 (br s, 2H, C*H*$_2$-OH), 2.41-2.07 (m, 5H, *H*C-C=CH-C*H*$_2$-C*H*-C*H*H), 1.27 (s, 3H, C*H*$_3$), 1.17

(d, $J_{gem\ H\text{-}H}$ 9 Hz, 1H, CH-C*H*$_2$-CH), 0.82 (s, 3H, C*H*$_3$). ^{13}C NMR (63 MHz, $CDCl_3$) δ 147.7 (*C*=CH), 117.7 (+, H*C*=C), 65.8 (-, *C*H$_2$OH), 43.3 (+, CH$_2$-*C*H-C=C), 40.8 (+, CH$_2$-*C*H-CH$_2$), 37.9 (*C*-(CH$_3$)$_2$), 31.5 (-, *C*H$_2$-CH=C), 31.0 (-, CH-*C*H$_2$-CH), 26.0 (+, *C*H$_3$), 21.0 (+, *C*H$_3$).

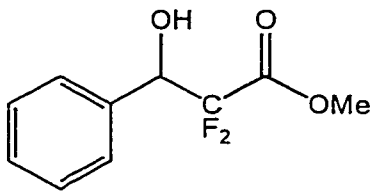
Myrtenallyl chloride (19)



In a dry 25 mL round bottom flask equipped with stir bar myrtenol **18** (0.10 g, 0.66 mmol) was dissolved in 12 mL dry THF. The mixture was cooled to -40°C and hexachloroacetone (0.15 mL, 0.26 g, 0.99 mmol) and triphenylphosphine (0.31 g, 1.2 mmol) were quickly added. The solution was stirred at -40°C for 15 minutes while turning brown in colour. After addition of 6 mL of dry toluene by syringe, the solution was warmed with stirring at room temperature for 20 minutes. The reaction could be followed by tlc using 3:1 hexanes:ethyl acetate as eluent. The reaction mixture was concentrated and purified by a short silica gel column using the previously described eluent. The desired product was obtained as a yellow oil in quantitative yield (0.11 g).[197] ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.63-5.60 (m, 1H, *H*C=C), 3.99 (br s, C*H*$_2$-Cl), 2.47-2.19 (m, 4 H, C*H*H-*H*C-C=CH-C*H*$_2$), 2.13-2.07 (m, 1H, CH$_2$-C*H*-(C(Me$_3$)$_2$)-CH$_2$), 1.29 (s, 3H, C*H*$_3$), 1.22 (d, J = 9 Hz, 1H. CH-C*H*H-CH), 0.85 (s, 3H, C*H*$_3$).

Trial of Reformatsky conditions for fluorinated synthons[165]

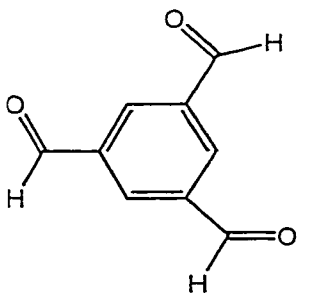
The goal of this experiment was to test whether benzaldehyde reacted to indicate formation of compound 21.



In an oven dried 25 mL round bottom flask equipped with stir bar, a solution of methyl chlorodifluoroacetate (340 mg, 2.35 mmol) and benzaldehyde (250 mg, 2.35 mmol) in 10 mL of dry DMF was prepared. To this solution, freshly activated zinc powder[198](170 mg, 2.60 mmol) was added. The mixture was heated to 70°C for 20 hours. The yellow-green solution was diluted with CH_2Cl_2, and washed with 1 M HCl (3 x 10 mL). The organic fraction was dried over $MgSO_4$ and concentrated to yield a yellow oil. NMR spectroscopy of the crude product showed a modest yield of the desired product (estimated 20%).[199] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52-7.35 (m, 5 H, Aryl*H*), 5.18 (d br. d, *J*=15, 8 Hz, 1H, *CH*OH), 3.85 (s, 3H, C*H*$_3$), *2.78* (br, 1H, O*H*), comparable to literature values.

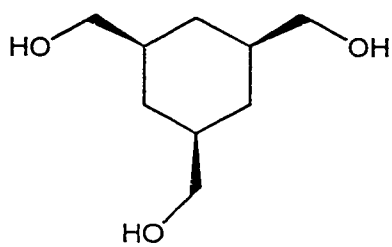
1,3,5-Triformylbenzene (22)[167]

In a 100 mL round bottom flask equipped with stir bar tribromide **14** (2.0 g, 5.6 mmol) and hexamethylenetetramine (4.7 g, 34 mmol) were suspended in 50 mL of 50% aqueous acetic acid. This mixture was refluxed for 2 hours. After, 15 mL of concentrated HCl was added and reflux was continued for an additional 15 minutes. The reaction mixture was cooled and extracted with CH_2Cl_2



(3 x 50 mL). The combined organic fractions were washed with water, sat. sodium bicarbonate solution and brine and dried over $MgSO_4$. The crude product was isolated under reduced pressure and purified by recrystallisation from ether. The desired product was obtained in poor yield (0.17 g, 20%) as a white crystalline solid. Mp 153°C (lit.[200] mp 155°C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.19 (s, 3H, *H*C=O), 8.83 (s, 3H, Aryl*H*).

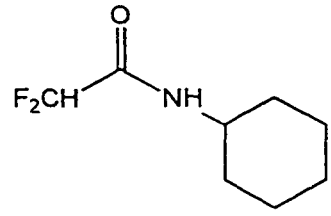
cis-1,3,5-Tris(hydroxymethyl)cyclohexane (23)[168]



In an oven dried 100 mL round bottom flask equipped with stirbar, $LiAlH_4$ (2.0 g, 76 mmol) was suspended in 30 mL of dry THF and cooled to 0°C. A second solution of *cis*-1,3,5-cyclohexane-tris(carboxylic acid) (2.0 g, 9.2 mmol) dissolved in 20 mL dry THF was prepared in a 100 mL oven dried dropping funnel. The acid solution was dropped slowly into the $LiAlH_4$ suspension. The final mixture was refluxed 16 hours, cooled to 0°C and quenched with minimal quantities of water. The resultant slurry was diluted with ethanol at 0°C, warmed to room temperature and stirred for 3 hours. This thick solution was then filtered through a glass frit. The collected solid was washed with boiling ethanol (2 x 50 mL). The filtrates were concentrated to a solid which could be recrystallized from hot dioxane. The desired product was obtained in poor yield (0.24 g, 15 %). Mp 107-109°C (lit.[168] 114-117°C) ^{1}H NMR (300 MHz, D_2O) δ 3.28 (d, J = 5 Hz, 6H, C*H*$_2$O), 2.63-2.59 (m, 3H, *H*CH), 2.54-2.35 (m, 3H, C*H*CH$_2$OH), 0.52-0.38 (m, 3H, HC*H*). ^{13}C NMR (75 MHz, D_2O) δ 67.7(-, *C*H$_2$OH), 38.9 (+, ring, *C*H), 32.2 (-, ring *C*H$_2$).

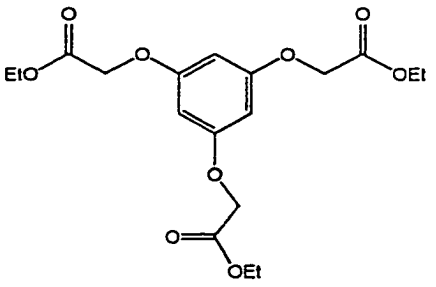
N-Cyclohexyl-1,1-difluoro-2-acetamide (24)

NOTE: This product was prepared in excellent yield while attempting to prepare *t*-butyl-1,1-difluoroacetate in the following experimental procedure.[170]



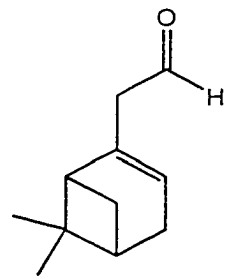
In a 50 mL round bottom flask equipped with a stir bar, difluoroacetic acid (1.0 mL, 1.5 g, 16 mmol) was dissolved in 25 mL of CH_2Cl_2. To this solution t-butanol (1.7 mL, 1.3 g, 18 mmol), DCC (3.5 g, 18 mmol) and DMAP (0.18 g, 1.5 mmol) were added. The reaction was stirred for 16 hours and the resulting urea precipitate was filtered off. The reaction mixture was diluted with a further 50 mL of CH_2Cl_2, washed with water and sat. aq. $NaHCO_3$. The organic fraction was concentrated under reduced pressure to yield a white solid which could be recrystallised from ether. This side product was revealed by NMR and MS to be **24**. ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.20 (br, 1H, N*H*), 5.86 (t, J_{HF} = 54 Hz, 1H, CF_2H), 3.83-3.74 (m, 1H, C*H*N), 1.95-1.90 m, 2H, ring CH_2), 1.76-1.70 (m, 2H, ring CH_2), 1.68-1.57 (m, 1H, ring CH_2), 1.43-1.24 (m, 2H, ring CH_2), 1.24-1.11 (m, 3H, ring CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (t, J_{CF} = 29 Hz, *C*=O) 108.5 (t, J_{CF} = 251 Hz, CF_2H), 48.4 (+, ring *C*H), 32.6, 25.3, 24.6 (-, ring CH_2's). ^{19}F NMR (338 MHz, $CDCl_3$ in δ) -126.4. CI MS *m/z* 178 (MH$^+$, 100%), 206 (M+29, 30%), 218 (M+41, 7%).

Ethyl 2-{3,5-bis[(ethoxycarbonyl)methoxy]phenoxy}acetate (26)



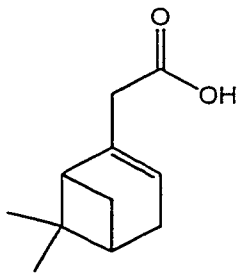
In a 50 mL round bottom flask equipped with a stirbar, phloroglucinol (0.50 g, 3.1 mmol) was dissolved in 20 mL of acetone. To this solution 18-crown-6 (0.30 g, 1.1 mmol) and K_2CO_3 (1.5 g, 10.9 mmol) were added followed by ethyl bromoacetate (6.0 mL, 7.2 g, 5.2 mmol) by syringe. The mixture was heated to reflux under N_2 for 16 hours. After cooling, the reaction mixture was diluted with 30 mL of ether, washed with water (3 x 20 mL) and dried over $MgSO_4$. The organic fraction was concentrated to yield a yellow oil which could be purified by removal of excess starting material with gentle heating under vacuum. The desired product was obtained in good yield (0.83 g, 70%). Long term storage at room temperature of the oil gives a white crystalline solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 3H, Aryl*H*), 4.55 (s, 6H, CH_2C=O), 4.22 (q, J = 7 Hz, 6H, OCH_2), 1.26 (t, J = 7 Hz, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5 (*C*=O), 159.6 (Aryl*C*O), 95.2 (+, Aryl*C*H), 65.3 (-, OCH_2C=O), 61.3 (-, OCH_2), 14.1 (+, CH_3). CI MS *m/z* 385 (MH^+, 100%), 413 (M+29, 10%), 425 (M+41, 5%).

Nopal (27)[150]



In a 250 mL round bottom flask equipped with a stirbar, nopol (1.3 g, 8.0 mmol) was dissolved in 70 mL of CH_2Cl_2. With vigorous stirring $Zn(ClCrO_3)\cdot 9H_2O$[150] (12 g, 24 mmol) was added in four separate portions over 15 minutes. The reaction was stirred for 10 hours at room temperature, diluted to 150 mL with CH_2Cl_2 and filtered. The precipitate was washed thoroughly with CH_2Cl_2. A small amount of silica gel was stirred in the filtrate for 10 minutes before filtering through a silica pad. The resulting organic solution was concentrated to yield an orange oil. The desired material could be purified by vacuum distillation yielding 0.45 g (35%) of pale yellow oil. Bp 110°C, 30 mmHg (lit.[202] bp 68-71, 1.0 mmHg) ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (t, J = 2 Hz, 1H, C=O*H*), 5.42-5.38 (m, 1H, C=C*H*), 3.03-3.00 (m, 2H, CH_2C=OH), 2.52 (dt, J = 9, 6 Hz, 1H, ring C*H*), 2.30 (dt J = 6, 2 Hz, 1H, bridgehead C*H*), 2.26 (br dd, J = 18 Hz, 2H, ring CH_2), 2.17-2.11 (m, 1H, bridgehead C*H*), 1.26 (s, 3H, CH_3), 1.24 (d, J = 9, 1H, ring C*H*), 0.80 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3 (s, *C*=OH), 149.4 (*C*=CH), 123.8 (+, *C*H=C), 46.0 (+, bridgehead *C*H), 43.0 (-, *C*H_2C=OH), 40.7 (+, bridgehead *C*H), 37.7 (*C*$(CH_3)_2$), 31.7 (-, ring *C*H_2), 31.3 (-, ring *C*H_2), 26.1 (+, *C*H_3), 20.6 (+, *C*H_3).

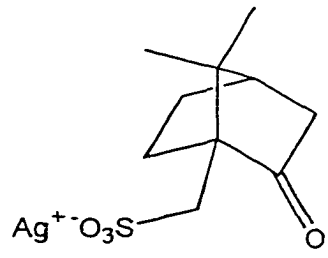
Nopoic acid (28)



In a 50 mL round bottom flask equipped with stir bar nopol (1.0 g, 6.0 mmol) was dissolved in 10 mL of acetone and N_2 was bubbled through the solution. The reaction flask was cooled with an ice-bath during the dropwise addition of Jones' Reagent.[182, 183] Jones' Reagent was added until the orange colour persisted. The reaction was stirred at room temperature for 10 minutes. The reaction solution was diluted with ether (50 mL) and washed (3 x 25 mL) with 1 M HCl. The desired product was then extracted into the aqueous layer by washing the organic fraction with a sat. $NaHCO_3$ solution and subsequent water washes (3 x 20 mL). The aqueous fraction was then acidified and the purified desired product was extracted into ether (3 x 25 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated to yield a pale yellow oil in good yield (0.65 g, 60 %).[201] ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.76 (br. s, 1H, COO*H*), 5.46-5.42 (m, 1H, C=C*H*), 3.05-3.02 (m, 2H, C*H*$_2$COOH), 2.40 (dt, J = 9, 6 Hz, 1H, ring C*H*), 2.31-2.21 (m, 2H, ring C*H*$_2$), 2.14 (dt J = 6, 2 Hz, 1H, bridgehead C*H*), 2.12-2.06 (m, 1H, bridgehead C*H*), 1.28 (s, 3H, C*H*$_3$), 1.24 (d, J = 9, 1H, ring C*H*), 0.84 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7 (*C*OOH), 140.3 (*C*=CH), 121.3 (+, *C*H=C), 45.8 (+, bridgehead *C*H), 42.3 (-, *C*H$_2$COOH), 40.4 (+, bridgehead *C*H), 38.0 (*C*(CH$_3$)$_2$), 31.7 (-, ring *C*H$_2$), 31.4 (-, ring *C*H$_2$), 26.2 (+, *C*H$_3$), 20.8 (+, *C*H$_3$).

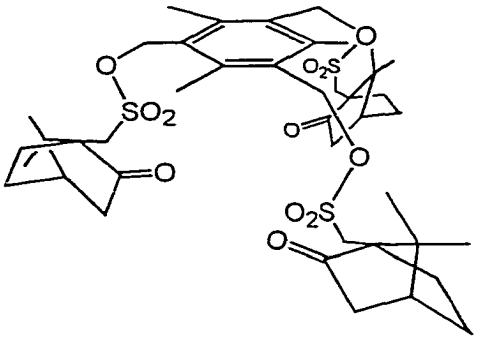
Silver camphor sulfonate (31)

In an oven dried 500 mL round bottom flask equipped with stirbar, oven dried camphor sulfonic acid (3.0 g, 13 mmol) was dissolved in 200 mL of freshly distilled CH_3CN. To this solution Ag_2O powder (3.0 g, 13 mmol) was added with vigorous stirring.[187] This suspension was stirred at room temperature for 30 minutes while being protected from light. The resulting silver salt **34** could be isolated by filtering the resulting solution through celite and concentrating the filtrate under reduced pressure. This method resulted in the quantitative yield of a pale grey solid. ^1H NMR (300 MHz, D_2O) δ 3.17 (d, J = 15 Hz, 1H, SO_3CHH), 2.72 (d, J = 15 Hz, 1H, SO_3CHH), 2.36-2.21 (m, 2H, $C{=}OCH_2$), 2.08-1.79 (m, 3H, ring CH's), 1.51-1.41 (m, 1H, ring CH), 1.34-1.23 (m, 1H, ring CH), 1.88 (s, 3H, CH_3), 1.66 (s, 3H, CH_3). ^{13}C NMR (75 MHz, D_2O) δ 213.2 ($C{=}O$), 58.9 (CCH_2SO_3), 48.6 ($C(CH_3)_2$), 47.5 (-, CH_2SO_3), 43.0 (-, $CH_2C{=}O$), 42.7 (+, bridgehead CH), 26.6 (-, ring CH_2), 25.0 (-, ring CH_2), 19.3 (+, CH_3), 19.1 (+, CH_3).



In the preparation of the desired chiral ligand **33a** or **b** this product was not isolated. The stirring was stopped and the insoluble materials were permitted to settle over a period of 30 minutes. The supernatant was then transferred by cannula into a vessel containing **14** or **35** dissolved in CH_3CN.

Chiral sulfonate ester cap (32a and 32b)

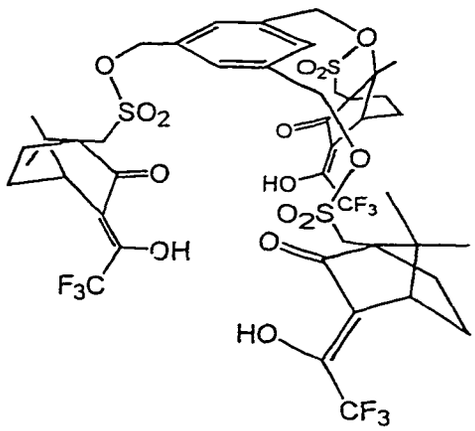


In an oven dried 500 mL round bottom flask equipped with stir bar, bromide cap **14** or **35** (1.6 g, 3.9 mmol for **14**) was dissolved in 50 mL of dry acetonitrile. A solution of silver salt **31** (as described on page 192) was transferred by cannula into the solution of bromide cap, being careful to exclude atmospheric moisture. Precipitate began to form immediately. The mixture was permitted to stir for 3 hours at room temperature under an atmosphere of N_2 with protection from light. Stirring was stopped and the precipitate was permitted to settle over 30 minutes. The supernatant was then transferred by cannula into a large Schlenk tube and dried in vacuo yielding a glassy white solid. This material was redissolved in dry CH_2Cl_2 and any unreacted silver salts remained in suspension as white cloudy material. To this solution $MgSO_4$ was added to assist in the removal of the unreacted silver salts. The $MgSO_4$ was stirred in solution for 1 hour and then permitted to settle overnight. The purified solution could then be transferred by cannula from the settled precipitates to a second Schlenk tube. In some cases, this procedure needed to be repeated several times until all unreacted silver salts were removed from solution. The final product was isolated as a sticky, white crystalline solid in good yield (2.1 g, 65%). ^{13}C NMR signals assigned with the aid of HETCOR spectra. **32a:** ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 3H, Aryl*H*), 5.30, 5.26 (ABq, J_{AB} = 14 Hz, 6 H, PhC*H*$_2$), 3.58 (d, J = 15 Hz, 3H, SO_3C*H*H), 2.98 (d, J = 15 Hz, 3H, SO_3CH*H*), 2.46-2.30 (m, 6H, C*H*$_2$C=O), 2.09-1.89 (m, 9H, ring C*H*'s), 1.62-1.56 (m, 3H, ring C*H*'s), 1.43-1.32 (m, 3H, ring C*H*'s), 1.02 (s, 9H, C*H*$_3$), 0.80 (s, 9H, C*H*$_3$). ^{13}C NMR (75 MHz,

$CDCl_3$) δ 214.4 (*C*=O), 135.2 (Aryl *C*CH_2), 129.4 (+, Aryl *C*H), 70.8 (-, Ph*C*H_2), 58.0 (bridgehead *C*CH_2SO_3), 48.1 (*C*$(CH_3)_2$), 47.5 (-, *C*H_2SO_3), 42.7 (+, bridgehead *C*H), 42.5 (-, *C*H_2C=O), 26.9 (-, ring *C*H_2), 24.9 (-, ring *C*H_2), 19.7 (+, *C*H_3), 19.6 (+, *C*H_3). LSIMS *m/z* 811.2 (MH^+, 50%), 579.2 (M-$CAMSO_3^-$, 100%). This compound decomposed upon standing and the LRMS was obtained only with difficulty. $CAMSO_3^-$ = camphor sulfonate group

32b: ^{1}H NMR (360 MHz, $CDCl_3$) δ centred at 5.46, 5.43 (ABq, J_{AB} = 14 Hz, 6 H, PhC*H*$_2$), 3.59 (d, J = 15 Hz, 3H, SO_3C*H*H), 2.98 (d, J = 15 Hz, 3H, SO_3CH*H*), 2.51 (s, 9H, PhC*H*$_3$), 2.49-2.33 (m, 6H, C*H*$_2$C=O), 2.11-1.91 (m, 9H, ring C*H*'s), 1.68-1.61 (m, 3H, ring C*H*'s), 1.46-1.39 (m, 3H, ring C*H*'s), 1.07 (s, 9H, C*H*$_3$), 0.84 (s, 9H, C*H*$_3$). ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.5 (*C*=O), 141.8 (Aryl *C*CH_2), 129.5 (Aryl *C*Me), 66.1 (-, Ph*C*H_2), 58.0 (bridgehead *C*CH_2SO_3), 48.0 (*C*$(CH_3)_2$), 47.5 (-, *C*H_2SO_3), 42.7 (+, bridgehead *C*H), 42.5 (-, *C*H_2C=O), 26.9 (-, ring *C*H_2), 24.8 (-, ring *C*H_2), 19.8 (+, *C*H_3), 19.7 (+, *C*H_3) 16.0 (+, Aryl*C*H_3).

Chiral sulfonate ester ß-diketone ligand (33a and 33b)



Into an oven dried 500 mL 2 necked round bottom flask, NaH (1.0 g, 42 mmol) was loaded in the dry box. This powder was suspended in 150 mL of dry THF with stirring under an atmosphere of N_2 at 0°C. To the NaH slurry was added ethyl trifluoroacetate (4.5 mL, 5.3 g, 37 mmol). The reaction vessel was fitted with a 100 mL dropping funnel. A solution of chiral cap **32a** or **b** (2.0 g, 2.5 mmol for cap **32a**) in 100 mL of dry THF was prepared in the oven dried dropping funnel. This solution was dropped slowly into the NaH/ester solution under an atmosphere of N_2. After addition the resulting reaction mixture was warmed to room temperature and stirred under N_2 for a further 24 hours. The reaction mixture was cooled to 0°C, diluted with 100 mL ether and quenched with 3 M HCl. The HCl solution was added until the water layer was acidic (pH 2). The organic layer was washed with 1M HCl (2 x 100 mL). The organic fraction was dried over $MgSO_4$ and concentrated to yield a viscous orange oil which occasionally yielded a beige crystalline solid at low temperature from ether/hexanes. The yield of the crude oil product was excellent (2.3 g, 80%), while the yield of the crystalline material was consistently poor. The crude oil product was shown by NMR to be approximately 80% desired product **33a** or **b**. ^{13}C NMR signals assigned with the aid of HETCOR spectra.

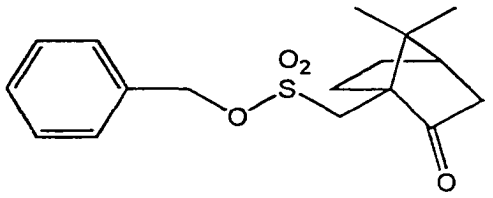
33a: ^1H NMR (360 MHz, $CDCl_3$) δ 7.52 (s, 3H, Aryl *H*'s), 5.35, 5.33 (ABq, J_{AB} = 14 Hz, 6H, $PhCH_2$) 3.60 (d, J = 15 Hz, 3H, SO_3CHH), 3.07 (d, J = 15 Hz, 3H, SO_3CHH), 2.90 (br s, 3H, bridgehead *CH*), 2.52-2.44 (m, 3H, ring C*H*'s),2.19-2.15 (m, 3H, ring

C*H*'s), 1.79-1.73 (m, 3H, ring C*H*'s), 1.57-1.51 (m, 3H, ring C*H*'s), 1.24 (br s, 3H, H_2O), 1.06 (s, 9H, CH_3), 0.86 (s, 9H, CH_3). ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.3 (*C*=O), 149.3 (q, J_{CF} = 38 Hz, *C*-OHCF$_3$), 135.2 (Aryl *C*CH$_2$), 129.4 (+, Aryl *C*H), 119.0 (q, J_{CF} = 276 Hz, *C*F$_3$), 116.3 (C=O*C*C=O), 70.8 (-, PhCH$_2$), 57.8 (bridgehead *C*CH$_2$SO$_3$), 50.6 (*C*(CH$_3$)$_2$), 47.0 (-, *C*H$_2$SO$_3$), 46.7 (+, bridgehead *C*H), 26.4 (-, ring *C*H$_2$), 25.4 (-, ring *C*H$_2$), 20.3 (+, *C*H$_3$), 18.7 (+, *C*H$_3$). ^{19}F NMR (338 MHz, $CDCl_3$) δ -70.3. LSIMS *m/z* 1121.2 (M + Na$^+$, 12%), 771.2 (M - $CF_3COCAMSO_3^-$, 8%), 443.1 (M + H - 2($CF_3COCAMSO_3^-$, 100%). This compound readily decomposed upon standing and the LRMS was obtained only with difficulty. $CF_3COCAMSO_3^-$ = trifluoroacetylated camphor sulfonate

33b ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.42, 5.38 (ABq, J_{AB} = 14 Hz, 6H, PhCH_2) 3.42 (d, J = 15 Hz, 3H, SO$_3$C*H*H), 2.99 (d, J = 15 Hz, 3H, SO$_3$CH*H*), 2.80 (br s, 3H, bridgehead *CH*), 2.42-2.20 (m, 3H, ring C*H*'s), 2.25 (s, 9H, Aryl CH_3) 2.20-2.14 (m, 3H, ring C*H*'s), 1.81-1.75 (m, 3H, ring C*H*'s), 1.45-1.40 (m, 3H, ring C*H*'s), 1.19 (br s, 2H, H_2O), 0.94 (s, 9H, CH_3), 0.78 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.2 (*C*=O), 149.8 (q, J_{CF} = 38 Hz, *C*=OCF$_3$), 139.4 (Aryl *C*CH$_2$), 134.4 (Aryl *C*H$_3$), 117.9 (q, J_{CF} = 276 Hz, *C*F$_3$), 117.0 (+, C=O*C*HC=O), 69.9 (-, PhCH$_2$), 57.6 (bridgehead *C*CH$_2$SO$_3$), 50.6 (*C*(CH$_3$)$_2$), 47.0 (-, *C*H$_2$SO$_3$), 46.6 (+, bridgehead *C*H), 26.4 (-, ring *C*H$_2$), 25.4 (-, ring *C*H$_2$), 20.2 (+, *C*H$_3$), 18.7 (+, *C*H$_3$), 16.2 (+, Aryl *C*H$_3$). ^{19}F NMR (338 MHz, $CDCl_3$ in δ) -70.2.

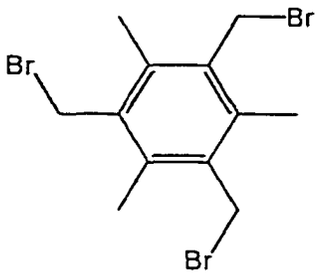
Trial conditions for the reaction benzyl bromide with silver salt 31

The goal of this experiment was to test whether reaction conditions indicated formation of 34.



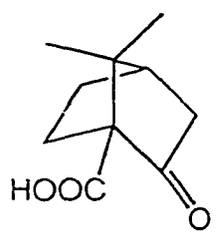
In a 50 mL round bottom flask equipped with a stirbar, silver salt **31** (0.25 g, 0.74 mmol) was dissolved in 30 mL of dry acetonitrile. To this solution was added benzyl bromide (0.10 mL, 0.12 g, 0.87 mmol) via syringe. The solution turned cloudy immediately. The reaction was stirred at room temperature for 3 hours with protection from light. The solution was then filtered through celite and the desired product **34** was obtained in good yield (0.15 g, 60%) as a white fluffy solid upon concentration of the filtrate. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H, Aryl *H*), centred at 5.23, 5.21 (ABq, J_{AB}= 15 Hz, 2H, PhC*H*$_2$), 3.49 (d, J = 15 Hz, 1H, SO_3C*H*H), 2.85 (d, J = 15 Hz, 1H, SO_3CH*H*). 2.42-2.24 (m, 2H, C*H*$_2$C=O), 2.02-1.82 (m, 3H, ring C*H*'s), 1.62-1.50 (m, 1H, ring C*H*'s), 1.37-1.28 (m, 1H, ring C*H*'s), 1.02 (s, 3H, C*H*$_3$), 0.78 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.4 (*C*=O), 133.6 (Aryl *C*CH_2), 129.2, 128.9, 128.8 (+, Aryl *C*H's), 72.0 (-, Ph*C*H_2), 58.0 (bridgehead *C*CH_2SO_3), 48.0 (*C*$(CH_3)_2$), 47.6 (-, *C*H_2SO_3), 42.7 (+, bridgehead *C*H), 42.5 (-, *C*H_2C=O), 26.9 (-, ring *C*H_2), 24.9 (-, ring *C*H_2), 19.8 (+, *C*H_3), 19.6 (+, *C*H_3). The diagnostic appearance of the benzylic AB quartet established that these reaction conditions were viable for the preparation of the tripodal version, **32a** and **32b**.

1,3,5-Tris(bromomethyl)-2,4,6-trimethylbenzene (35)[188]



In a 500 mL round bottom flask equipped with a stir bar, KBr (96 g, 0.80 mol) was dissolved in 200 mL of acetic acid. To this mixture mesitylene (21 mL, 18 g, 0.15 mol) and paraformaldehyde (21 g, 0.70 mol) were added with vigorous stirring. The mixture was heated to 95°C for 6 hours with continued stirring. Then stirring was stopped and the reaction mixture was allowed to stand overnight. The resulting slurry was poured into 1 L water. The resulting flocculate solid was collected on a glass frit and dried in vacuo. The product could be purified by recrystallisation from 1,2-dichloroethane in good yield (45 g, 75%) as a white crystalline solid. Mp 185 - 188°C (Lit.[188] 186 - 188°C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (s, 6H, CH_2), 2.42 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9 (Aryl*C*), 133.3(Aryl*C*), 29.9(-, CH_2), 15.4(+, CH_3).

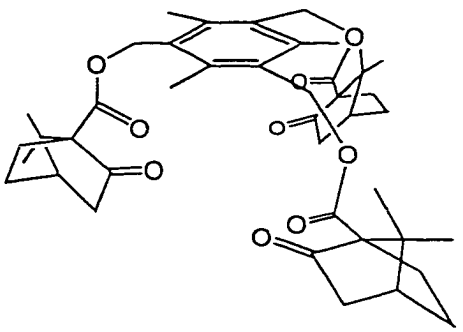
Ketopinic acid (36) (camphor carboxylic acid)[189]



In a 250 mL round bottom flask equipped with a stirbar, K_2CO_3 (10 g), and $KMnO_4$ (10 g) were dissolved in 150 mL hot water. The solution was heated to very near boiling. With vigorous stirring, camphor sulfonyl chloride (10 g) was added quickly in four equivalent portions, with enough time in between additions to ensure the reaction did not bubble over. The reaction was refluxed for 1 hour and cooled to room temperature. Any excess $KMnO_4$ was reduced with an acidified solution of Na_2SO_3. The reaction mixture was made strongly acidic with a 20% sulfuric acid solution. Sodium sulfite was slowly added

until a colourless solution was obtained. This water layer was then extracted with ether (4 x 100 mL). The combined organic fractions were then concentrated to yield a white flaky solid. The product was recrystallised from boiling water to yield the desired carboxylic acid **36** in modest yield (2.5 g, 40%). Mp 235-236°C (lit.[203] mp 237-239°C) (This product has recently become commercially available).

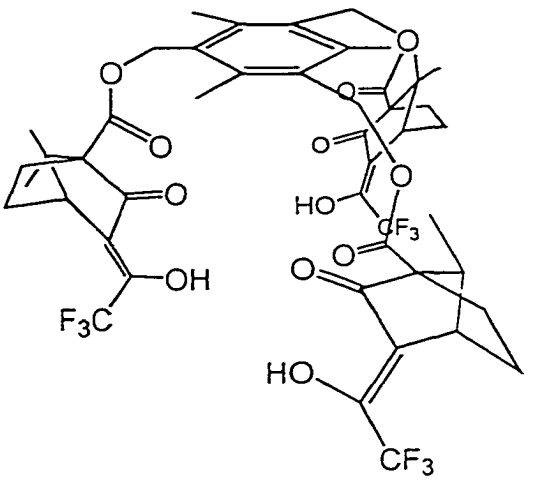
Chiral carboxylate ester cap (38)



In an oven dried 250 mL round bottom flask equipped with a stir bar, carboxylic acid **39** (3.3 g, 18 mmol) was loaded and dried in vacuo with gentle heating for 2 hours. Under an atmosphere of N_2, **39** was dissolved in 100 mL dry acetonitrile. To this solution Ag_2O (4.2 g, 18 mmol) was added and stirred with protection from light for 1 hour. The stirring was stopped and the insoluble materials were permitted to settle over a period of 1 hour. In a second oven dried 250 mL round bottom flask equipped with a stir bar cap **36** (1.8 g, 4.5 mmol) was dissolved in 50 mL of dry acetonitrile under an atmosphere of N_2. The remainder of the reaction procedure, work-up and isolation is identical to the procedure described in the preparation of **32.** The final product was isolated as a sticky, white crystalline solid in good yield (2.0g, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (br s, 6 H, PhC*H*$_2$), 2.40 (s, 9H, PhC*H*$_3$), 2.44-2.26 (m, 6H, C*H*$_2$C=O), 2.19-1.67 (m, 12H, ring C*H*'s), 1.36-1.31 (m, 3H, ring C*H*'s), 1.10 (s, 9H, C*H*$_3$), 1.02 (s, 9H, C*H*$_3$). ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.7 (*C*=O), 169.6 (*C*=OO) 141.8 (Aryl *C*CH$_2$), 129.5 (Aryl *C*Me), 68.0 (bridgehead *C*C=OO), 65.9 (-, PhCH$_2$), 49.4

($C(CH_3)_2$), 44.4 (+, bridgehead *C*H), 43.9 (-, $CH_2C{=}O$), 26.4 (-, ring CH_2), 26.4 (-, ring CH_2), 21.3 (+, CH_3), 19.8 (+, CH_3) 16.2 (+, ArylCH_3). IR (Nujol) cm^{-1} 1751(s) (COO), 1718(s) (CO), 1313, 1282, 1220, 1018. LSIMS *m/z* 835.3 ($M + Cs^+$, 11%), 725.2 ($M + Na^+$, 5%), 521.3 (M - CAMCOO$^-$, 45%), 339.1 (M - 2(CAMCOO$^-$), 100%). HRMS (+LSIMS) calcd for $C_{42}H_{54}NaO_9$: 725.3658; found: 725.3658. CAMCOO$^-$ = camphor carboxylate

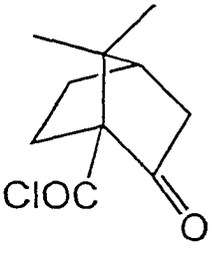
Chiral carboxylate ester ß-diketone ligand (39)



Into an oven dried 250 mL 2 necked round bottom flask, NaH (0.29 g, 12 mmol) was loaded in the dry box. This powder was suspended in 100 mL of dry THF with stirring under an atmosphere of N_2. To the NaH slurry was added ethyl trifluoroacetate (1.3 mL, 1.5 g, 11 mmol). The reaction vessel was fitted with a 100 mL dropping funnel. A solution of chiral cap **38** (0.50 g, 0.71 mmol) in 50 mL of dry THF was prepared in the oven dried dropping funnel. This solution was dropped slowly into the NaH/ester solution under an atmosphere of N_2. After addition the resulting reaction mixture was stirred under N_2 for a further 24 hours. The reaction was cooled to 0°C, diluted with 50 mL ether and quenched with 3 M HCl. The HCl solution was added until the water layer was acidic (pH 2). The organic layer was washed with 1M HCl (2 x 50 mL). The organic fraction was dried over $MgSO_4$ and concentrated to yield a viscous red oil. The yield of the crude oil product was

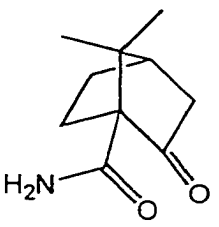
0.42 g (65%), and was shown by NMR to be approximately 70% desired product **39**. Ligand **39** was never successfully purified. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.41 (br s, 3H, O*H*), 5.27 (br s, 6H, PhCH_2), 2.86 (br. s, 3H, bridgehead C*H*), 2.42 (s, 9H, PhCH_3), 2.58-2.26 (m, 3H, ring C*H*'s), 2.17-1.63 (m, 6H, ring C*H*'s), 1.46-1.32 (m, 3H, ring C*H*'s), 1.08 (s, 9H, CH_3), 0.90 (s, 9H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.2 (*C*=O), 168.7 (*C*=OO) 149.2 (q, J_{CF} = 38 Hz, *C*-OHCF$_3$), 139.8 (Aryl *C*CH$_2$), 130.4 (Aryl *C*Me), 119.2 (q, J_{CF} = 280 Hz, *C*F$_3$), 117.2 (C=O*C*HC=O), 67.6 (bridgehead *C*C=O), 55.0 (-, PhCH$_2$), 51.6 (*C*(CH$_3$)$_2$), 47.3 (+, bridgehead *C*H), 26.3 (-, ring *C*H$_2$), 26.2 (-, ring *C*H$_2$), 21.7 (+, *C*H$_3$), 19.4 (+, *C*H$_3$) 16.0 (+, Aryl*C*H$_3$).

Ketopinic acid chloride (camphor acid chloride) (40)



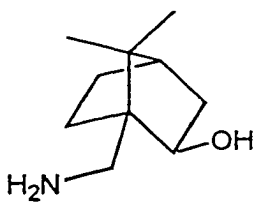
In a 50 mL round bottom flask equipped with a stir bar, carboxylic acid **36** (0.40 g, 2.2 mmol) was cooled in an ice bath. PCl_5 (0.46 g, 2.2 mmol) was added to the stirring solid. The reaction mixture slowly began to liquify at 0°C. Once completely liquid, the reaction mixture was permitted to sit at room temperature for 1 hour. Upon completion of the reaction, side products were removed under vacuum leaving the desired pale yellow crystalline material which was usually used immediately without any further purification or characterisation.[190] In the literature this compound was prepared with $SOCl_2$ instead of PCl_5.

Ketopinamide (camphor amide) (44)



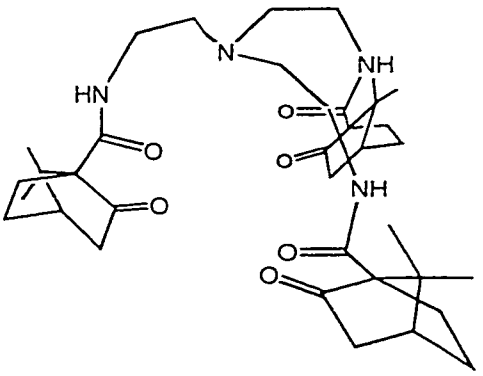
A 50 mL round bottom flask, equipped with a stirbar and freshly prepared acid chloride **40** (0.44 g, 2.2 mmol), was cooled in an ice bath. The solid was suspended in ammonium hydroxide and warmed to room temperature. After stirring for 20 minutes a clear pale yellow solution was obtained. The solution was diluted with 50 mL of water and the desired product was extracted into ether (3 x 100 mL). The combined organic fractions were washed with brine and dried over $MgSO_4$ and concentrated under reduced pressure to give a white solid in quantitative yield.[191] Mp 189-194°C (lit.[190] mp 192-195°C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (br. s, 1H, NH*H*), 5.53 (br. s, 1H, N*H*H), 2.52-2.42 (m, 2H, C*H*$_2$C=O), 2.16-2.02 (m, 2H, ring C*H*$_2$), 1.93 (d, J = 19 Hz, 1H, ring C*H*), 1.62-1.53 (m, 1H, ring C*H*), 1.42-1.33 (m, 1H, ring C*H*), 1.19 (s, 3H, C*H*$_3$), 0.94 (s, 3H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.8 (*C*=O), 171.5 (*C*=ONH$_2$), 64.9 (bridgehead C'CONH$_2$), 50.2 (*C*(CH$_3$)$_2$), 43.7 (-, *C*H$_2$C=O), 43.3 (+, bridgehead *C*H), 28.3 (-, ring *C*H$_2$), 27.7 (-, ring *C*H$_2$), 20.8 (+, *C*H$_3$), 20.4 (+, *C*H$_3$). CI MS *m/z* 165 (M-O, 40%), 182 (MH$^+$, 100%), 210 (M+29, 16%), 222 (M+41, 7%) HRMS (EI) calcd for $C_{10}H_{15}NO_2$: 181.1103; found: 181.1101.

Camphane amine alcohol (45)[191]



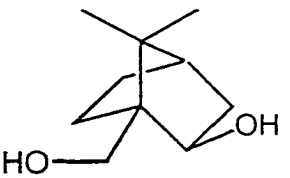
In an oven dried 2-necked 250 mL round bottom flask, $LiAlH_4$ (0.80 g, 21 mmol) was suspended in 50 mL of dry THF under an atmosphere of N_2. The reaction vessel was cooled with an ice bath and fitted with a 100 mL oven dried dropping funnel. A solution of amide **44** (1.2 g, 6.6 mmol) in 50 mL of dry THF was added dropwise to the cooled $LiAlH_4$ slurry. Upon completion of the addition the reaction was heated to reflux under an atmosphere of N_2 for 16 hours. The reaction mixture was cooled with an ice bath, diluted with 100 mL of ether and quenched with dropwise addition of water. The resulting precipitate was filtered and washed with ether. The organic fraction was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield a pale yellow gummy semi-solid.[191] (Cited reference reports this compound as an oil.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93-3.88 (m, 1H, C*H*OH), 3.02 (br d, *J* = 13 Hz, 1H, C*H*HNH$_2$), 2.78 (br. d, *J* = 13 Hz, 1H, CH*H*NH$_2$), 2.59 (br. s, 5H, O*H*, N*H*$_2$, *H*$_2$O), 1.87-1.57 (m, 6H, ring C*H*$_2$, THF), 1.37-1.32 (m, 1H, ring C*H*), 1.18 (s, 3H, C*H*$_3$), 1.01-0.94 (m, 2H, ring C*H*$_2$), 0.76 (s, 3H, C*H*$_3$) ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.3 (+, *C*HOH), 63.1 (-, *C*H$_2$NH$_2$), 52.2 (bridgehead *C*CH$_2$NH$_2$), 46.5 (*C*(CH$_3$)$_2$), 46.0 (+, bridgehead *C*H), 39.9 (-, *C*H$_2$CHOH), 31.0 (-, ring *C*H$_2$), 26.9 (-, ring *C*H$_2$), 21.2 (+, *C*H$_3$), 20.6 (+, *C*H$_3$). CI MS *m/z* 152 (MH$^+$- H$_2$O, 100%), 170 (MH$^+$, 58%). HRMS (EI) calcd for $C_{10}H_{19}NO$: 169.1467; found: 169.1469.

Tren chiral amide cap (46)



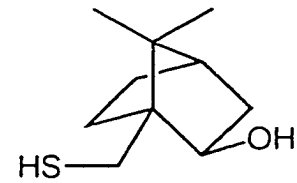
In a 50 mL round bottom flask equipped with a stirbar, freshly prepared acid chloride **40** (1.9 g, 9.4 mmol) was dissolved in 15 mL CH_2Cl_2. To this solution was added freshly distilled triethyl amine (15 mL). By syringe, tren (0.50 mL, 0.69 g, 3.3 mmol) was added with stirring. There was immediate formation of precipitate. The reaction was stirred for a further 2 hours. The mixture was diluted with 100 mL ether and washed with 1 M HCl (2 x 50mL) and water. The organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure to give a white crystalline solid in good yield (1.3 g, 68%). The isolated product required no further purification, but can be recrystallized from ether at 5°C. Mp 132-133°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (br. s, 3H, N*H*), 3.30 (t, J = 7Hz, 6H, C*H*$_2$NHC=O), 2.64-2.55 (m, 6H, NC*H*$_2$CH$_2$), 2.48-2.39 (m, 6H, C*H*$_2$C=O), 2.11-1.98 (m, 6H, ring C*H*$_2$), 1.86 (d, J = 19 Hz, 3H, ring C*H*), 1.58-1.51 (m, 3H, ring C*H*), 1.38-1.29 (m, 3H, ring C*H*), 1.19 (s, 9H, C*H*$_3$), 0.92 (s, 9H, C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8 (*C*=O), 169.1 (NH*C*=O), 64.8 (bridgehead *C*C=ON), 54.1 (-, *C*H$_2$NC=O), 50.0 (*C*(CH$_3$)$_2$), 43.8 (-, *C*H$_2$C=O), 43.3 (+, bridgehead *C*H), 37.4 (-, CH$_2$*C*H$_2$N), 28.3 (-, ring *C*H$_2$), 27.7 (-, ring *C*H$_2$), 20.9 (+, *C*H$_3$), 20.5 (+, *C*H$_3$). IR (Nujol) cm^{-1} 3347 (HNCO), 1725 (CO), 1653 (NCO), 1522 (NCO). LSIMS (mNBA) *m/z* 639.3 (MH^+, 65%). HRMS (+LSIMS, mNBA) calcd for $C_{36}H_{55}N_4O_6$: 639.4122; found: 639.4122 Anal. calcd for $C_{36}H_{54}N_4O_6$: C, 67.68%; H, 8.52%; N, 8.77%; found: C, 67.23%; H, 8.55%, N, 8.51%.

Camphane diol (47)



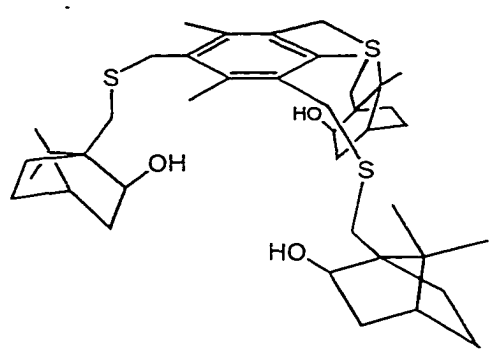
In an oven dried 2-necked 500 mL round bottom flask, $LiAlH_4$ (2.0 g, 55 mmol) was suspended in 100 mL of dry THF under an atmosphere of N_2. The reaction vessel was cooled with an ice bath and fitted with a 100 mL oven dried dropping funnel. A solution of carboxylic acid **39** (2.5 g, 14 mmol) in 100 mL of dry THF was added dropwise to the cooled $LiAlH_4$ slurry. Upon completion of the addition, the reaction mixture was heated to reflux under an atmosphere of N_2 for 16 hours. The reaction mixture was cooled with an ice bath, diluted with 100 mL of ether and quenched with 1 M HCl. The organic fraction was washed with 1 M HCl (3 x 70 mL) and brine, dried over $MgSO_4$ and concentrated under reduced pressure to yield a white solid in quantitative yield. Mp 125-127°C (lit.[204] mp 249°C, for purified diastereomer) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94-3.90 (m, 1H, C*H*OH), 3.82 (d, *J* = 13 Hz, C*H*HOH), 3.66 (d, *J* = 13 Hz, CH*H*OH), 2.31 (br. s, 2H, O*H's*), 2.25-2.16 (m, 1H, ring C*H*), 1.80-1.55 (m, 4H, ring CH_2), 1.50-1.23 (m, 1H, ring C*H*), 1.18 (s, 3H, CH_3), 1.12-0.98 (m, 1H, ring C*H*), 0.79 (s, 3H, CH_3) ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.7 (+, *C*HOH), 63.4 (-, *C*H_2OH), 52.9 (bridgehead *C*CH_2OH), 46.5 (*C*$(CH_3)_2$), 46.0 (+, bridgehead *C*H), 40.5 (-, *C*H_2CHOH), 30.0 (-, ring *C*H_2), 26.7 (-, ring *C*H_2), 21.7 (+, *C*H_3), 20.6 (+, *C*H_3). IR (Nujol) cm^{-1} 3349 (OH), 1069, 1007 (OH).[204] CI MS *m/z* 181 (M - H_2O + 29, 9%), 153 (MH^+ - H_2O, 100%), 135 (M - H_2O - OH, 85%). Anal. calcd for $C_{10}H_{18}O_2$: C, 70.55%; H, 10.66%; found: C, 70.08%; H, 10.34%.

Camphane thiol alcohol (49)



In an oven dried 2-necked 500 mL flask equipped with stir bar, $LiAlH_4$ (5.3 g, 140 mmol) was suspended in 150 mL of dry THF under an atmosphere of N_2. The vessel was cooled in an ice bath and fitted with an oven dried 100 mL dropping funnel. A solution of camphor sulfonyl chloride (5.0 g, 20 mmol) in 100 mL dry THF was dropped slowly into the $LiAlH_4$ slurry, with cooling. The reaction mixture was heated to reflux for 4 hours, and allowed to cool. The mixture was diluted with 100 mL ether and cooled in an ice bath before quenching with 1 M HCl. After quenching, 3 M HCl was added to the reaction mixture, until the aqueous layer was strongly acidic. The organic fraction was further diluted with 100 mL of ether and extracted with 1 M HCl (3 x 100 mL). The organic fraction was then washed with aq. sat. $NaHCO_3$, followed by brine. The organic layer was dried over $MgSO_4$ and concentrated to yield a colourless sticky semi-solid in 90% yield.[192] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94-3.90 (m, 1H, C*H*OH), 2.72 (A of AMX, J_{AM} = 14 Hx, J_{AX} = 11 Hz, 1H, CH_aH$_b$SH), 2.48 (M of AMX, J_{MX} = 6 Hz, 1H, CH$_a$$H_b$SH), 2.16 (br s, 1H, O*H*), 2.14 (X of AMX, 1H, S*H*, obscured by OH signal), 1.81-1.57 (m, 5H, ring C*H* and H_2O), 1.44-1.32 (m, 1H, ring CH_2), 1.23-1.18 (m, 2H, ring CH_2), 1.01 (s, 3H, CH_3), 1.06-0.96 (m, 1H, ring C*H*), 0.77 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 76.4 (+, *C*OH), 52.9 (bridgehead *C*CH$_2$SH), 47.5 (*C*(CH$_3$)$_2$), 45.7 (+, bridgehead *C*H), 39.4 (-, *C*H$_2$SH), 30.3 (-, *C*H$_2$CHOH), 26.8 (-, ring *C*H$_2$), 23.7 (-, ring *C*H$_2$), 20.6 (+, *C*H$_3$), 19.9 (+, *C*H$_3$). CI MS *m/z* 169 (MH^+ - OH, 100%).

Chiral sulfur-linked alcohol ligand (50)



In a 500 mL round bottom flask equipped with a stir bar, thiol **42** (3.7 g, 20 mmol) was dissolved in 220 mL of a 10% THF in EtOH solvent mixture. To this solution, cap **35** (2.4 g, 6.0 mmol) and Cs_2CO_3 (6.5 g, 20 mmol) was added with vigorous stirring. The reaction mixture was stirred at room temperature for 2 hours, diluted with 250 mL ether and washed repeated with water (4 x 200 mL) and brine (1 x 200 mL) before drying the organic fraction over $MgSO_4$ and concentrating under reduced pressure. The desired product was isolated as a white crystalline solid in excellent yield (4.0 g, 95%). The product was dried and further purified by heating under vacuum until if began to melt. The heat was then reduced and the product maintained under vacuum for a further 30 minutes. X-ray quality crystals were grown from hexanes in the glove box. ^{13}C NMR chemical shifts assigned with the aid of a HETCOR spectrum. Mp 128°C. ^1H NMR (360 MHz, $CDCl_3$) δ 3.96-3.70 (m, 9H, C*H*OH and PhC*H*$_2$), 2.86 (d, J = 11 Hz, 3H, C*H*HS), 2.60 (d, J = 11 Hz, 3H, CH*H*S), 2.46 (s, 9H, ArylC*H*$_3$), 2.30 (br. s, 3H, O*H*), 1.81-1.64 (m, 12H, ring C*H*'s), 1.55-1.46 (m, 3H, ring C*H*), 1.25-1.16 (m, 3H, ring C*H*), 1.04 (s, 9H, C*H*$_3$), 1.05-0.97 (m, 3H, ring C*H*), 0.83 (s, 9H, C*H*$_3$). ^{13}C NMR (90 MHz, $CDCl_3$) δ 135.0 (Aryl*C*CH$_2$), 132.8 (Aryl*C*CH$_3$), 77.2 (+, *C*OH), 52.3 (bridgehead *C*CH$_2$S), 47.7 (*C*(CH$_3$)$_2$), 45.0 (+, bridgehead *C*H), 39.1 (-, Ar*C*H$_2$), 33.8 (-, *C*H$_2$S), 32.8 (-, ring *C*H$_2$), 31.2 (-, ring *C*H$_2$), 27.2 (-, ring *C*H$_2$), 20.6 (+, *C*H$_3$), 20.0 (+, *C*H$_3$), 16.1 (+, Aryl*C*H$_3$). IR (Nujol) cm^{-1} 3451(br) (OH), 1071(s) (C-O), 875(m) (symm. arom.), 721(w) (C-S). LSIMS (mNBA)

m/z 713.4 (M - 1, 98%), 561.3 (M - CAMOH, 100%). HRMS (-LSIMS, mNBA) calcd for $C_{42}H_{65}O_3S_3$: 713.4174, found: 713.4096. Anal. calcd: C, 70.54%; H, 9.30%; found: C, 70.49%; H, 9.42%.

Yttrium complex of ligand 50

Prepared following the general procedure given on page 166. The reaction of $Y(N(SiMe_3)_2)_3$ (0.16 g, 0.28 mmol) with ligand **50** (0.20 g, 0.28 mmol) in 20 mL of dry toluene, afforded a good yield (0.18 g, 80%) of white powder. It was insoluble in all available dry solvents. Mp 153°C. IR (Nujol) cm^{-1} 1081(s) (C-O), 878(m) (symm. arom.), 727(m) (C-S). Anal. calcd for $C_{42}H_{63}O_3S_3Y$: C, 62.97%; H, 7.92%; found: 62.99%; H, 8.01%.

Cerium and neodymium complexes were prepared in an analogous fashion with the following analytical data and IR spectra. Anal. calcd for $C_{42}H_{63}O_3S_3Ce$: C, 59.19%; H, 7.45%; found: C, 56.30%; H, 7.21%. IR (Nujol) cm^{-1} 1077(s) (C-O), 877(m) (symm. arom.), 722(m) (C-S). Anal. calcd for $C_{42}H_{63}O_3S_3Nd$: C, 58.90%; H, 7.41%; found: C, 57.50%; H, 7.26%. IR (Nujol) cm^{-1} 1081(s) (C-O), 878(m) (symm. arom.), 727(m) (C-S).

6.3 Molecular Mechanics Methodology[205]

The molecular mechanics and dynamics was performed by the CAChe Scientific program suite implemented on a Macintosh IIx. The potential field used in the simulations

was the standard MM2 force field,[206] including bond stretching, angle bending, stretch-bend, torsion, hydrogen bonding, and Van der Waals terms, where appropriate. The dynamics simulations were done at constant temperature, after an initial equilibration period, and the velocities updated using the Verlet second order numerical integration algorithm,[207] forming a microcannonical ensemble. Starting from a local minimum, each molecule was thermally excited to a minimum of 100°C and then allowed to reach a thermal equilibrium over 500 time steps. The actual trajectory was a total of 10 000 time steps, with a sampling every 20 time steps. The sampled geometrics were first differentiated by total energy into high, medium and low energy groups. The low energy groups were then inspected in order to assess differences between them. Those which were significantly different were then optimized to the corresponding local minimum using the molecular mechanics modules.

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